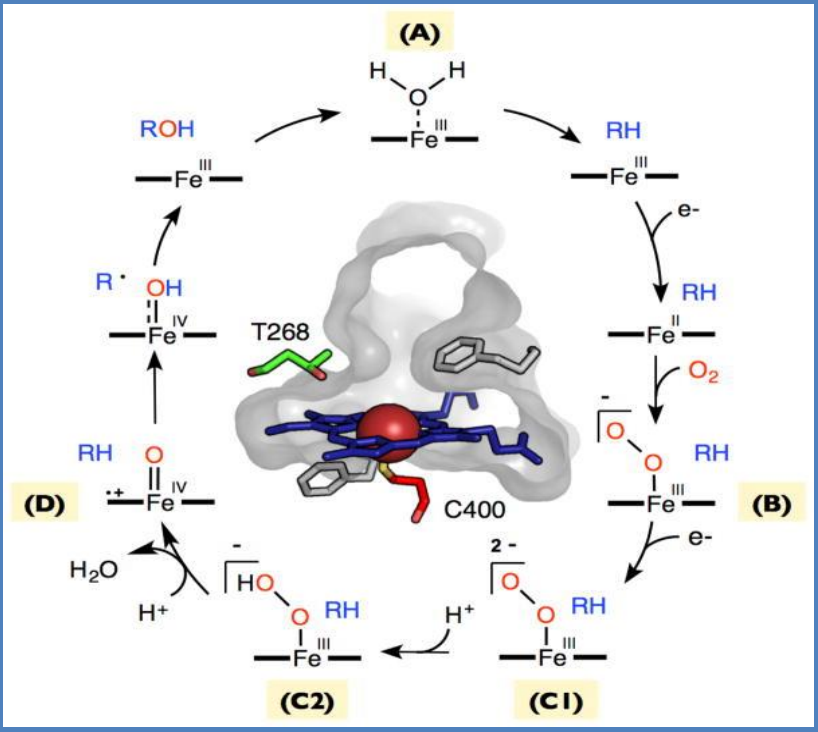
Pavol Jozef Šafárik University in Košice

CYTOCHROME P-450:
genetic and population aspects



I.R.Mavlyanov, A.Kh.Ashirmetov, Z.I.Mavlyanov,
G.J. Jarilkasinova

Košice 2017

CYTOCHROME P-450: genetic and population aspects

Scientific monograph

Authors Mavlyanov Iskandar Rahimovich
Ashirmetov Abdurashid Khamidovich
Mavlyanov Zafar Iskandarovich
Jarilkasinova Gavhar Januzakovna

Reviewers Prof. Ren Junguo, PhD
Basic Medical Institute of Xiyuan Hospital of China Academy of Chinese Medical Sciences
assoc. prof. RNDr Janka Vašková, PhD.
Department of Medical and Clinical Biochemistry, Pavol Jozef Šafárik Univerzity in Košice, Faculty of Medicine

Available at: https://unibook.upjs.sk/en/15-medicine

ISBN 978-80-8152-526-1

CYTOCHROME P-450:
genetic and population aspects

Scientific monograph

Mavlyanov I.R. M.D., Manager of clinical pharmacology department of the Tashkent institute of doctors improvement the Republic of Uzbekistan

Ashirmetov A.Kh. M.D., Chief researcher of scientific research institute of a hematology and hemotransfusion the Republic of Uzbekistan

Mavlyanov Z.I. Assistant of clinical pharmaceutics course of the Tashkent pharmaceutic medical institute the Republic of Uzbekistan

Jarilkasinova G.J. PhD, Dean of faculty of improvement of doctors of the Bukhara state medical institute the Republic of Uzbekistan

Need of carrying out a pharmacological genotyping for providing the individualized pharmacotherapy is shown in the monograph based on the analysis of own and literary data of the central link of drug pharmacokinetics– systems of cytochrome P-450, taking into account its genetic polymorphysm.

The monograph is intended for the clinical pharmacologists, geneticists and experts dealing with this problem.

2017

TABLE OF CONTENTS

Abbreviations **7**

INTRODUCTION **9**

I. GENERAL CONCEPTS IN STRUCTURE AND FUNCTIONS OF MONOOXYGENASE ENZYMES **11**

I.1. CYTOCHROME P-450 NOMENCLATURE, BASED ON EVOLUTIONARY DEVELOPMENT 12

I.2. FUNCTIONAL CLASSES OF CYP GENES 21

I.3. STRUCTURE AND LOCATION OF HUMANS CYP GENES 23

I.3.1. Family CYP1 24

I.3.2. Family CYP2 25

I.3.2.1. Subfamily CYP2A: CYP2A6, CYP2A7, CYP2A13 26

I.3.2.2. Subfamily CYP2B: CYP2B6 26

I.3.2.3. Subfamily CYP2C: CYP2C8, CYP2C9, CYP2C18, CYP2C19 28

I.3.2.4. Subfamily CYP2D 30

I.3.2.5. Subfamily CYP2E 30

I.3.2.6. Subfamily CYP2J 30

I.3.3. Family CYP3 31

I.3.4. NADP-H cytochrome P-450 reductase 32

I.4. HUMAN CYP PROTEIN STRUCTURES 33

I.5. TISSUE DISTRIBUTION OF HUMAN CYP ISOFORMS EXPRESSION 40

REFERENCES 46

II. MONOOXYGENASE SYSTEM REGULATION AND OPERATION **59**

II.1. FEATURES OF MONOOXYGENASE SYSTEM OPERATION 59

II.2. INDUCTION AND INHIBITION OF THE MONOOXYGENASE ENZYMES ACTIVITY 65

II.3. INFLUENCE OF FOOD FACTORS ON FUNCTION AND EXPRESSION OF THE CYP ISOFORMS 72

II.3.1. Role of food components in the CYP2A-E isoforms regulation 73

II.3.2. Nutritional components in the regulation of CYP3A and CYP4 families 74

II.3.3. Clinical applications 74

REFERENCES 77

III. THE WAYS OF MONOOXYGENASE ENZYMES REGULATION **87**

III.1. EPIGENETIC REGULATION OF CYP EXPRESSION AND ACTIVITY 88

III.1.1. Epigenetic regulation types of CYP expression 88

III.1.2. Role of pregnane X receptor in CYP enzymes regulation 90

III.1.3. Complexity of receptor regulation of CYP enzymes 94

III.2. NON-GENETIC REGULATION OF MONOOXYGENASE ENZYMES ACTIVITY -PHYSIOLOGICAL FACTORS 97

III. 2.1. Sexual activity determinism of monooxygenase enzymes 97

III. 2.2. Pregnancy as a factor influencing the on activity of monooxygenase enzymes 99

III.2.3. Age-related aspects of the monooxygenase enzymes activity regulation..... 101
III.2.4. Stress as a major factor regulating the activity of monooxygenase enzymes.... 104
REFERENCES..... 109

IV. CYTOCHROME P-450 AND ITS ISOFORMS AS THE BASIS FOR THE DEVELOPMENT OF PERSONALIZED PHARMACOTHERAPY 121
IV.1. INFLUENCE OF PATHOLOGICAL FACTORS ON MONOOXYGENASE ENZYMES ACTIVITY 121
IV.1.1. Changes in CYP expression and activity in liver disease..... 121
IV.1.2. Effect of kidney failure on the activity of monooxygenase enzymes..... 123
IV.1.3. Monooxygenase enzymes activity at some surgical disorders 126
IV.1.4. Expression of CYP isoforms and oncologic diseases..... 126
IV.1.5. Monooxygenase enzyme activity in some diseases of the cardiovascular and respiratory systems 128
IV.1.6. Changes in monooxygenase enzymes activity in some endocrinological diseases..... 129
IV.1.7. Monooxygenase enzymes activity in some diseases of the nervous system..... 129
IV.1.8. Monooxygenase enzymes activity in some diseases, accompanied by changes in the immune system 130
IV.1.9. Monooxygenase enzymes activity at some other diseases 132
IV.2. POPULATION VARIATIONS OF CYP GENE EXPRESSION..... 132
IV.2.1. Cluster of CYP3A genes..... 134
IV.2.1.1. CYP3A5..... 134
IV.2.1.2. CYP3A4..... 136
IV.2.2. CYP2D6..... 138
IV.2.3. Clusters of CYP1A2 and CYP2C genes..... 139
IV.2.4. Another types of CYPs 146
IV.3. APPLIED ASPECTS OF PERSONALIZED PHARMACOTHERAPY..... 150
REFERENCES..... 161

CONCLUSION..... 183

ATTACHMENT..... 187

ABBREVIATIONS

AD - Alzheimer's disease
ADRs - Adverse drug reactions
AhR - aryl hydrocarbon receptor
AR - adrenergic receptor
C/EBPa - CCAAT/enhancer binding protein A
CAR - constitutive androstane receptor
CDS - support system pharmacogenomic clinical solutions
CHNLD - chronic non-specific lung diseases
CHRF - chronic renal failure
CNV - copy number variations
CPA - cyclophosphamide
CYB5 - cytochrome b_5
CYP - genes of cytochrome P-450
EM - extensive metabolisers
EPR - electron paramagnetic resonance imaging
ER - endoplasmic reticulum
FAD - flavin adenine dinucleotide
FC-(E, S,X) - functional classes -(E,S,X)
FDA - The Food and Drug Administration Office of the Ministry of Health USA
FDX - ferredoxin
FDXR - ferredoxin reductase
FMN - flavin mononucleotide
FXRs - farnezoid X receptor
GH - growth of hormone
GPMs - genetic variant poor metaboliser
GR - glucocorticoid receptor
GSTP - glutathione transferase
HATT - tuberculosis treatment
HNF-4α - hepatocyte nuclear factor 4 alpha
ID - acute intestinal diseases
IM - intermediate metabolizer
IT - information Technology
LKM-1 - liver-kidney microsomal antibody type 1
MCT - medium chain triglycerides
miRNA - microRNA
MOC - monooxygenase system
MPMs - metabolic poor metaboliser
MRNA - RNA messengers
MRS - urinary metabolic coefficient for sparteine
NAFLD - no alcoholic fatty liver
NASH - non-alcoholic steatohepatitis
NSAIDs - nonsteroidal antiinflammatory drugs
OBCA - organic anion-transporters

OCT - organic cation-transporters
PAH - polycyclic aromatic hydrocarbons
PCB - polychlorinated biphenyls
PD - Parkinson's disease
PM - poor metabolizer
POR - P-450 oxidoreductase, NADP-H cytochrome P-450 reductase
PRL - prolactin
PTM - post-translational modification
PXR - pregnane X receptor
ROR - retinoic acid relative orphan receptor
SHP - typical target gene farnesol X receptor, which serves as a bile-acid sensor in the liver
SNP - single-nucleotide polymorphism
SRS - nonsynonymous substitutions
TATA - part of the DNA in the promoter region of gene, defining a matrix circuit for transcription
TNE - total nicotine equivalent
TSS - transcription start site
UGT - uridineglucuronyl transferaze
UM - ultra-rapid metabolizer
VDR - vitamin D receptor

INTRODUCTION

Present time special relevance has acquired by questions of optimization and personification of a pharmacotherapy. In clinical practice, many drugs are now used, but they are effective only at 25-60% of patients whereas adverse reactions of drugs, because of treatment, have estimated at billions of US dollars and tens of thousands of death. For the obvious ethical reasons, possible toxicity of potential drugs in the course of development hasnot tested normally in public *in vivo*. Of course, systems of replacement, such as, animals are for this purpose developed for *in vivo* of researches either human or animal cells in culture. However, in these systems of replacement, a biotransformation of drugs very often substantially deviate from what occurs at people in *in vivo* and consequences can be drama.

Besides, or insufficient efficiency of monotherapy led existence at the patient of several diseases to a wide circulation of the combined use of drugs in modern clinical practice, especially to a polypragmazy. Potentially dangerous combinations of drugs become a serious clinical problem. There are data that from 17 to 23% of the combinations of drugs prescribed by doctors are potentially dangerous. Only in the USA because of unforeseen interaction of drugs 48 thousand patients a year dies.

The differences in the elimination rate of drugs, revealed by different people, often due to inadequate pharmacologic response to injection drugs, so the development of personalized medicine cannot be without studying the metabolic processes and excretion of medicinal substances and the organism's response to the drug.

Now it divided into three phases of detoxification or elimination of drugs where:

The phase-I is a reaction, during which xenobiotic pass a compound more hydrophilic, by joining or the release of active functional groups (for example, -OH, -NH_2, -SH) using monooxygenase system enzymes;

The phase-II is a synthetic reaction, alsocompound (conjugation) of xenobiotic and/or their metabolites from endogenous substances, thereby forming hydrophilic conjugates.

The phase-III is active secretion, carried glycoprotein-P, conveyors and organic anions and cations, xenobiotics and/or their metabolites in urinary or biliary tract.

A key role in biotransformation of xenobiotics belong monooxygenase system (MOS) enzymes. Thus, its activity in relation to a drug is determined by, mainly, concentration and functional ability, i.e., activity-specific for its cytochrome P-450.

Other components of the system NADP-H-dependent reductase and cytochrome b_5, as a rule, are not limiting factors in monooxygenase reactions and, so the individual characteristics of the drug compounds metabolism defined personal profile - concentration and the activity of cytochrome P450.

To study the molecular mechanisms of action of drugs we need a thorough knowledge of the concentration and the activity of these enzymes, as well as their changes under the influence of various factors.

It known, that the chemical compounds, especially drugs, contents can affect the activity of the cytochromes and P-450, both enhancing their functional ability (induction), and reducing (inhibition). Properties inducers and inhibitors of enzymes may benot only drugs, also and food ingredients, pollutants air and water, compound, contained in cigarette smoke, alcohol, and other.

A through understanding of the interaction mechanisms of cytochrome P-450 – drug, it allows experts to prevent or significantly reduce the potentially negative effects of drugs, and thus increase the effectiveness of therapy, and in some cases and save the patient's life. Cytochrome P-450 and essential drugs interaction laws knowledge, as a preliminary finding of the drug degradation by one of the cytochrome P-450 isoforms, often enough for the termination of investigations of this drugs by the pharmaceutical companies.

A study of such interactions at the level of changes in the activity of the monooxygenase system is important in the development of new drugs, since the tracking of possible inhibitory and inducing effects is a necessary stage of clinical trials.

History of studies of the metabolism of drugs and the development of industry and production has gone through several stages. From the identification of metabolites, released from waste products and the lack of knowledge at the same time on the metabolism and the fate of drugs in the body, researchers have directed search and predicting interspecies differences, individual variations and drug interactions, due to drug compounds metabolism enzymes. At present, the current level of knowledge makes researchers and the pharmaceutical industry to take into account the genetic determinants of future patients, to study drug metabolism at the level of pre-clinical screening and clinical trials of new candidates for drugs. At the same time it is obvious, you need to know the profile of cytochrome isoforms for the safe and effective therapy P-450 each patient to determine potential drug interactions, including competition for specific isoforms and individual variability, associated with high polymorphism isoforms P-450 and possibly their induction etc.

The rapid development of optimization and personalization of pharmacotherapy requires a deep study of mechanisms of action of drugs and the body's response. It has known that the response of an organism to a drug has defined as the result of the interaction of genetic factors and sets of environmental factors. This variability can expected as the effects of drugs, and the possibility of the risk of complications of pharmacotherapy.

Since all processes pharmacokinetics and pharmacodynamics of drugs, mediated by receptors, ion channels, carriers, metabolic enzymes are DNA – dependent genetically caused individual differences in drug effects in terms of mechanisms of interaction of drugs with the body should considered as an obvious pattern.

Genetic polymorphisms can profoundly affect the levels or activity of the drug-metabolizing enzymes. Genotyping can identify patients –poor metabolizers without or with very low these enzymes activity, which could be at risk of serious toxic responses, in order to carry out optimization drug dosages substances. Pharmacotherapy can win in attracting clinical pharmacists and laboratory technicians, in addition to the responsibility of clinicians to participate in the process of treatment, leading to a reduction in the therapeutic errors, adverse drug reactions and the cost of health care costs.

HEAD I. GENERAL CONCEPTS IN STRUCTURE AND FUNCTION OF MONOOXYGENASE ENZYMES

In the cells of all living beings it is widely represented a unique class of enzymes - monooxygenase which catalyze redox reactions involving molecular oxygen. They are involved in the synthesis and metabolism of many important classes of physiological compounds -steroid hormones, bile acids, vitamins, neurotransmitters, fatty acids, prostaglandins and other, however, the main physiological function of these enzymes has considered the detoxification of xenobiotics by hydroxylation. Introduction of hydroxyl groups in the substrate molecule increases its polarity, solubility and thus facilitates the excretion. This reaction has called the mixed function oxidase reaction, since one oxygen atom is included in the hydroxylation of the substrate, while the other has reduced to water molecules.

Cytochrome P-450 it is an essential component of monooxygenase system, responsible for the activation of molecular oxygen and substrate binding. To activate molecular oxygen for subsequent oxidation, cytochrome P-450 reducing equivalents required by either NAD·HorNADP·H. Cytochrome P-450 cannot accept electrons directly from NAD·HorNADP·H, consequently, to the reduction of microsomal heme P-450 need cytochrome P-450 reductase, containing flavoprotein and FAD. NADP·H cytochrome P-450 reductase serves as a carrier of electrons from the reduced NADP on cytochromeP-450. In addition to the cytochrome P-450 and NADP·H cytochrome P-450 reductase, in the composition of this system include cytochrome b_5 and NAD·H cytochrome b_5 reductase. Thus, cytochrome b_5 capable of receiving electrons not only from the reduced form of NADP·H, butand from NAD·H, participating in the operation NAD·H dependent electron transport chain.

Cytochrome P-450, representing Protogenes covalently bound to the protein was first detected in 1958 in rat liver microsomes by M. Klinberg and D. Garfinklin [1]. It got its name because of the painting (P – from English word Pigment) and displays a maximum absorbance at absorption of light waves in the wave length 450 nmin compulsory binding conditions with CO (carbon monoxide) reduced form of protoheme. Based on the analysis of the spectrum of iron heme molecule due cytochrome P-450 with carbon monoxide (CO) against the spectral difference intact heme cytochrome P-450 method was developed for determination of cytochrome P-450 (expressed in nmol/mg microsomal protein) [2].

Substrates can change the optical properties P-450 to, so-called, associated substrate spectrum [3, 4]. Substrate binding can lead to a high-spin state of P-450 with the absorption of light waves around a maximum of about 390 nmand a minimum of about 420 nm (Type I substrate binding spectrum) or to promote the transition to a low-spin state with an absorption peak at about 417 nm and a minimum of about 390 nm (Type II substrate binding spectrum) [3, 4]. Figure1.1 shows the binding spectra (Type II spectrum) with increasing concentrations DMSO or pyrazole, known CYP2E1 ligand, added it to clean.

In general, it appeared that created by nature for the synthesis of secondary metabolites at various stages of evolution cytochrome P-450 has an amazing perfection.

Cytochrome system P-450 refers to one of the most ancient of enzyme systems, it is wide spread and found in all prokaryotes and eukaryotes, but its functional significance has its differences in organisms standing at various stages of the evolutionary ladder.

Depending on the origin, cytochromes P-450 it differs significantly in structural organization, substrate specificity and in implementing redox reactions, therefore a characteristic feature of cytochrome P-450 is its multifunctionality [6].

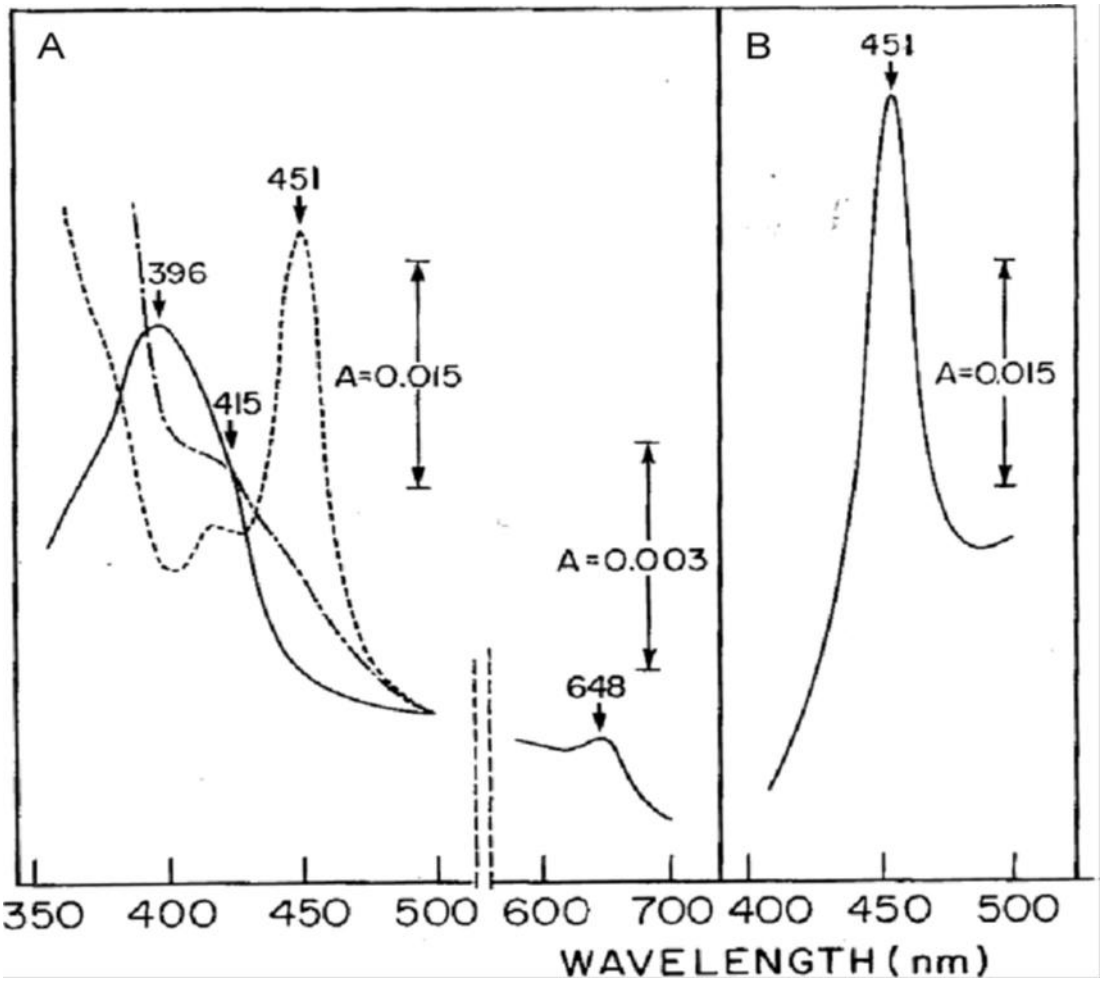


Figure 1.1. Spectral characteristics of cytochrome P-450. Scheme represented respectively by [5].

For Cytochrome P-450 inherent a variety of forms, that caused by ad novo synthesis of different proteins, and is not in the result of polypeptide interconversion.

I.1. CYTOCHROME P-450 NOMENCLATURE, BASED ON EVOLUTIONARY DEVELOPMENT

Due to the explosive development of molecular biology from 1980 it became clear that genes P-450 (CYP) they exist in virtually all types (except for anaerobes) from prokaryotes to humans [7], and a lignment of the deduced amino acid sequences has led to the suggestion of the first system of nomenclature gene superfamily, based on the emerging divergence [8]. It develops the concept also implies that all genes CYP it originated from a single ancestor that probably appeared more than 3 billion years ago. 30 genes for which was first reported in 1987, were derived from six vertebrates (rat, mouse, human, rabbit, cows and chickens), yeast and Pseudomonas putida [8]. In twenty-five years superfamily expanded and formed to the nomenclature system online, the number of genes that are reached in December 2011 to 16000, and the 22 august 2012, include

18687 renamed the protein-encoded genesP-450, having the intended function and grouped in 700 the families and 800 subfamilies (http://drnelson.uthsc.edu/cytochromeP450.html).

Nowadays, the number of families and subfamilies exceed respectively 1000 and 2500, already known 39417 CYP from 236 species of organisms, including 22675 CYP allocated from 129 fungal species (57,53%) and 16742 CYP from animals, plants, protozoa, bacteria and Archaea (42,47%).

This explosive growth in the detection of new information demonstrates the growing interest in the urgent problem of evolutionary development CYP systems.

Nomenclature CYP clustered into families and subfamilies according to certain principles. Genes CYP formed by multigene families encoding proteins with amino acid sequences identical [7-9]. Enzymes are used in more than or equal to 40 percent of identities assigned a particular family, a particular Arabic numeral. Each family includes the subfamilies with the amino acid sequences with more than or equal to 55 percent of identity defined letters. For instance, both sterol 27-hydroxylase and 25-hydroxy-D-1α hydroxylase, appointed family CYP27, because they distribute more than 40 percent sequence identity. However, sterol 27-hydroxylase, is related to «subfamily A» CYP27α, 25-hydroxy-D31α-hydroxylase to «subfamily B» CYP27, protein sequences as they constitute less than 55 percent identical. If it has found an additional enzyme, for which revealed more than 55 percent identity with the sterol 27-hydroxylase, then it should called CYP27A2 etc.

At the same time, members of the families of mammals CYP2, CYP3 and CYP4 chronologically called, regardless of type, according to their opening time; this explains why, for example, four human genes CYP3A - CYP3A4, CYP3A5, CYP3A7 and CYP3A43 represented thus. In fact, similar rules are now to accompany the range of hundreds of different genes in the superfamily database dozen vertebrates and invertebrates (http://www.genenames.org/).

There is a general trend to determine the average size of the family (the average number of genes per family), which can be small in lower organisms, such as prokaryotes and protists, fungi, and intermediate in large animals and plants. It turns out that this is due to higher circulating indicator of some classes of CYP genes of plants and animals, due to the intensive expansion (also called "bloom" [10]) duplication, rapid loss or other methods pseudogenes.

In this case, the family CYP2, CYP3 and CYP4 genes contain much more than 15 other families [11]. This expansion to the three families linked to the apparently "elevated response" of these families on environmental factors (diet, chemical inducers, drugs etc.). In fact, many of the genes in these three families, plus CYP1 family - induced many diverse stimuli, since genes in the remaining 14 families often have only a single element, rarely even if the "inducible", often unnecessary and is included more directly in critical situations life [7, 11, 12]. Consequently, this can attributed to the remaining 14 families, which are also more likely that they can be associated with serious human diseases, if an important gene has mutated or lost.

The development and application of this beautiful logical nomenclature system has eliminated the majority of the confusion that often accompanies the assignment of gene names, gene families and superfamily.

Accordingly, the subcellular position cytochromes P-450 (CYP), found in the mitochondria of eukaryotic cells and bacteria, referred to as “type I”, and those that are found in the endoplasmic reticulum (EP) eukaryotic cells, characterized as "type II" [13]. Three type CYP it is a cytosolic form. While all cytosolic CYP identified in prokaryotes, while soluble CYP and extremely rare in eukaryotic cells.

In evolutionary terms is the most ancient, monooxygenase aerobic bacteria consists of a soluble cytochrome P-450, FAD-containing flavoprotein and iron-sulfur protein. Thus, the absolute substrate specificity was a characteristic feature of this system. A higher level of structure and function monooxygenase, as incorporation of cytochrome P-450 in the membrane EP, accompanies the evolutionary transition from prokaryotes to eukaryotes. It has assumed that the incorporation into the membrane increases the interface between the oxidation NAD·HorNADP·Hand reduction of cytochrome P-450 [14].

For example, cytochromes P-450 together with flavoprotein plants and possibly with Fe-S-protein, electron transfer is carried out in microsomes using oxygen desaturation for (administering cis-D9-double bond) saturated fatty acids in monoenoic unsaturated fatty acids [15]. In addition, invertebrates, in particular insects, microsomal cytochrome P-450 involved in the regulation of molting process performing biosynthesis enzyme composition ecdysteroides ecdysone-20-monooxygenase [16].

Adrenal mitochondrial monooxygenase systems situated on an intermediate step of the evolutionary ladder, since it has the features of a soluble bacterial systems also consists of three one components. Although - cytochrome P-450 - is integrated into the membrane, the other two - flavoprotein FAD-containing (NADP·H- or NAD·H-dependent reductase) and non hemin sulfur containing protein (adrenodoxin) - water-soluble and are localized in the mitochondrial matrix. Nevertheless, high substrate specificity of mitochondrial monooxygenase makes this system more similar to bacterial.

At the highest level of the evolutionary ladder stands liver microsomal monooxygenase system comprising membrane-related cluster of 12 cytochromes P-450, three-cytochrome b_5 and one flavoprotein, which generally has a wide spectrum of reactions catalyzed by both endogenous and exogenous substrates.

Animals CYP primarily localized on the membrane of the endoplasmic reticulum (EP), but some of them are also present in other parts of the cell, such as mitochondria and cell surface where enzymes exhibit catalytic activity towards specific CYP substrates [17-20]. Microsomal CYP aimed at EPby its N-terminal leader, which includes the transmembrane helix connected to the catalytic domain by means of polar connector and segregated on the cytoplasmic side of the membrane. In the EP, NADP·H donates electrons to diflavinprotein of P-450 oxidoreductase, which then passes them on to CYP type II (Figure 1.2). FAD group of P-450 oxidoreductase accepts electrons from the NADP·H, causing conformational changes in the oxidoreductase to FAD could donate electrons to FMN and return to its original state [21, 22]. Heme in both types of P-450 eventually receives electrons and donates molecular oxygen to it as a terminal electron acceptor, binding catalysis. In some cases, cytochrome b_5 (CYB5), acts as an allosteric factor facilitating interaction oxidoreductase with P-450 type II, and rarely can act as an alternative donor to a second, but not the first electron in the P-450cycle; therefore action oxidoreductase essential for all P-450 Type II.

CYP11A1, CYP11B1, CYP11B2, CYP24A1, CYP27A1, CYP27B1 and CYP27C1 - seven CYP exclusively located in the mitochondria, which consequently considered type

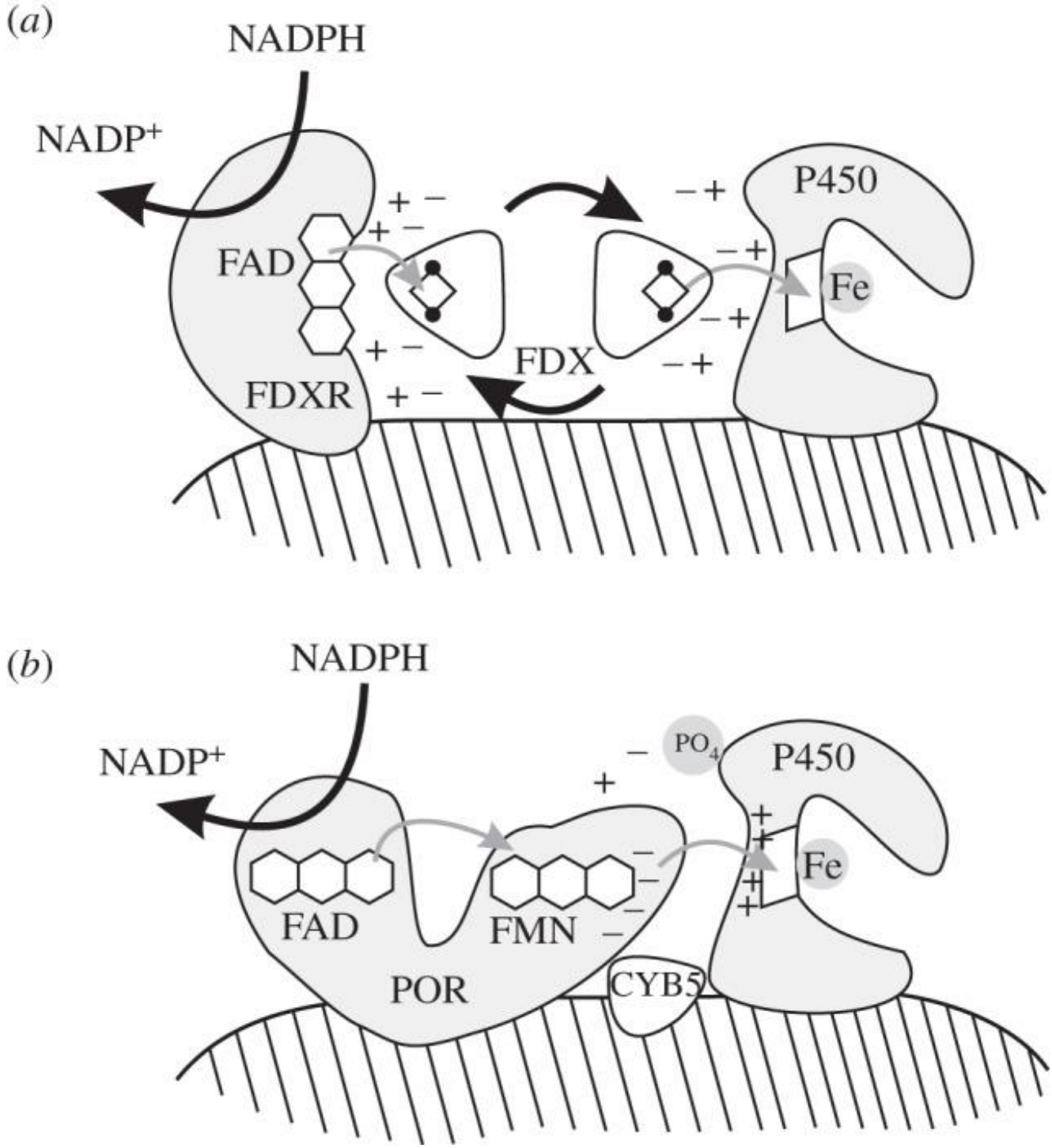


Figure 1.2. Schematic representation (a) P-450 type I and (b) P-450 type II

Note: FAD, flavin adenine dinucleotide; FDX, ferrodoxin; FDXR, ferrodoxin reductase; FMN, flavin mononucleotide; POR, P-450 oxidoreductase; CYB5, cytochrome b_5. The scheme has borrowed from [23].

I CYP. In the mitochondria, NAD·Hor NADP·H can donate electrons to the membrane-bound flavoprotein ferrodoxin reductase, which then sends them to the iron-sulfur protein

ferrodoxin to donate electrons to the type I CYP. Several CYP bimodal focused on the mitochondria, including human CYP1A1, CYP1A2, CYP1B1, CYP2E1 and CYP2D6 and rat Cyp2b1 [18]. These CYP target on mitochondria as well as on the EP that is a consequence of the unique N-terminal signal. These are essential elements for the targeting on both organelles.

The human genome contains 18 CYP families, divided into 43 subfamilies encoded protein encoding functional genes to CYP 57 and 58 pseudogenes (namely: CYP 1, 2, 3, 4, 5, 7, 8, 11, 17, 19-21, 24, 26, 27, 39, 46 and 51) (http://drnelson.uthsc.edu/cytochromeP-450.html). Human CYP genes include seven groups: CYP2ABFGST, CYP2C, CYP2D, CYP2J, CYP3A, CYP4ABXZ and CYP4F.

Although the human genome is established the presence of 57 active genes CYP, their exact number can vary from person to person. Gene products function as key enzymes that metabolize a wide range of the lipophilic components, including steroids, fatty acids, eicosanoids and xenobiotics.

The ability of these enzymes to metabolize the drug is a secondary product, which has believed to be their "primordial" role. Paralogs CYP 450 exist in a variety of prokaryotic and eukaryotic species and genes, and probably there were on the planet over 2 billion years ago [24]. It is believed that the ability of exogenous enzymes CYP 450 metabolize components developed 400-500 million years ago, to allow the animals to absorb chemical substances and plants creating water soluble components that should easily stand out from the body [25].

Despite the fact that the metabolic pathways of synthesis and degradation of physiologically important components well studied in mammalian evolution sources of these CYP genes are often unclear. Since the genomic sequences of many organisms are now available knowledge of the problem and the inspection can achieved by comparing the potential genes CYP, encoded in the genome. Using as a source of 63 representative sequences of P-450, a group of authors conducted a search and prediction of CYP genes in 34 «metazoan» (metazoal) genomes of different evolutionary sources, using mapping tools and splice alignment Spaln [26], accompanied by an iterative purification [27]. Figure 1.3 illustrates a number of genes CYP, identified by the method of representative genomes. It is sometimes difficult to distinguish true genes from pseudogenes adopted in an automated procedure. On the other hand, a large number of genes can omit when a large part of the genomic sequence is incomplete.

Thus, these results may over- or underestimate the actual number of genes. With this in mind, the following conclusions had made:

1) All identified thus CYP genes into the metazoalgenomes belong to one of seven groups (I-V, VII, and X). Although the vast majority of genes of vertebrates, insects and nematodes belong to known families, according to the criteria mentioned above, many of the genes in other lineages remain unclassified. For example, a recently identified 16-th family, only found in the genomes of marine animals (Figure 1.4). They observed a moderate association with the families of CYP26/CYP120, belonging to group IV, and a single copy of each form represents them. These observations suggest that their physiological function relates to retinoid metabolism [28], which is very important for marine animals, but is not essential for tetrapods.

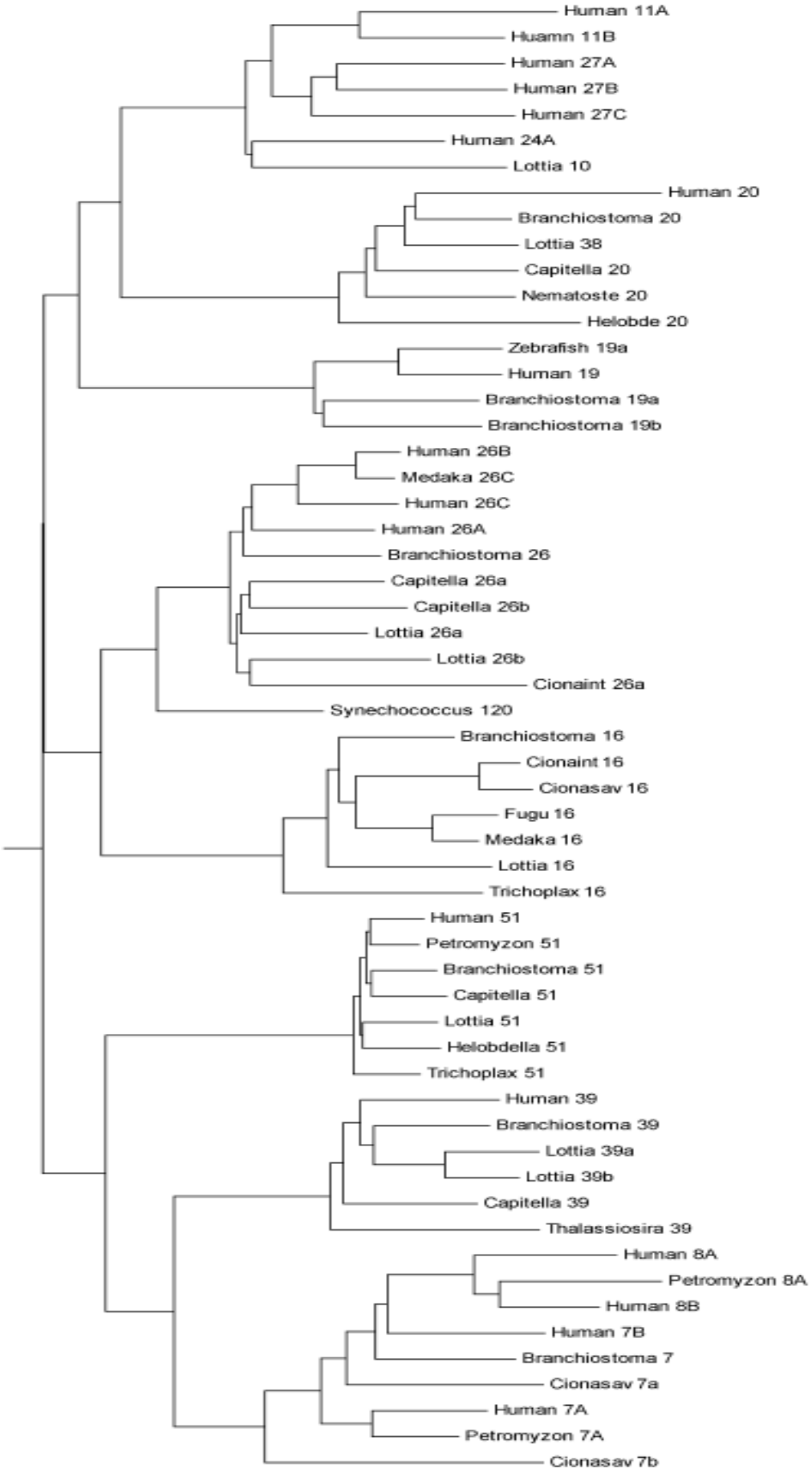


Figure 1.3. Phylogenetic relationships among a limited number of CYP genes of animals

Note: It has shown that a large part of the tree that had created by the method of Neighbor-Joining from a multiple alignment of amino acid sequences of representative 427 animal CYPs. The families 16 is a new family will probably specific to marine animals. Data presented respectively by [56].

2) Groups of genes I, II and III often show an intense increase. A striking example discovered beside lancelet Branchiostoma floridae, which may encode more than 170 genes of the group I and at least 60 genes of the group II on haploid. Also deserves attention that up to 10 genes of the group III (mitochondrial) match proliferative nature of this group of insects. The increasing of CYP genes has frequently observed in plants and fungi, while B. floridae genome demonstrates that this may also occur in chordates.

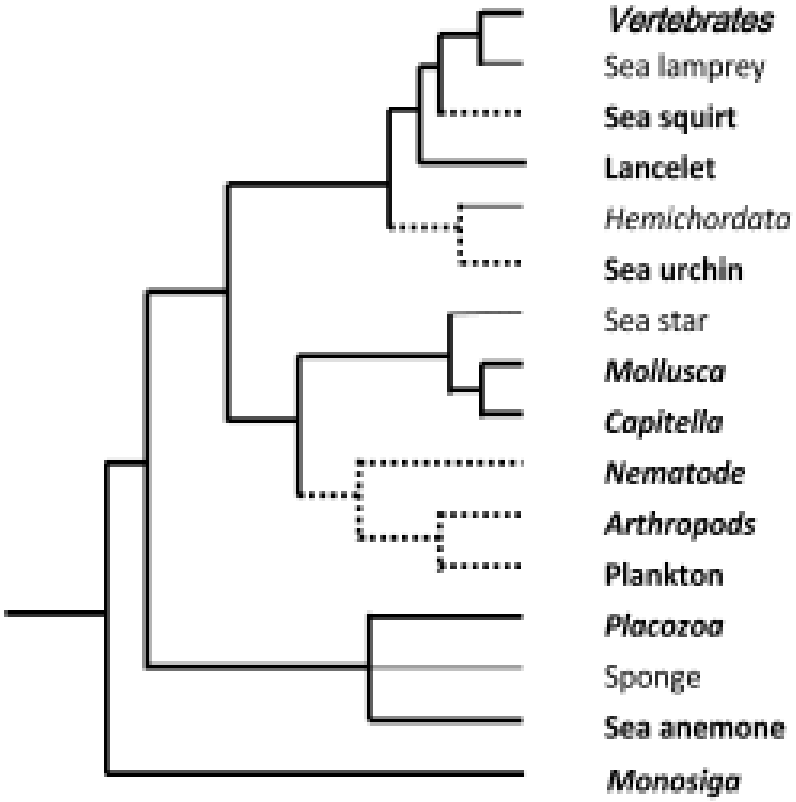


Figure 1.4. Loss of CYP51 gene in some lineages of metazoan origin

Note: The bold solid line indicates preservation of the CYP51 gene, a thin solid line shows the uncertainty, and the dotted line indicates a loss or absence of CYP51 gene. Data presented respectively by [56].

3) The battery of genes CYP, present in humans, mostly preserved among vertebrate animals from fish to mammals. The majority of these genes from vertebrates also shares amphioxus. On the other hand, the sea urchins have no basic number of genes CYP, which play an important role in mammals in the synthesis and the decomposition of steroids and other physiologically active components.

4) As known, CYP51 is one of the oldest CYP genes, and widespread in all kingdoms: bacteria, protists, fungi, plants, and animals [29]. However, in certain large

animal branches, such as nematodes and insects, CYP51 gene together with other groups of genes (IV, V, VII and X) are absent. As the "lower" animals have the CYP51 gene (Figure 1.4), it is most likely that CYP51 was lost in the lineage, which led to present time insects and nematodes. Similar minor losses could potentially occur in CYP19, CYP20, CYP26, CYP39 and CYP46 families.

5) Certain CYP genes encoding steroidogenic enzymes or enzymes which catalyze the biosynthesis of other endogenous substrates, such as, CYP5, CYP11, CYP17, CYP21, and CYP27 origin probably arose recently, so identified in vertebrates. The closest families for CYP17/21 in our dataset are multiple paralogues found in the genomes of sea anemone, and hydra. Perhaps these genes recruited from a xenobiotic-metabolizing gene pool in some time of the evolutionary process. This observation is consistent with recent reports from independent sources steroidogenic enzymes and receptors in vertebrates and arthropods [7, 10]. It had postulated that xenobiotic-metabolizing enzymes derived from enzymes that catalyze endogenous substrates [8]. Although such cases are well-documented [9], some observations suggest that the more dominant scenario is probably the opposite option, at least in highly developed multicellular organisms.

For example, we give the evolution of one of the human CYP genes. Figure 1.5 presents the family tree constructed based on Ensembl Release 81 and the human genome assembly - GRCh38.p2. Figure 1.5 shown, that CYP2D6 has many orthologous genes from different species of primates, rodents, Laurasiatheria, placental mammals, Sauropsida, fish and other species, including invertebrates. Accordingly, the representation, CYP2D6 gene is present in the common ancestor of chordates and saved from frogs to humans. Furthermore, phylogenetic analysis for CYP2D genes suggests that the origin of the CYP2D subfamily can traced back to the differences between amphibians and amniotes about 312 million years ago [30]. CYP2D6 homologs are chimpanzee CYP2D6, Rhesus monkey CYP2D6, rat Cyp2d3, chicken CYP2D6 and frog CYP2d6. CYP2D6 paralogs include CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D7, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1 and CYP2W1.CYP2D6 has a plurality of orthologous genes from various species of primates, rodents, placental mammals, fish and other species including invertebrates. Thus, representative CYP2D6 include orthologs: CYP2D6 of cats, CYP2D6 of chimpanzee, CYP2D19 of white-tufted-ear marmoset, MGC127055 of cattle, CYP2D19 of Ma'snight monkey, CYP2D14 of fox, CYP2D14 of Arabian camel, CYP2D14 of bison, CYP2D17 of eagle, CYP2D3 of cuckoo roller, CYP2D17 of cormorant, CYP2D17 of emperor penguin, CYP2D15 of Pacific walrus, CYP2D14 of sheep, CYP2D19 of Bolivian squirrel monkey, CYP2D15 of giant panda, CYP2D14 of platypus, etc. [11].

There are significant differences between rodents and humans in a number of CYP2D active genes. While the mouse has nine different active Cyp2d genes [31], and the rats six functional Cyp2D genes, people carry only one, which is also absent in 7% of the Caucasian population. In mice, except Cyp2d nine different genes, including Cyp2d9-2d13, Cyp2d22, Cyp2d26, Cyp2d34 and Cyp2d40 and has seven pseudogenes (2d32p, 2d33p, 2d35p-2d39p and 2d41p) [31, 32, 33]. All mouse Cyp2ds have high amino acid sequence identity (65-75%) to human CYP2D6 and rat Cyp2d3-2d5(71-85%). It believed

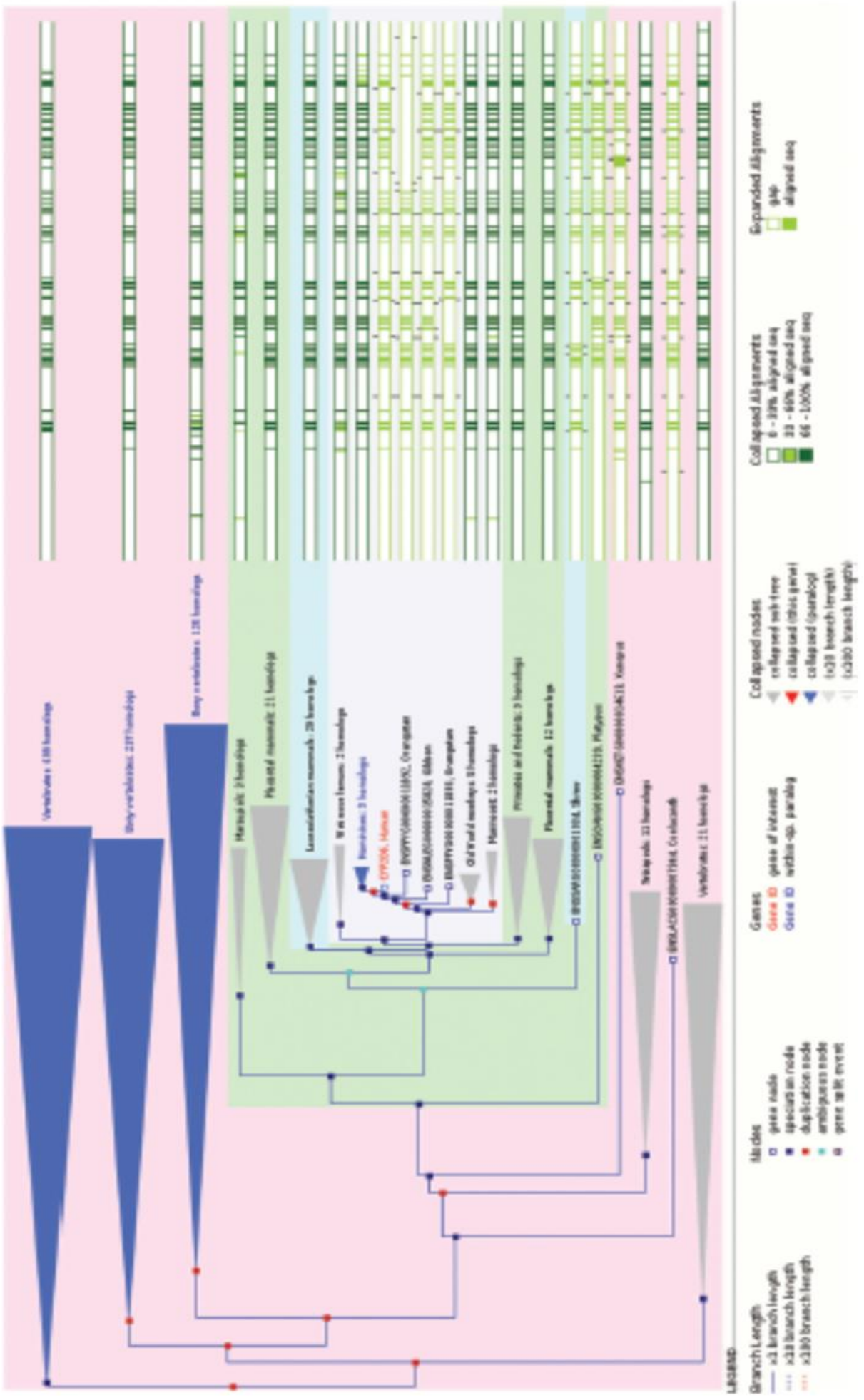


Figure 1.5. Gene tree for human CYP2D6 and its homologs (respectively by [11]).

that Cyp2d22 might be a human orthologs of functional CYP2D6. At the same time, the rat Cyp2d3, but not Cyp2d1, Cyp2d2 or Cyp2d4, turned out to be homologous to CYP2D6 of human, chimpanzee, Rhesus monkeys and chickens, as well as frog Cyp2d6 and 2d20.

The evolution of the human locus of CYP2D involves the removal of the three genes, inactivation of the two (CYP2D7P and CYP2D8P) and partial inactivation of one (CYP2D6). Based on the identification and characterization of non-functional CYP2D7P gene and 2D8P pseudogene suggested that CYP2D6 and CYP2D7P may arise in the case of gene duplication and gene conversion events that have occurred in the following, can generate CYP2D8P. CYP2D7 gene duplicated from CYP2D6in the stem origin of humans and the great apes, and the source of CYP2D6 and 2D8P genes in the human genome can traceat the division of the New World monkeys and Catarrhinistem origin in the following. Two functional CYP2D isoforms had observed in macaques and monkeys, although the number of CYP2D gene copies varies among individuals macaques [34, 35].

Further analysis of windows and statistical tests led to the discovery that in primates entire genomic sequence paralogous genes highly homogenized by gene conversion in the process of CYP2D genes molecular evolution [36]. Connecting adjacent tree branches, based on the genomic sequences in unidentified substrates sites show that CYP2D6 and 2D8P clustered together, owing to gene conversion. In contrast, phylogenetic tree, using the amino acid sequences identified sites in substrates not cluster CYP2D6 and 2D8P, suggesting that a functional limitation in substrate specificity is one of the reasons for purifying breeding sites identified substrates. It revealed that the gene subfamily CYP2D evolve, from apes to support regio-selectivity between individual enzymes during the hydroxylation of substrates, even if there was an intense conversion of the coding sequences of CYP2D gene.

It is logical to assume that mice and rats kept active its Cyp2d genes due to the need for dietary detoxifying potential as a more limited food, taking people in the past, suggests the use of the intellectual possibilities of information exchange between the generations as to the suitability of food, which is the resulting loss of selective pressure to retain gene activity.

I.2. FUNCTIONAL CLASSES OF CYP GENES

From a functional point of view, the P-450 enzymes can divide into three classes, as an experiment, certain functional classes (FC)-E, FC-S and FC-X, according to characteristics of their substrates and products. Enzymes FC-E essential for the synthesis and degradation of endogenous components, such as hormones, prostaglandins and vitamins. FC-X enzymes directly involved in detoxification of xenobiotics, as FC-S enzymes involved in the biosynthesis and the catabolism of the secondary metabolites. It should note that this classification is not strict, and the boundaries between functional classes often remain unclear. For example, mammalian CYP1-4 detoxifying enzymes are generally considered; however, they are also involved in the metabolism of steroids and eicosanoids, which have considered critical for the life processes of mammals [37].

Usually found in the genome of lancelet, a specific CYP subfamily has a significant number of its members, while others are unique or small. The number of unique gene copies is retained as a constant, probably because of their loss and duplication destroy genes dosing balance, which can have harmful effects on the body, although this

restriction can be relaxed rare events of duplication of a genome and/or differentiation of tissue-specific expression as it is observed for the aromatase genes in fishes [38], and pig [39]. These phylogenetically stable genes most probably belongs FC-E, as phylogenetically unstable genes, the copy number of which varies rapidly inherent FC-S or FC-X. Moreover, the increase in number of genes normally achieved double duplication of the parent gene, potentially accompanied by local rearrangements, including segmental inversions. A remarkable example of this is a cluster of ca.30 CYP genes on the first stage of the genomic sequence version of 2.0 Phanerochaete chrysosporium [40].

Another feature distinguishing enzymes FC-E by enzymes FC-X is the pattern of changes in the amino acid sequence of nucleotides encoding or among closely related paralogs and orthologs.

More precisely, no synonymous substitutions (amino acid substitutions) tend to accumulate in the substrate recognition sites of six (SRS) [41] enzymes in FC-X, because they relatively suppressed in FC-E enzymes commonly present CYP51 [29]. Close association between SRS and hyper variablesites found for the first timein CYP2 family members of mammals and rationalized as anadaptive evolution to fight with a wide range of toxic xenobiotics [41]. Using modern method for identification thepositive evolutioning codon sites [37-39], several researchers [45-47] confirmed preceding the observation relating to the detection of genes CYP2 and similar associations in CYP3, but not in CYP4 genes. These observations are in good agreement with some data previously proposed [41, 48], but it is clearly different from the close association between SRS and variable sites in CYP4 gastropods [49].

The reason for the weak and SRS association variable sites in mammalian CYP4 can explained in two ways. Firstly, CYP4 - no enzyme typical FC-X, but it is quite important for the physiological metabolism of fatty acids and eicosanoids [37]. Secondly, substrate specificity generally can be defined conformation around the inlet channel substrate and not catabolic perfect conformation. The latter assumption is understandable if they become available to study crystal structures of some members of this family. It should also note that the association between SRS and variable sites only confirmed for enzymes FC-X, but not formally confirmed for the FC-S enzymes. So as of now identified numerous paralogs in the genomes of plants and fungi, patterns of variations of these sequences are ready to study.

If the varied substrate specificity is useful for the kind of begs the question - whether there was any association between the SRS and the polymorphic sites. Data from large catalogs human polymorphic sites [50-52], indicate only weak, if any detected course, an association between the SRS and the polymorphic sites, although only a few-nucleotide polymorphisms (SNP) have been found yet within SRS [53]. Most SNP are rare and often damage encoding catalytic or possibility of own genes, which suggests that they are not resident and not yet recorded in the human population.

Another important point in the evolution of CYP is a potential co-evolutionary relationship with transcriptional regulators. While such studies have focused, for the most part, in the co-evolution of aromatase and transcription factors of steroid receptors family [54-59]. Interesting combinations between specific nuclear receptors and their target CYP genes, for example, CYP1 and AhR, mitochondrial steroidogenic CYP genes and

AD4BP/SF-1/NR5A1, CYP7A, FXR/NR1H4 and many others remain unexplored with another co-evolutionary perspective. Although there may be less specific and similar correlation between the FC-X expansion or FC-S CYP and their enzymes, functioning in the upper or lower directions of metabolic pathways [60]. Bioinformatics analysis of a large number of genomic sequences evolutionarily divergent organisms is now available for implementation that will help pave the way to understanding these urgent problems.

I.3. STRUCTURE AND LOCATION OF HUMANS CYP GENES

So far identified about 500 different CYP encoding genes [61], as well as more than a thousand variants of their alleles, which can be involved in the metabolism of drugs (http://www.cypalleles.ki.se/cyp2c9.htm). There CYP isoforms have much differentions in the number, identifying the largest number of alleles for CYP2D6 - 141 and descending order for CYP2C9 - 64, for CYP2C19 – 16 etc. (Figure 1.6).

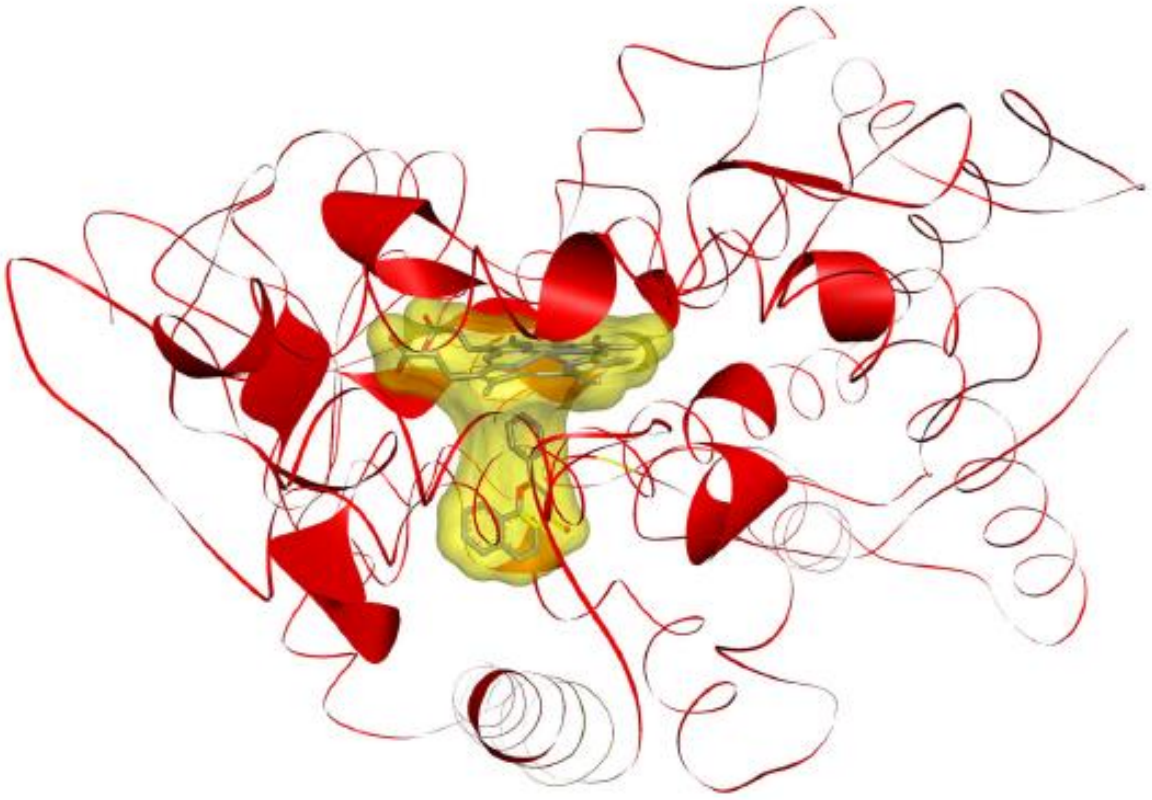


Figure 1.6. 3D structure of cytochrome P-450 with heme and ligand localization often identified SNPs

Note: Frequent SNPs in the four most polymorphic CYPs (1A2, 2C9, 2C19 and 2D6) tagged in this 3D model. Consequently, the tape enlarged in suitable positions. The binding side (transparent, orange-painted surface), contains an iron ion and porphyrine ring (heme). Frequent CYP mutations at the binding-side occurred at the following positions: 67, 89, 107, 117, 118, 120, 125, 132, 151, 201, 227, 261, 325, 377, 382, 386, 410, 454, 456, 469 and 470. Data presented respectively by [62].

I.3.1. Family CYP1

Family CYP1 includes three functional genes into two subfamilies. Highly stored CYP1A1 and CYP1A2 genes are composed of seven exons and six introns located on chromosome 15q24.1, whereas CYP1B1 consists of only three exons located on chromosome 2p22.2, which nevertheless encodes the largest human P-450 view point of mRNA size and number of amino acids [63].

CYP1A1 and CYP1A2 genes are guided one by one, using 23 kb bidirectional promoter which contains at least 13 Ah-receptor (AhR) corresponding to the element, some of which, it turns out, in a coordinated regulate the transcription of both genes [64].

Of the four common variants, originally characterized by m1 to m4, m2 only no synonymous variant (CYP1A1*2C, 2454A>G, Ile462Val) is closely related to 6.12-fold increased enzyme activity to 17β-estradiol and estrone [65]. This version has a global minor allele frequency (gMAF) 12%, but it is more common among Asian populations and Spain than in other populations (see. Table 1 in the attachment).

On CYP allele's website are lists of 21 specific alleles and many options of haplotypes, some of which are associated with altered expression or inducibility or coded for proteins with altered enzyme activity. Arg431Trp substitution (CYP1A2*6), which is arranged in "meander" peptide in the critical region for the operation in the protein tertiary structure, isresulted by production of non-functional protein [66]. However, because of their rare occurrence, these and other amino acid variants often have their clinical significance [67].

5'-top variant 3860G>A (CYP1A2*1C) associated with a reduction in smoking inducibility that identified based on the promoter analysis and reduced caffeine 3-demethylation of the Japanese smokers [62]. Intron 1 polymorphism -163C>A (CYP1A2*1F), located below the no translated first exon, associated with increased enzyme inducibility of smokers in Germany and Sweden and the Swedish and Serbian coffee consumers [68, 69].

The opposite effect was observed in the two variants of the carriers combined genotypes CYP1A2*1C/*1F, which are not induced by omeprazole [70]. However, there are also some controversial researches, and it is unclear whether the SNP rs762551 is it self a causal variant, or its relationship to other VAR versions may be responsible for other registered results in different populations. It should also note that the C allele considered as reference allele, even if it is rare in most populations the allele and that some authors use the notation opposite allele. In addition to the SNP CYP1A2, copy number variants have not found in recent studies where CYP1A2 resequenced in individuals from different populations [72].

Despite this multiplicity of polymorphism of CYP1A2, attempts to explain the alleged heritability in the phenotype of CYP1A2, linking common SNP phenotype, brought disappointment, and it was assumed that none of the single SNP or haplotypes in the gene CYP1A2 has no clear predictive value [73]. Klein and Soave are investigated the influence of non-genetic parameters and polymorphisms of genes in the 136 location of CYP1A (15 SNP) and 16 other possible genes respectively different paths express RNA protein and hepatic CYP1A2, as well as the phenotypes activity phenacetin O-deethylation. Of the 10 SNP genes in ARNT, AhR, HNF1α, IL1β, SRC-1 receptor and

vitamin D (VDR) in any of CYP1A-loci have identified with consistent association univariate analysis [74].

Multivariate linear modeling showed that only genetic polymorphism can explain only about 35% of the changes of hepatic CYP1A2 activity as a little more than 40% of the variance must attributed elaborated on the joint genetic and non-genetic characteristics. This analysis showed that additional genetic indicators outside the locus CYP1A might have a greater impact on the phenotype of CYP1A2, than polymorphism CYP1A location.

CYP1B1 found bylinkage genetic analysis and research of mutations as the causal gene of primary glaucoma innate, inherited neuro-degenerative disease that leads to blindness [69]. Over 80 mutations, mostly missense or nonsense mutations, deletions, insertions and/or duplication, found in patients with various forms of glaucoma [75-77]. Since these mutations are rare in the general population, their value as tumor markers or markers of altered drug metabolism is limited. Polymorphisms that are more common include five amino acid variants in different combinations.

Functional analysis of various proteins coexpressed P-450 reductase in E.coli showed a 3-fold increase in Km 17β - estradiol for Leu432Val option (CYP1B1*3), but little impact Arg48Gly, Ala119Ser and Asn453Ser options [78]. Nevertheless, it was not reproduced in yeast expression analysis using the same substrate as the decrease and increase of Km V_{max} to 17β-estradiol was observed in the combination of alleles CYP1B1*6 and CYP1B1*7 [79]. In addition, it turns out that CYP1B1.7 version has a lower activity of benzopyrene hydroxylation.

Variant Leu432Val correlated with changes in the ratio of estrogen metabolites in urine, indicating the contribution of CYP1B1 in vivo in an estrogen catabolism [80]. These studies suggest that the overall amino acid variations are moderate or low substrate dependent effects on the catalytic properties of the enzyme.

I.3.2. Family CYP2

CYP2 family contains 16 complete genes, all of which have nine exons and eightintrons. This family includes, along with the most important hepatic drug-metabolizing enzymes, and extrahepatic enzymes and several "orphan" P-450 [81] with more obscure function.

Genes have distributed in different chromosomes and have organized into multigene clusters containing one or several subfamilies [63, 82]. The three largest gene cluster CYP2ABFGST located on chromosome 19q13.2, which contains the genes CYP2A6 and CYP2B6, CYP2C cluster on chromosome 10q23.33 genes CYP2C8, CYP2C9 and CYP2C19, and CYP2D cluster on chromosome 22q13.1-2 with a single functional CYP2D6 gene. In the evolution of rodents, CYP2 many subfamilies greatly enhanced, making the identification of true orthologs between mouse and human P-450 is particularly challenging [63]. Most important pharmacologically CYP2 genes are highly polymorphic, particularly CYP2A6, CYP2B6, CYP2C9, CYP2C19 and CYP2D6.

I.3.2.1. *Subfamily CYP2A: CYP2A6, CYP2A7, CYP2A13*

Three complete human gene CYP2A - CYP2A6, CYP2A7, CYP2A13 and digested pseudogene CYP2A18P found on the gene cluster of 370 kb on chromosome 19q13.2, which contains the genes and pseudogenes subfamilies CYP2A, CYP2B, CYP2F, CYP 2G, CYP2S and CYP2T [63, 82]. Of these, only CYP2A6 and CYP2A13 are functional, as evident CYP2A7 gene encodes a non-functional, and cDNACYP2A7 generates immunoreactive protein that was not able to incorporate heme [82].

Currently, the 38 distinct alleles with star-duplication or deletion of the gene with a gene conversion, deletions and insertions of nucleotide and encoded and encrypted SNP disclosed in websites CYP allele. In some of these embodiments are shown mRNA expression changes and/or protein levels, which affect the structure and function of the protein. Loss of function alleles include CYP2A6*2 [Leu160His] and *4A-H deletion alleles which show complete reduction of the enzyme activity in vivo in homozygous or hemizygous combinations, resulting in a poor metabolizer phenotype in individuals. The most common null alleles in Asian populations are from *4A to *4H hybrid-deletion allele, which consist of a 5' portion and a 3' part of CYP2A7 derived from CYP2A6 source. Reduced the number of copies of the gene is associated with the identification of these gene deletions leading to a decrease in the expression and activity [83, 84].

In a study of 156 liver samples from Caucasian populations it was found 33 haplotypes, of which two (*9B, containing - 48T>G TATA-block polymorphism, and 2A7/2A6 *12B recombinant allele) were major genetic determinants associated with a decrease in hepatic expression [83]. Additional functional alleles influence include CYP2A6 *7, *10, *17 and *35 associated with reduced activity of the enzyme in homozygous or hemizygous individuals. *7 [Ile471Thr] and *10 [Ile471Thr; Arg485Leu] Asia-specific alleles, and *17 [Val365Met] were found only in African Americans. CYP2A6 *5, *6, *11, *19 and *20 alleles lead to a decrease in the activity of heterologous expression. Further embodiments of affecting the expression or function of several promoter variants also lead to a decrease in the expression [85]. Except for the low copy number variants with deleted CYP2A6, variants with an increased copy number, and named * 1X2A * 1X2B, correlate with increased activity [86].

I.3.2.2. *Subfamily CYP2B: CYP2B6*

Functional and non-functional gene CYP2B6 pseudogene CYP2B7P arranged in a tandem head to tail manner within CYP2ABFGST large gene cluster on chromosome 19 [63]. Although the genomic structure of the genes of human and rodent CYP2B very diverse, with the presence of more functional genes expressed in animals, the characteristic feature is the strong CYP2B gene and its inducibility phenobarbital similar mechanisms in humans and animals. The major discovery in this area has been the identification of Orphan nuclear receptor CAR (NR1I3) as the primary regulator of CYP2B6 drugs and other xenobiotics through phenobarbital - responsive amplifier module (PBREM) to -1.7 kb promoter CYP2B6. Later it had found that PXR (NR1I2) also promotes the induction of CYP2B6 through distal xenobiotic - responsive amplifier module (XREM, -8.5 kb) [87].

CYP2B6 gene is highly polymorphic with numerous variants in the coding and noncoding regions of the gene [88-91]. The CYP allele’s website now assembled a list of

29 distinct star-alleles with different amino acid sequence, or with proven functional effect. More than 30 SNP codes for amino acid changes that occur in other combinations and further embodiments and SNP haplotype are not defined in particular alleles. The most common allele is CYP2B6*6 with two amino acid changes (Gln172His and Lys262Arg), in combination with other identified changes, mainly in the promoter. *6 allele occurring at a frequency of 15% to 60% in different populations is associated with 50-75% reduction in protein expression in the liver [88, 89, 92]. The main option as the reason for the decreased expression, defined as the 15631G>T [Gln172His] polymorphism that causes abnormal splicing of pre-mRNA CYP2B6, leading to a shortening of the mRNA, where there are no 4-6 exons [93]. This polymorphism is an example of no synonymous variants leading to the main effects that have not related to the amino acid exchange, but haveassociated to changes in the level of mRNA [94, 95]. Only with appropriately designed study of RT-PCR can detect quantitative and qualitative changes in mRNA, associated with that particular genetic variant [93]. CYP2B6 genotyping, testing 15631G>T as a marker to identify the *6 allele is simpler. Nevertheless, we must not forget that this results in the detection of complex mixtures of related haplotypes with additional top region SNP (-1456T>C and -750T>C) and second no synonymousvariant 18053A>G [K262R]. C promoter variants, appears to be related only marginal changes [93], and the differential functional effects caused by amino acid variant K262R. Option K262R (*4 allele frequency of ~ 2-6%) were associated with higher activity to several substrates, including bupropion, nicotine [96], efavirenz [97], artemether [98] and selegiline [99].

However, the expressed variant K262R was not able to metabolize 17-α-ethinyl estradiol and further studies indicate damaged the topology of the active site - variant ending a disconnected reaction kinetics [100]. In contrast, activation of cyclophosphamide increases as recombinant variant Q172H, but decreases with K262R variant [101,102]. These findings underscore the need to perform detailed genotyping of CYP2B6 variants involved in order to get the results, in particular, of the in vivo studies. Further differential effects of amino acid variants identified with respect to inactivation of the enzyme. The opposite of the wild type enzyme recombinant expressed variant K262R was not inactivated by efavirenz, but both enzymes were inhibited irreversibly by 8-hydroxiefavirenz [103]. The lower sensitivity to inhibition K262R variants and *6 (Q172H/K262R) dual version has also been found in respect sertraline, clopidogrel and other drugs - strong inhibitors of CYP2B6 [104]. Taken together, low-expresser phenotype 15631G> T variant partially offset by higher specific catalytic activity, at least for some substrates that allows to explain a little bit contradictory data on the observations made in the liver microsomes, the system heterozygous expression or in studies in vivo. It is also revealed that this is the reason for the *5 variants (25505C>T [R487C]), which express very low levels of apparently very active enzyme with bupropion [88], as well as efavirenz [92] and explained why it was not associated with efavirenz pharmacokinetics in patients [105].

Another important functionally deficient allele is the CYP2B6*18 (21011T>C [I328T]), which is found mainly in African populations with allele frequencies of 4-12% [106]. CDNA version does not form functional protein in transfected mammalian cells, tested by bupropion [90], and the lack of activity detected in vitro for 7-EFC and selegiline [99], as well as artemether [98]. Allele*18 thus is a phenotypic void allele. At least 12

additional invalid or low-active alleles have described and analyzed using various substrates [88, 90, 97, 98, 99]. Although they are relatively rare in all populations studied, they can have a profound effect on the metabolism of drugs, if present in the composition will be heterozygous genotypes, for example, in combination with *6 or *18 [97]. Allele CYP2B6*22 is to grow a functional variant associated with increased transcription in vitro [91] and an increased activity in vivo [97]. It shown, that 82T>C-exchange unit changes the TATA-binding site in a functional CCAAT/expander-associated protein, which causes increased transcription of the alternative initiation site below [91]. It was also revealed that the polymorphism -82T>C defines a synergistic increase in CYP2B6 inducibility using PXR ligand rifampicin in human primary hepatocytes [107]. Recently it has been described a number of additional SNP CYP2B6 and haplotype variants until *29 [91,108].

I.3.2.3. *Subfamily CYP2C: CYP2C8, CYP2C9, CYP2C18, CYP2C19*

Human CYP2C subfamily consists of four highly homologous genes CYP2C18-CYP2C19-CYP2C9-CYP2C8, which are located in the following order (from the centromere to telomere) in ~ 390 kb gene cluster on chromosome 10q23.3. Although mRNA CYP2C18 strongly expressed in the liver, the transcript has translated into a protein efficiently and makes a significant contribution to drug metabolism.

CYP2C9 - most strongly expressed term expression in a similar or even a higher protein level, in comparison with the CYP3A4, whereas CYP2C19 and CYP2C8 have expressed respectively in a ~ 2-fold and 10-fold lower levels [109,110]. Dramatic differences in expression between CYP2C9 and 2C19 have shown, at least partially because of the impossibility of CYP2C19 promoter activated by HNF4α, despite having similar HNF4α-binding sites in both gene promoters [111].

CYP2C9 has more than 50 different alleles of which the most common are CYP2C9 *2 and CYP2C9*3. Alleles "wild" type is the CYP2C9*1 (Argl44-Ile359), with respect to which comparison of enzyme activity. Decrease of enzyme activity detected in the presence of CYP2C9*2 formed by replacing at C430T exon 3, which leads to transformation Arg144Cys [112]. If there CYP2C9*3 allele is even lower enzymatic activity. This allele replacement C1075T formed in CYP2C9 gene exon 7, resulting in a change in protein synthesis substituting Ile359Leu [113].

The alleles CYP2C9*6 (818delA, rs9332131) and CYP2C9*4 (option I359T) are quite rare. Moreover, the first activity lack of enzymatic characterized by a breach of splicing, which causes a shift in the reading frame, resulting in a defective protein synthesis [114], and the second is a single nucleotide substitution C1076T in the seventh exon of the gene, resulting in an isoleucine for threonine substitution at position 359. With low enzymatic activity was also associated alleles CYP2C9 *5 (D360E), *6, *8 (R150H) and *11 (R335W), and CYP2C9*14, CYP2C9*16, CYP2C9*17 and CYP2C9*19. Moreover, CYP2C9 *15 and CYP2C9 *18 alleles had not catalytic activity [115].

CYP2C8 enzyme encoded by the gene which located on chromosome 10q24 in a cluster "-2C18-2C19-2C9-2C8-centromere telomere" 2C gene to close the proximal zone of the CYP2C9 gene. CYP2C8 is one of the smallest human CYP2C gene occupying the region in the 31-kb and contains nine exons [116]. It has 74% sequence homology with CYP2C9 [117].

In the CYP2C8 gene found almost 100 no synonymously single nucleotide variations (SNV) and short deletions, as well as options sites. Most do not synonymous variants are rare and occur with a frequency of minor allele of 0.01 or less in all the populations studied.

The existence of common invalid alleles explains the great variability and a strong correlation between the phenotype-genotype detected for CYP2C19. The two most important allele detected invalid: CYP2C19 *2 - almost exclusively in Caucasians and CYP2C19 *3 - mainly in Asians. Causal mutation *2, located in exon 5, leading to aberrant splicing [118], whereas the mutation *3 in exon 4 creates a premature stop codon [119]. Future clinically important option is a promoter variant of -806C> T (*17), which causes an increase in the expression and activity against mephenytoin and omeprazole through the mechanism is unclear [120]. There are also additional rare invalid allele CYP2C19 *4- *8 and variants of unknown phenotypic manifestations.

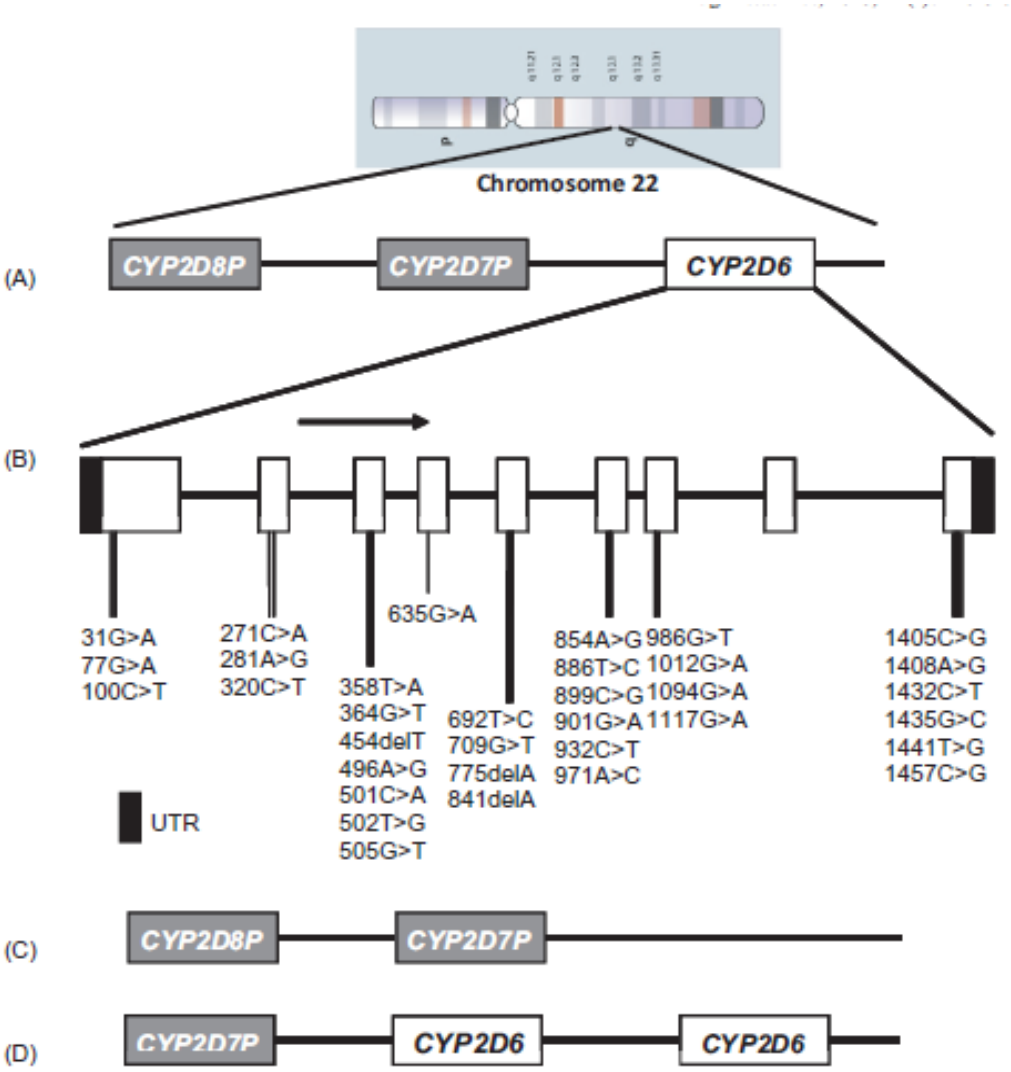


Figure 1.7. The human CYP2D6 locus on chromosome 22q13.1 and common SNPs of CYP2D6

Note: CYP2D6 belongs to a gene cluster of highly homologous inactive pseudogenes CYP2D7P and 2D8P. Scheme represented respectively by [11].

I.3.2.4. *Subfamily CYP2D*

Gene CYP2D6 is located on chromosome 22q13.1 and consists of nine exons with openly readable frame of 1491 base pairs that encode 497- amino acid protein (Figure 1.7.) [121]. CYP2D6 is located in NC_000022.11 zone (42 125 656-42 135 378) in the current human genome assembly GRCh38.p2. According Ensembl 81, this gene is alternatively spliced produces five copies encoding four distinct proteins consisting respectively of 497, 494, 446 and 180 amino acids.

It is known that a member of the CYP2D6 gene cluster highly homologous inactive pseudogenes CYP2D7P and 2D8P. CYP2D7P contains T-insertion in exon 1 violating readable frame, whereas CYP2D8P encompasses numerous insertions and deletions of exons in their [121]. It should note that the generic version CYP2D7P with narrow framework 138delT mutation in exon 1, is expressing an active form in the human brain, which can only convert codeine into morphine [122]. This CYP option is exclusively specific for the brain.

However, other studies have failed to identify the functional CYP2D7P copies in the Asian, European, or African-American individuals [123]. Subcellular localization CYP2D7P also unusual because in insect cells, it found primarily in the mitochondrial fraction, but not in microsomes [124].

I.3.2.5. *Subfamily CYP2E*

CYP2E1 - one gene subfamily CYP2E located on chromosome 10q26.3.

Closely linked RsaI and PstI polymorphisms in the 5' flanking region of the gene were described. Increased transcriptional and Fermi-commutative activity relative to wild-type allele was inherent in a rare mutant allele (C2; +Pst I/-Rsa I; CYP2E1*5B) [125].

It found that among healthy individuals of Caucasian population Dra I allele detected from two to four times more often than RsaI. Moreover, its frequency was higher among patients with alcoholic liver disease [126] and among alcoholics without liver disease [127]. Using Taq I, to demonstrate polymorphism CYP2E1 gene intron 7, showed that it is more often detected in Caucasian population than Dra I (with frequency 0.08-0.10) [128, 129].

I.3.2.6. *Subfamily CYP2J*

Human CYP2J subfamily has only a single gene - CYP2J2, which encodes a 502 amino acid protein of microsomal P-450. Like all other members of the family CYP2, CYP2J2 gene contains nine exons and eight introns, which have distributed in an area covering about 40 kb on chromosome 1. The promoter of the gene CYP2J2 no TATA-part and the main activity is regulated mainly through of Sp1, for which there are, at least four different binding sites within the first 100 bp 5'-upper sequences [130]. This placement of the promoter in the nature of "housekeeping" of the P-450 gene, which is not inducible bytypical P-450 inducers.

Significant individual variations on CYP2J2 expression observed in the genetic polymorphism. There are 10 distinct starryalleles, eight of which are no synonymous SNP. Some of these variants (*2: T143A; *3: R158C; *4: I192N; *6: N404Y), showing a

decrease of catalytic active-AA in cases of a combination of the system of insect cells [130]. The significance of these variants of the amino acid substrates for drug-CYP2J2 not yet studied.

The most common variant of CYP2J2 alleles with functional relevance – it is CYP2J2*7, that revealed a frequency of ~ 2-17% in different populations. Key SNP rs890293 located in the proximal promoter (-76G>T), where one of the broken binding sites SP1, which results in ~ 50% decrease of promoter activity relative to the wild type promoter [131].

I.3.3. Subfamily CYP3

Human CYP3 family consists of only one subfamily - CYP3A, which is located on chromosome 7q22.1 and has a size of 231 kb. It includes four genes CYP3A4, CYP3A5, CYP3A7 and CYP3A43 (Figure 1.8.). Murine Cyp3a cluster contains seven genes fully extended but has no orthologous pairs between the murine and human genes, suggesting that only CYP3A gene is present in a common ancestor that regardless expanded over the last 75 million of years [63].

Currently, more than 200 known polymorphisms and mutations in the genes CYP3A (www.cypalleles.ki.se, www.pharmgkb.org).

CYP3A4 gene has a length of about 27kb, and consists of 13 exons and 12 introns [133]. More than 19 variants of CYP3A4, and a series of subvariants (1B*through*20) have been identified to date. CYP3A4 *1A is defined as the wild type. 349 SNPshas found in the sequences of CYP3A4 and 13 exons in the NCBI dbSNP. Among these SNP, a 26 no synonymous detected in exons 1 and 3-13.

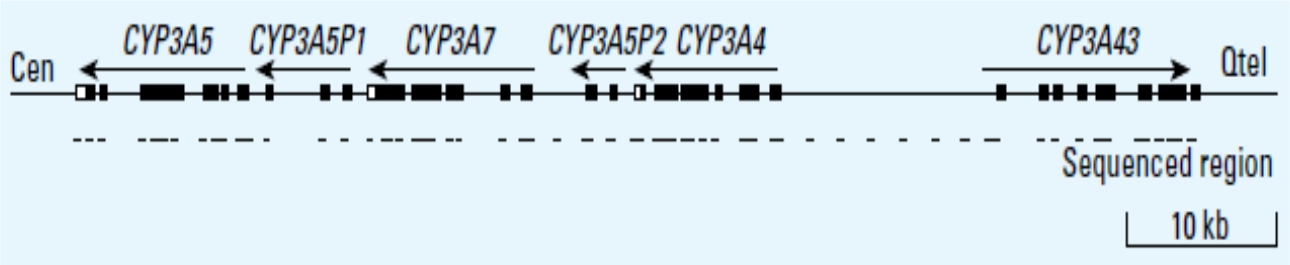


Figure 1.8. The genomic structure of genes and pseudogenes at the CYP3A locus

Note: Cen, the centromere; Qtel, the telomere. Exons of genes and pseudogenes shown as boxes; arrows indicate transcriptional orientation, and broken lines indicate sequenced regions. Scheme represent respectively by [132].

CYP3A4*1B (i.e., CYP3A4-V), contains a mutation -392A>G in the nifedipine-specific response element of gene5'-regulatory region [134]. CYP3A4*2 containing 664T>C SNP (leading to a change S222P) proves to encoding with altered substrate CYP-dependent kinetics, compared with the wild type enzyme. CYP3A4 *4 and *5 allele contain 352A>G (I118V) and 653C>G (P218R), respectively, in exons 4 and 5 [135]. CYP3A4*6 is a narrow loop mutation (831insA), arising from the introduction of A17776 in exon 9, terminating early a stop codon. Functionally *4, *5 and *6 alleles also

associated with decreased CYP3A4 activity. Further, in alleles of CYP3A4*7 with 167G>A SNP [136] and CYP3A4*20 with introduction of the A between 1461 and 1462 nucleotides lead to the complete enzyme defect [137].

To date, at least found 10 variants (up from *1B*11) and series of CYP3A5 subvariants. CYP3A5*1 is considered the wild type with normal expression of the enzyme activity [138]. The CYP3A5 sequences revealed 270 SNP in exon 13 and NCBI dbSNP, among which 15 no synonymous regions in exons 2, 4, 7, 9, 10, 11, 12 and 13.

Polymorphic expression of CYP3A5 exhibits a sufficient degree of inter- and intra-ethnic differences [138]. Approximately, 10-25% of Europeans, 30-50% of the population in Asia and South America, 55-95% of African Americans the personnel detector protein levels of CYP3A5 [138, 139] can be detected. Four CYP3A5 allele is the most common determinants of interethnic variability in their protein expression. The first allele - CYP3A5*1, is considered the main, which defines the expression of the phenotype. Each of the CYP3A5*3, CYP3A5*6 and CYP3A5*7 allele is defined as the derivative exhibiting phenotypes of low activity or complete absence [138, 140, 141].

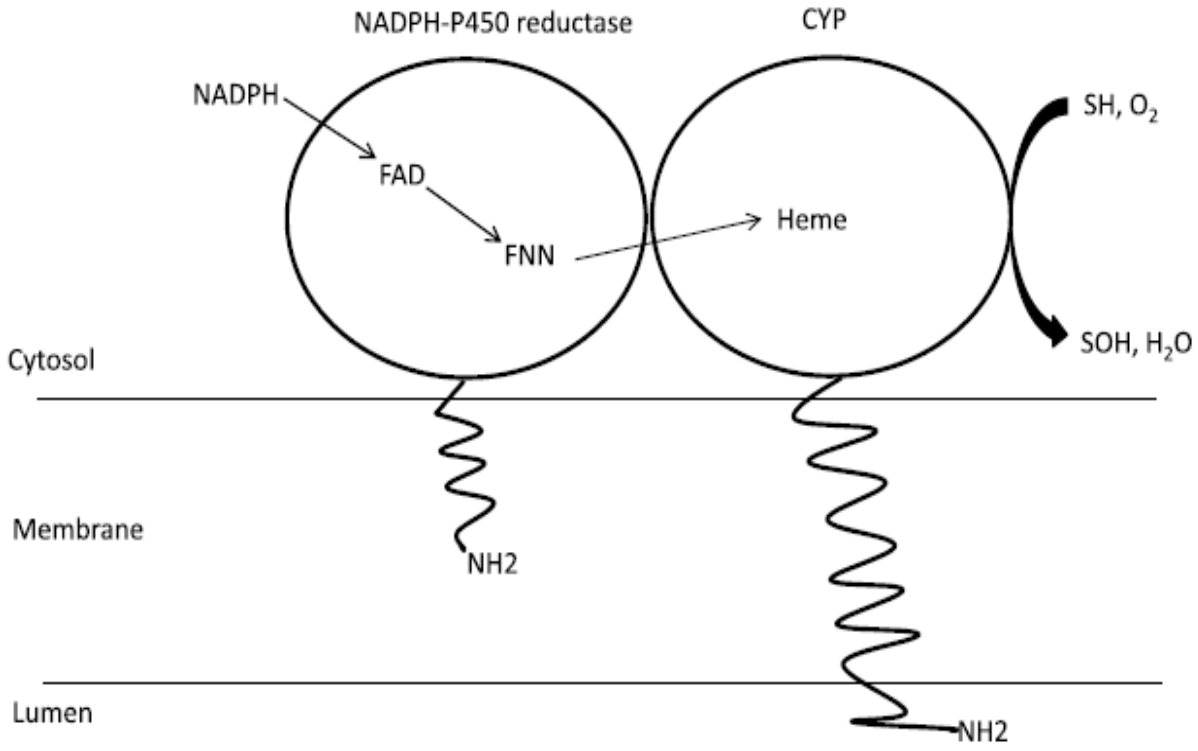


Figure 1.9. The monooxygenase system elements interaction
Presented by Cederbaum AI [153].

I.3.4. NADP·H cytochrome P-450 reductase

In contrast, CYP plurality mammals have only a single gene NADP·H cytochrome P-450 reductase (POR). In humans, the gene is located on chromosome 7q11.2 and comprises about 72 kb, encoding 680 amino acid protein that uses flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) as a prosthetic group. Complete

removal of POR gene in mice gives the fetal death, most likely due to lack of adrenocortical steroidogenesis [142]. On the other hand, liver-specific knock out POR leads to phenotypically and reproductively normal mice that accumulate lipids in the liver and have dramatically weakened the ability of hepatic drug metabolism [143].

The number of POR in human liver slender metrically ~ 5-10-fold lower CYP microsomal pool, indicating that it is a limiting factor for the monooxygenase [144]. Although individual variability POR expression in human liver is, lower in comparison with the majority of the microsomal drug-metabolizing enzymes, it shown that there is a significant correlation with the activity of several CYP monooxygenase, supporting the possible level-limiting role in catalysis [145]. After the discovery of non-translating the first exon, it revealed the location of the promoter of the human POR and communication factors Smad3/Smad4 transcription, as well as receptors of thyroid hormone and TRα TRβ, confirmed via chromatin immunoprecipitation [146].

Variability POR expression partly caused by inducible POR gene under the influence of a PXR, and the CAR, as well as the hormonal effects on transcription [142], as other non-genetic factors, including gender, age, smoking and alcohol intake did not provide its significant influence [144, 147] .

In recent years, rare missense (erroneous) POR mutations in humans have discovered that cause disorders of steroidogenesis, ambiguous genitalia and Antley-Bixler syndrome [148]. On CYP allele's website currently lists, 41 presented clear star-alleles, most of which are rare variants identified in patients with symptomatic POR lack [149]. Causal mutations in these alleles are either the result of amino acid changes that greatly damage the function of the POR, or at the wrong translation [150].

I.4. HUMAN CYP PROTEIN STRUCTURES

The protein part of most cytochrome P-450 consists of approximately 400-500 amino acids with a molecular weight of about 50,000 Da. About half of the amino acids are non-polar. Previously believed that the cytochrome P-450 immersed in the membrane now recognized that the majority of P-450 molecule protrudes from the membrane and attached to the microsomal membrane amino-endings. Similarly, NADP·H-cytochrome P-450 reductase, mostly also protrudes from the membrane (Figure1.9).

The axial ligand for the heme iron consists of a cysteine residue, which is well preserved during evolution near the carboxy-end of the protein and used to attach to a protein heme [151, 152].

Sixth iron coordination position can filled with water or to be blank in the oxidized state, or with carbon monoxide and oxygen in the reduced state. Addition of the substrate may move, followed by water influence on the redox potential of the heme. Potential reduction of oxidative determined by titration using a redox dye was very low. Agents that react with sulfhydryl groups or disrupt hydrophobic interactions, P-450 converted to an inactive form, called P-420, which based on the detection of the maximum absorption of the heme complex with carbon monoxide at 450 nm. Conversion of P-450 to P-420 usually results in a loss of substrate-induced spectral changes.

The molecule of cytochrome P-450 mainly formed of α-helices marked A to L, starting with the N-terminal region (Figures 1.10, 1.11, 1.12). Helices F and G form the roof of the enclosed active site and between I and L helices lies prosthetic group of heme

B, also called iron-containing protoporphyrine IX. It is present in all of P-450 and provides proximal ligand to heme through a sulfur atom in cysteine. Protoporphyrine IX and a small group of neighboring residues generates region of initial part heme that is highly conserved.

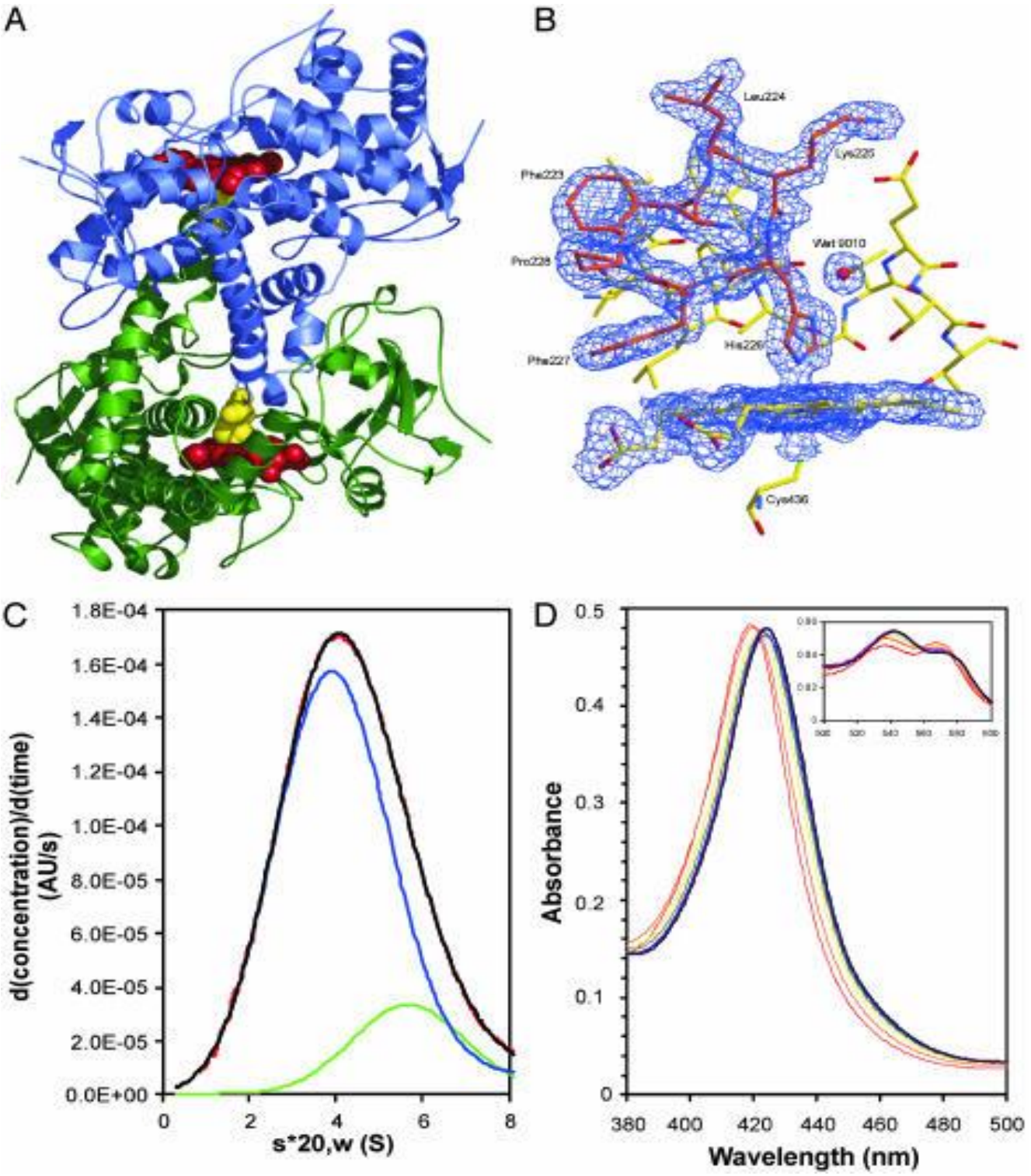


Figure 1.10. The three-dimensional molecular structure diagram of the cytochrome P-450 and its spectral characteristics. Scheme respectively represented by [169].

Helix I has really saved the bend above the active site, which can facilitate the transfer of a proton. Otyepka et al. [154] described the mammalian CYP isoforms (families 2 and 3) based on available crystal structures.

Typically, the available crystal structures of the two sets of mutations made to facilitate their purification and crystallization. Helices F', G', F/G of the loop and N-terminal region presumably makes contact with the membrane area; consequently, a large hydrophobic transmembrane anchor at the N-terminus is replaced by a shorter section of more hydrophilic chain.

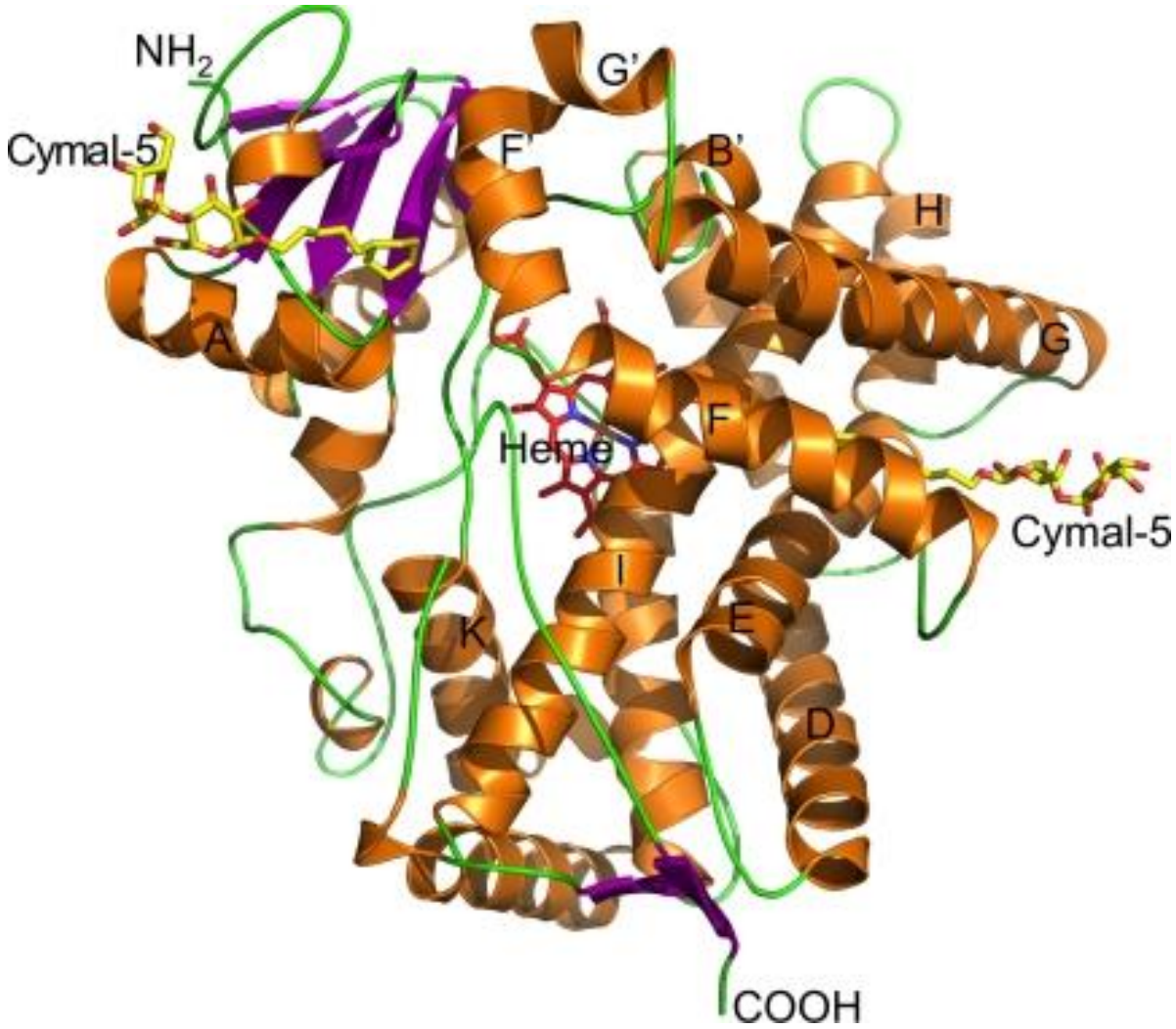


Figure 1.11. Presentation of ligand-free cytochrome P-450 2B4dH in the closed conformation

Note: β-sheet, α-helices and the loop shown in purple, orange and green color, respectively. Heme shown in red, and CYMAL-5 - in yellow color. Scheme respectively represented by [157].

Second, in by four of the five polyhistidine sequences included in the C-terminal region. It generally accepted that such changes do not modify the reactive properties of the enzyme (Figure 1.11) [11, 155].

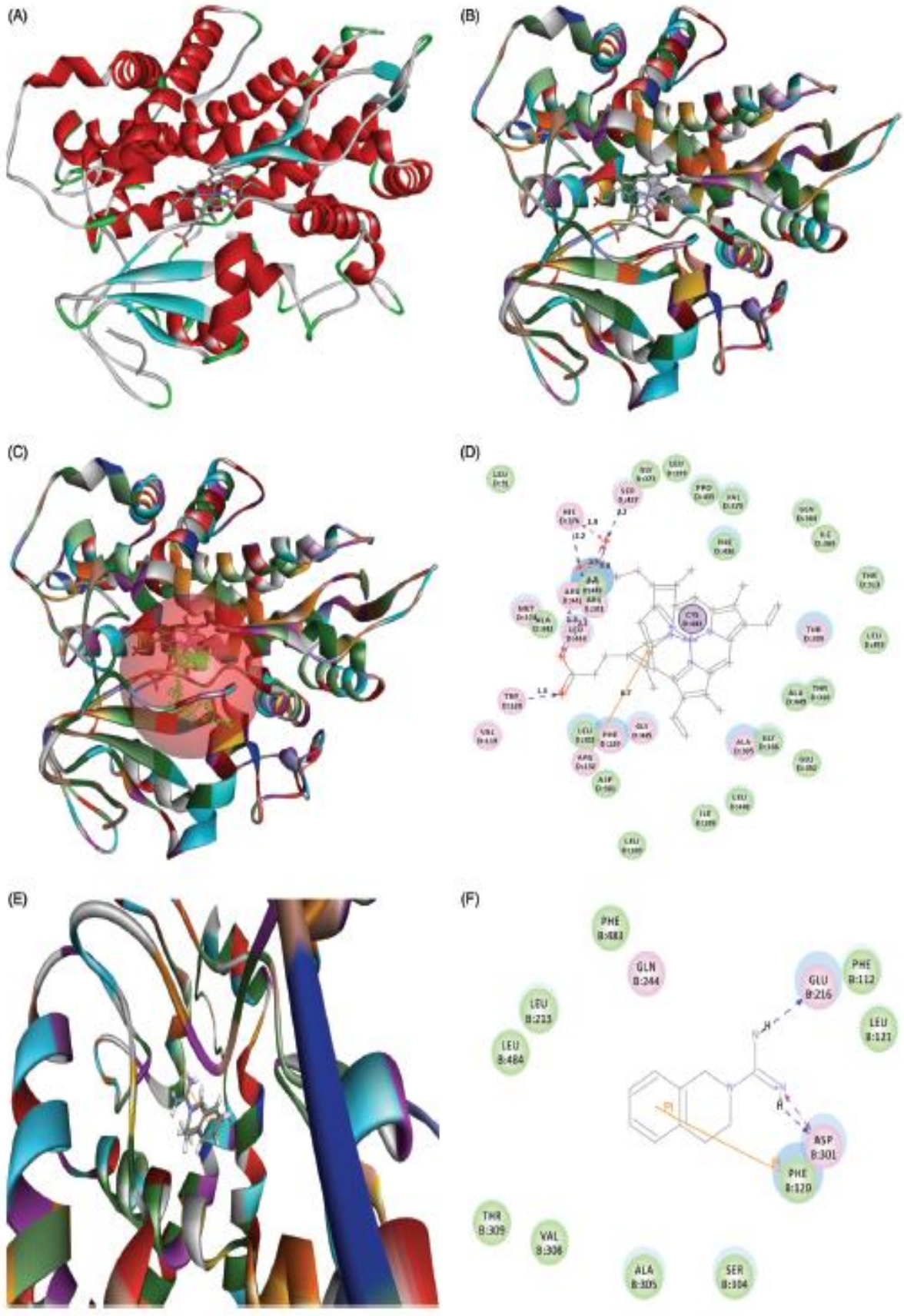


Figure 1.12. The three-dimensional structure of the scheme and the functioning of the molecules of cytochrome P-450 CYP2D6

Note: The explanations in the text. Scheme represented respectively by [11]

The amount of the active site of CYP isoforms varies as a function of the isoforms. Cruciani et al. [156] studied the structural characteristics of the binding sites of different isoforms, using the GRID. They noted the significant differences of active sites, calculated by using the hydrogen probe. For example, if for CYP1A2 the site volume was 630 Å3, the binding site of CYP3A4 model had length of up to 1500 Å3. They also ranked CYP isoforms on the predominance of hydrophilic regions in the binding pockets in the form of CYP2D6> CYP3A4> CYP1A2> CYP2C19> CYP2C9 and highlighted the strong dependence of the hydrophilic patterns of protein flexibility [156]. Otyepka et al. [154] divided CYP into three categories of mammals, ranging from the very large: CYP2C5, CYP2C8, CYP2C9, CYP3A4> CYP2B4, CYP2D6> CYP2A6.

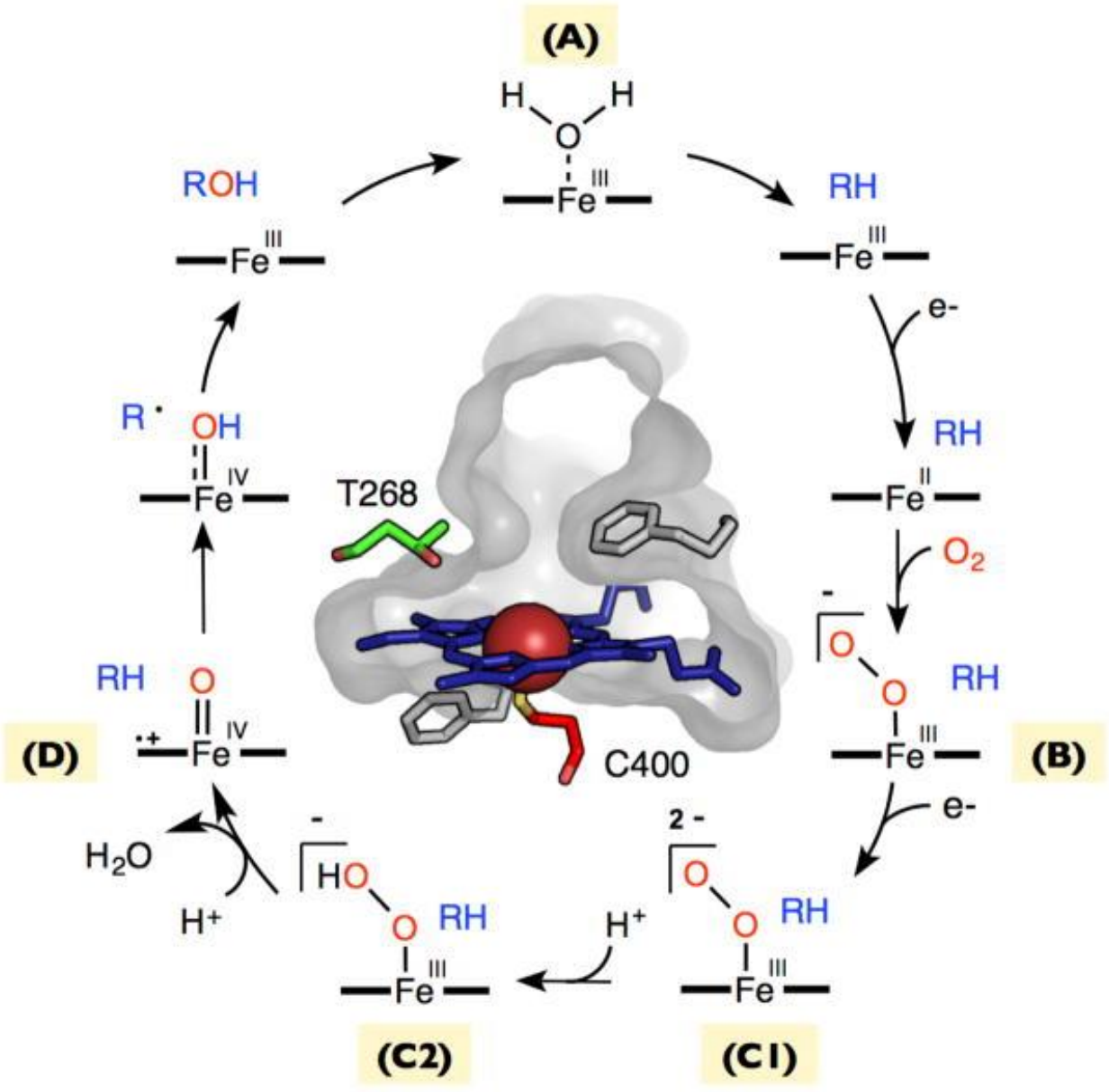


Figure 1.13. Catalytic cycle P-450 respectively by [160]

Note: Active centralized structure P-450$_{BM3}$ has shown in the center with a stored threonine (T268) and the axial cysteine (C400) as a dedicated figure. Key steps include: (A) free state of iron, (B) an intermediate state of the iron superoxide, (C1, C2) of iron-proxy- or hydroperoxo-intermediate states and (D) the state I.

Like other human CYP enzymes with known structures, CYP2D6 2F9Q structure shows its typical characteristics, mainly against CYP α-helical folding (Figure 1.12).

The length and orientation of the individual secondary structural elements consisting of α-helices A through L and four β-sheets, mimic those that occur in CYP2C9 and other CYP2 members, and E, J, K, L helices and I comprise a protein core. In the crystal structure, the active central cavity bounded heme and aligned residues Ile106, Leu110, Phe112, Phe120, Leu121, Gln117, Gly118, Val119, Ala122, Leu213, Glu216, Ser217 Leu220, Gln244, Phe247 and Leu248, Ile297, Ala300, Asp301, Ser304, Ala305, Val308, Thr309, Val370, Met374, Gly373, Phe483 and Leu484 (Figure 1.13). 2D6 structure has a well-defined active central cavity above the heme group with the volume that can easily accommodate a plurality of substrates with clear structures [158].

The structure 2F9Q, heme group is located at the connection site and coordinated by hydrogen bonds interacting with the side chains of Arg101, Trp128, Arg132, His376, Ser437 and Arg441. This is similar to CYP2C9 structures [151] and CYP2R1 [159].

Various ways have identified from the interior active site, leading to the appearance of the soluble exterior site [161]. For a comprehensive analysis, using as a tool CAVER [162] held naming schemes of these pathways [163]. CYP function within the catalytic cycle, with an atom of iron, undergoes the changes in its spin state, the amount of oxidation and ligand coordination, involved around ordered cycle (Figure 1.13) [164].

To date, adopted the following mechanism. In its first state, the state of rest, Fe (III) - is in a low-spin doublet state and ithexa-coordinated with a water molecule occupies a distal axial position. The substrate receipt biases axial water, which leads to the formation of a penta-coordinated Fe (III) in a sextet state. Changes in the redox potential, the associated displacement allows to accept an electron from NADP·H-P-450-reductase, thus forming the third state, Fe (II), which has a high-spin state. Then bind molecular oxygen, creating a fourth state and single tic oxy-ferrous complex. This singlet complex, easily accepts an electron from the second reductase, as a result leads to the formation of the fifth condition and iron-per Oxo anion. Protein environment facilitates the oscillation of the proton to form a sixth state, which also referred to as component 0.

The second proton accepted, accompanied by heterolytic splitting of molecular oxygen and a loss molecule of water to form the seventh state - electrophilic highly valentic Oxo-iron components. This kind of active, similar to the characterized Component I, which then oxidizes the substrate. Then, the product leaves the active site, and water molecule returns to the distal axial position, completing the cycle.

Component I–Ferryl-porphyrine-picationic radical has three unpaired electron. Two unpaired electron has localized on ferryl group and the other rotated between the sulfur atom in covalently binding cysteine and porphyrine. It is the same in all isoforms, as well as its electronic structure is the implementation of its protein environment function, has earned the title of Chemical Chameleon [165, 166]. Recently, with the help of electron paramagnetic resonance imaging (EPR) could provide experimental support for so long desired intermediate Component I [167].

Expression similarly truncated and N-terminally modified CYP2B1, CYP2B4 and CYP2B11 without further internal modifications, is creating large amounts of catalytically active CYP2B with increased solubility, which suitable for structural and functional analysis [168]. These data allow holding the first crystallization of rabbit CYP2B4 [169].

Although the analysis of ligand - bound and ligand - free structures of CYP2C5 [170] pointed out that the P-450-mobile enzymes widely open structure of CYP2B4, showed strong regrouping, which was later referred to as "plastic regions" [171]. This reorganization of the secondary structural elements creates fissure foraccess of substrate of a large size by moving the cassette in the region F-G, which includes helices F, F', G' and G on one side of the enzyme and B'/C loop and helix C for another [169]. In contrast, regions on the proximal side of the enzyme (helices E, J, K and L), remain relatively unchanged in relation to other structures of P-450 (Figure 1.14). In this structure, the open conformation is stabilized by the formation of a homodimer, where the remains of helices F'and G' is partially filled with the active site of the symmetrically related molecule, andimidazol-fixing His226 coordinates sixth ligand position of heme iron of the opposite strand. In consequence, all CYP2B4 structures determined by H226Y mutants, in order to prevent this dimerization.

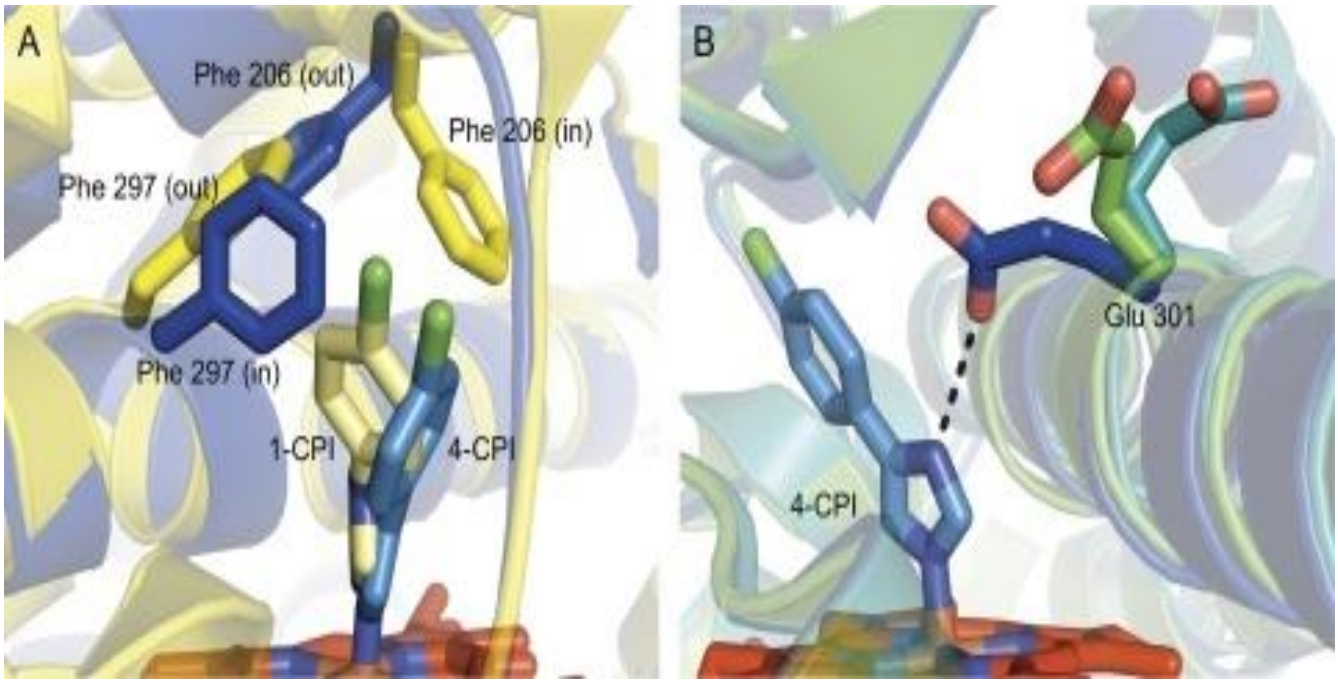


Figure 1.14. The three-dimensional structure of the scheme and the functioning of the molecules of cytochrome P-450 CYP2B4

Note: Explanations in the text. Scheme respectively represented by [213].

Analysis of the open structure of CYP2B4 showed that the active site residues in the helix I (Ser294, Phe297, Ala298 and Thr302) and the remains of those who are about β1-4 (Leu362, Ile363, and Val367), were in the immediate vicinity of the heme. However, many other active site residues identified by site-oriented mutagenesis and comparison with the structure of CYP2C5 (Ile101, Ile114, Phe115, Phe206, Ile209, Val477 and Gly478), located away from the heme and from each other. This protein conformation of CYP2B4 will be impossible to substrate binding in the active site, making contact with all of these residues, meaning there should be a need for some structural rearrangement of these residues on substrate binding to move in proximity to the ligand. It expected that the crystallographic study CYP2B4-ligand complex show conformational changes associated with the closing of the active site.

Cytochrome b_5 is a heme protein, which in contrast to cytochrome P-450 localized on the surface of the endoplasmic net. Molecule microsomal cytochrome b_5 membrane consists of two domains - a hydrophilic and hydrophobic. The hydrophilic portion is formed enzyme from 1-88 amino acid residues and contains a heme, a part of the active center. The hydrophobic domain of cytochrome b_5 formed by amino acid residues of the protein C-end of the molecule (amino acid residues 89-133).

The main function of this portion of the molecule is reacting with a membrane, such as the endoplasmic reticulum. With the help of computer, simulation shows that the C-terminal portion of the cytochrome b_5 molecule forms a loop and permeates through the lipid membrane [172]. Most hydrophobicity observed in the middle of the loop, which submerged in the membrane. It has suggested that the C-terminal part of the enzyme molecule plays an important role in embedding in the membrane and the enzyme orientation in the lipid bilayer, which ensures its functional activity [173].

I.5. TISSUE DISTRIBUTION OF HUMAN CYP ISOFORMS EXPRESSION

Chemical oxidation enzyme systems, containing CYP, found in all animal and human cells except erythrocytes. However, quantitatively the most content and thus active monooxygenase enzymes concentrated in the liver tissue, so the basic laws of functioning of microsomal monooxygenase originally established mainly in the study of this particular tissue. The liver is the largest organ in most mammals, with a weight of 2% by weight of the human body and 4% of the weight of animal body. Hepatic tissue metabolizes about two-thirds of the total number of exogenous chemicals entering in the body. Formed after the biotransformation of xenobiotics sulfur, glutathione and glucuronide conjugates of metabolites may release from the liver through the bloodstream, not only in the urinary tract, but also in the bile into the intestine (Figure 1.15). It found that 1g of human liver accounts for the total amount of 10-nmol cytochrome P-450 and 1 g of rat liver - even 30 nmol of enzyme.

The relative content of hepatic CYP defined as follows: CYP3A4 - 30%-12% CYP1A2, CYP2C9/10/19-20%, CYP2D6 and CYP2E1- 4%-6% [175], but the ratio proved to be somewhat different according to other authors: CYP1A1 (51%), CYP1A2 (4.4-16.3%), CYP2A6 (3.5-14%), CYP2B6 (1.7-5.3%), CYP2C8 (7.5%), CYP 2C9 (4.5-29%), CYP2C19 (0.9 - 3.8%), CYP2D6 (1.3-4.3%), CYP2E1 (5.5-16.5%), CYP2J2 (51%), CYP3A4 (14.5-37%) and CYP3A5 (1%) [176]. Apparently, the reason for these differences lies in the individual variations caused by both genetic characteristics (the representatives of different populations studied) and the influence of environmental factors.

Besides the liver, the genes encoding CYP, actively expressed and in extrahepatic tissues, but in much smaller amounts, with defined functional differences and selectivity for the isoforms that are apparently necessary for performing its organo-specific role in the homeostasis of the whole organism.

Thus, a microsomal fraction of brain revealed the presence of cytochrome P-450, cytochrome b_5, cytochrome P-450-NADP·H reductase, but the feature is the high content of cytochrome b_5, that in 2-3 times higher than the level of cytochrome P-450. In the

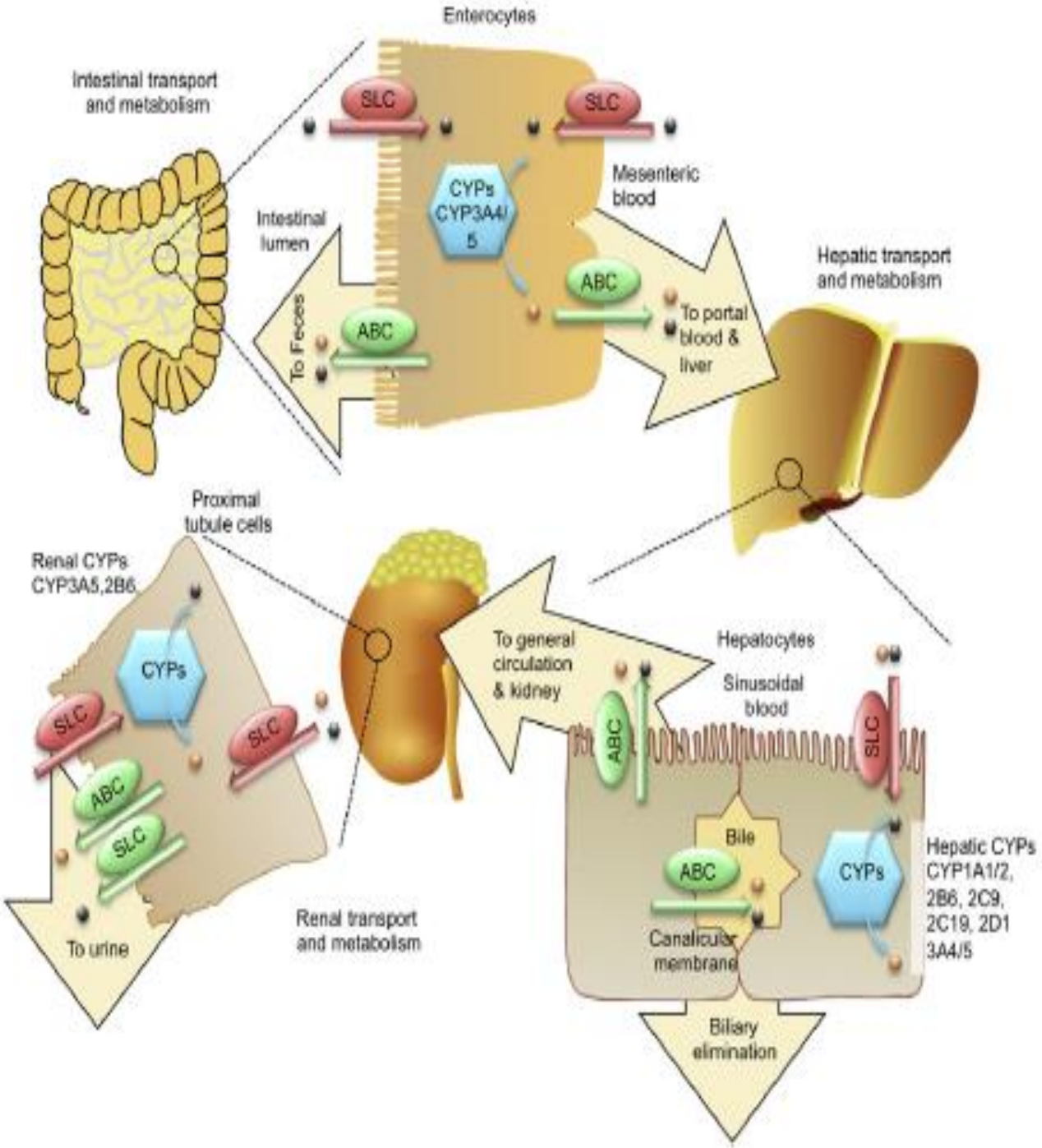


Figure 1.15. The role of cytochromes P-450 (CYPs) and drug transportproteins in absorption, metabolism,and excretion of drugs after their oral administration

Note: The conveyors shown as ovals in red and green. Black hexagons and orange circles represent the parent drug and its metabolites, respectively. Scheme represented respectively by Ladda and Goralski [174].

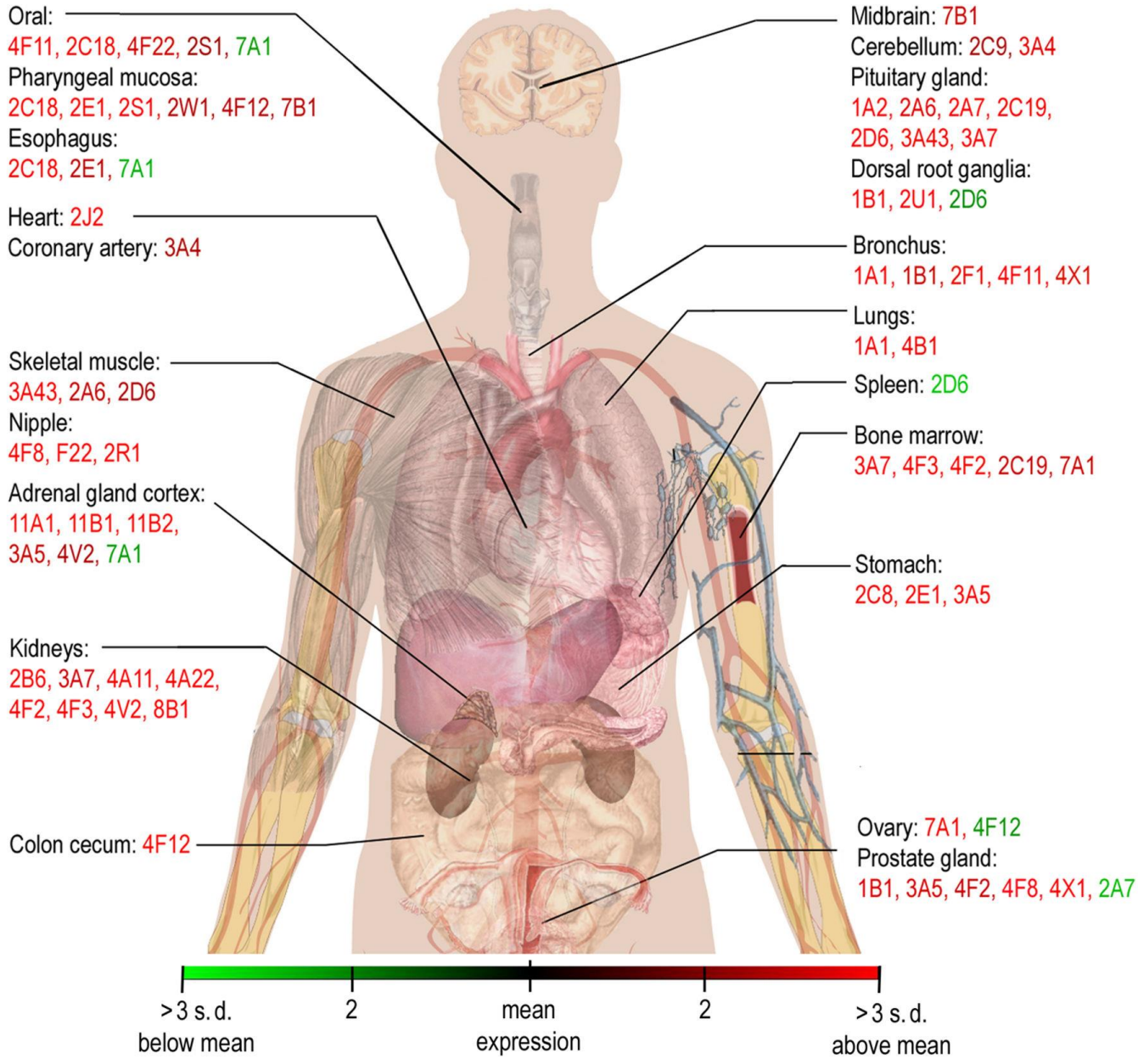


Figure. 1.16. Schematic map of the specific expression of different CYPs in human organs

Note: The expression values presented relative to the mean expression in all organs. At least three-fold higher expression of CYP in one organ shown by red text. At least three-fold lower expression indicated by green text. The scale illustrates the color range for the expression values. CYPswith average expression in one organ were not included. Respectively by Preissner et al [62].

adrenal glands, in contrast to other organs, CYP localized in the mitochondria, but not in the endoplasmic reticulum. Moreover, their main function is to ensure the hydroxylation reactions of the endogenous substrates, particularly steroids, and participate in cholesterol synthesis reactions [175, 176]. With the advent of new genetic techniques has become possible to identify the degree of expression and activity of CYP isoforms in specific tissues. Nishimura and colleagues work demonstrated differences in mRNA CYP

expression in various human tissues. For example, CYP2F1, CYP4B1, CYP4F8, CYP11S, CYP11A, CYP11B1, CYP 11B2, CYP19 and CYP24 not expressed in the liver [177]. Several studies have confirmed these results, details of which shown in Figure 1.16. Nishimura analyzed the mRNA levels of CYP isoforms of 30 to 11 types of tissue. Similarly, a later study conducted CYP isoforms expression 40 to 41 types of tissues where the liver considered separately in order identifying differences between the other tissues. The other 21 tissues observed heterogeneous distribution CYP. For example, 39 CYP isoforms exhibited a higher expression of mRNA, at least one or more tissue types. Significant differences observed in the adrenal cortex, which was detected 6-fold higher expression of CYP 11A1, 11B1 and 11B2, compared with the average value of their expression. It is amazing that other tissue did not show high levels of expression of these three CYP.

Most differentiation of expressions as compared to other tissues, as observed in the kidneys, where it was revealed six-fold increase in CYP4A22, 5-fold increase in CYP 8B1, and 4-fold increase in CYP4V2, CYP4F2, CYP4A11 and CYP2B6. In addition, 5-fold higher expression of CYP2C8 found in the lungs, CYP4F8 in the prostate; bone CYP4F3, CYP2F1 in the bronchial tubes and CYP2C8 in the stomach. CYP2C18 showed a high level of distribution in the area bounded by the oral, throat and esophagus. Two-time lower expression detected for the CYP2A1 in the esophagus, CYP2A7 in the prostate, and alsoCYP2C9 and CYP2D6 in the spleen.

In humans, CYP1A2 constitutively expressed at higher levels only in the liver (in average from ~ 18 to 25 pmol\mg microsomal protein) [110, 178].

In contrast, CYP1A1 and CYP1B1, which initially expressed as an extrahepatic enzyme [179-181], found in liver, respectively, below the 3-pmol\mg, and even outside detectable level.

Human CYP2A6, mainly expressed in the liver, where the average expression levels, respectively spectrometric studies were ~ 50-pmol\mg [110].

CYP2A13 encodes a catalytically active protein expressed predominantly in low levels in the respiratory tract, including the lungs, where the expression level decreases from the nasal mucosa to the peripheral tissues of lungs [182, 183].

CYP2B6 detected on the RNA and protein level in the human brain, where it was higher in the samples of smokers and alcoholics [184]. Low levels of CYP2B6 copies found in some extrahepatic tissues, including kidney [185], heart [186], and placenta [187] as well as in different tissues of the respiratory tract, including the lungs and nasal mucosa [188]. In contrast, CYP2B6 expression in the skin or keratinocytes [189] and intestine [190] was low or absent.

In humanized CYP2C18/CYP2C19 transgenic mouse lines only CYP2C19 expressed in the liver to a catalytically active enzyme, but no CYP2C18. Functional CYP2C enzymes also expressed in extrahepatic tissues, such as in the small intestine and cardiovascular tissues of humans, but at lower levels [187]. Together with CYP3A, CYP2C represent major intestinal CYP, constituting respectively about 80% and 18% of the total quantitative immune-content CYP [190, 192].

Although the content of CYP2D6 is only a small percentage of all of hepatic CYP (1.3-4.3%), nevertheless, it metabolized to 20% of the drug entering the human liver [176]. CYP2D6 has identified in kidney, intestine, breast, lung, placenta and the human brain in the range of low to moderate levels (Figure 1.18). CYP2D6 protein and enzyme activity

detected at low levels in the human intestine and differentially expressed along the whole length of the gastrointestinal tract.

There are large individual variations in the CYP2D6 enzyme activity. Carcillo et al. [193] found that the expression of mRNA CYP2D6 short fragments on mononuclear cells circulating in the peripheral blood, correlated with the in vivo activity of CYP2D6.

According Krovat etal. [194] in human lymphocytes, revealed mRNACYP2D6 short fragment without immunoreactive protein, which, however, does not exhibit the functional activity against dextromethorphan. Several authors [195, 196] also found CYP2D6, CYP1A2 and CYP3A4 mRNA in human lymphocytes, which induced by rifampin. However, it found that HNF-4α, nuclear receptor that regulates the CYP2D6 enzyme in the liver, is present in lymphocytes. In contrast to CYP2D6, human lymphocytes expressed CYP1A1, CYP1B1, CYP2E1, CYP3A4, CYP3A5 and CYP3A7 in respect of both mRNA and the protein level, and that function governed by other factors [196, 197].

In the human brain, mRNACYP2D6 primary expressed in neurons and glial cells, located in the neo cortex, caudate nucleus, putamen, spherical pallidum, hypothalamus, thalamus, substantia nigra, and cerebellum [198]. In contrast, CYP2D6 protein primarily localized in large main neurons such as pyramidal cells in the hippocampus and cortex as well Purkinje cells of the cerebellum, but CYP2D6 protein absent in glia cells. These results demonstrate the expression of CYP2D6 in certain regions of the brain may play a role in the disposition of certain drugs and endogenous components in the brain. In the human brain CYP2D6 detected at low levels, but constitutively [184], allowing the existence of endogenous function CYP2D6 in the metabolism of neurogenic chemical substances [199, 200]. Thus, CYP2D6 plays an important role in the metabolism of manyindole-alcylamine agents, analogues of 5-hydroxytryptamine (5-HT/serotonin), which are predominantly in the serotonin system [201].

CYP2D6 can also bioactivated procancerogens and neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1,2,3,4-tetrahydro-quinoline and indole-alcylamines [202]. In addition, MPTP is a neurotoxin and a strong inducer of experimental Parkinson's disease in primates and rodents [203]. In the study on CYP2D6-humanized mice lines, CYP2D6-5-methoxyindole-ethylamine-O-demethylase activity found that 5-methoxytryptamine - metabolite precursor and melatonin (N-acetyl-5-methoxytrytamine) with high speed metabolized by CYP2D6to 5-HT/serotonin [202]. The human CYP2D6 and rat Cyp2d4 are predominant enzymes of CYP2D in the brain and are activation of 21-hydroxylation in relation to progesterone and metabolite of 17α-hydroxyprogesterone [204]. Endogenous morphine likely synthesized in humans through a similar path, as well as in the poppy flowers, in which two of the steps involved are associated with CYP2D6, namely O-demethylation of thebaine to oripavine and O-demethylation of codeine to morphine.

Extrahepatic expression of CYP2E1 detected at lower levels in brain tissue, nasal mucosa, renal cortical part, testes, ovaries, gastrointestinal tract, and partly in the higher levels in cardiac tissue [186, 192, 205].

CYP2J2 highly expressed in the heart, particularly in cardiac myocytes and endothelial cells [186], and at a lower level expressed in lung, gastrointestinal tract and pancreas, as well as in certain regions of the brain. In the liver, CYP2J2 present in an amount less than 1% of the total P-450, and similar evaluations made with respect to the

expression in the small intestine [190]. In these tissues also observed prenatal expression of CYP2J2mRNA and protein [206].

CYP3A4 - the majority of individuals abundantly expressed in the liver, but with an extremely high variability of the population (more than 100-fold differences). Average microsomal content is estimated at between ~ 60 pmol\mg microsomal protein [103] and ~ 146 pmol\mg [207], equaling an average of ~ 14-24% in the pool microsomal P-450 [110]. Expression of three minor isoforms, CYP3A5, CYP3A7 and CYP3A43 are usually lower compared to CYP3A4, CYP3A5 although contribution carriers CYP3A5*1 allele may be dominant among low expresser of CYP3A4 [208]. According to the mass-spectrometric evaluation, average protein fractions CYP3A4, CYP3A5, CYP3A7 and CYP3A43, relative to the total microsomal protein content of CYP3A, are, respectively, 85.4% (range, 6.2-270 pmol\mg), 5.4% (2.5-17.1pmol\mg) and 3.4% (less than 9.4pmol\mg) and 5.8% (less than 6.4 pmol\ mg) [110].

However, if we exclude one sample with high expression CYP3A5 (the genotype was not determined), the expression of CYP3A5 would be fluctuating within 2.5-4.3 pmol\mg. CYP3A4 was the most-expressed P-450 in intestinal enterocytes, with a conductive uncorrelated - levels to those in the liver, which contributes significantly to the first pass metabolism of orally administered drugs [204]. CYP3A7 more abundantly expressed in fetal liver than in adult liver, but the mechanism of this has not studied in detail [209]. In other extrahepatic tissues, including the respiratory tract, brain, lungs, and kidneys, expression of CYP3A5 was a predominant or similar CYP3A4 [208, 210].

Even polymorphic CYP isoforms show a heterogeneous distribution in tissues. In particular, CYP1A2, CYP2C19 and CYP2D6 are highly expressed in the pituitary. In addition, the high level of CYP2C9 expression detected in the cerebellum, while the highest expression of the CYP2D6 and CYP2B6 detected in skeletal muscle, and kidney. Effect of mutations in the CYP-specific bodies remains uncertain and requires further research.

Differential CYP distribution can have an impact on specific drug adversive effects. For example, treatment with cyclophosphamide (CPA) can lead to hypernatremia. CPA prodrug is converted via CYP2B6 the active form [211]. Because of hypernatremia-increased expression of aquaporin 1 and 7, which are induced CPA [212] and CYP2B6 is highly expressed in the kidney, it is likely that a higher level of active CPA manifest in the kidneys and lead to undesirable side effects.

Variable expression of functionally separate CYP isoforms in various types of tissues indicates that certain isoforms play a specific role in a tissue-dependent manner. This may be useful for the development of new prodrugs activated by specific CYP predominantly highly expressed in target tissues, since, after all, lead to enhanced bioavailability of these tissues and reduce side effects. On the other hand, the variable CYP expression in other tissues, in contrast, may affect the efficiency of drugs in certain tissues. Such an event typically occurs when drugs undergo inactivation through CYP more highly expressed in their target tissues. Here, of course, require further clinical studies.

REFERENCES

1. Omura T., Sato R. The carbon monoxide-binding pigment of liver microsomes. I: Evidence for its hemoprotein nature. Journal of Biological Chemistry, 1964;239:2370–2378.

2. Guengerich FP, Martin MV, Sohl CD, Cheng Q. Measurement of cytochrome P450 and NADPH-cytochrome P-450 reductase. Nature Protocols, 2009; 4:1245–1251.

3. Schenkman JB, Jansson I. Spectral analyses of cytochromes P-450. Methods in Molecular Biology, 2006; 320:11–18.

4. Isin EM, Guengerich FP Substrate binding to cytochromes P-450. Analytical and Bioanalytical Chemistry, 2008;392(6):1019–1030.

5. Cederbaum AI Molecular mechanisms of the microsomal mixed function oxidases and biological and pathological implications. RedoxBiology, 2015;4:60–73.

6. Guliaeva LF, Vavilin VA, Liahovichm VV. Xenobiotics biotransformation enzymes in chemical carcinogenesis. Novosibirsk, 2000. – 84p.

7. Markov GV, Tavares R., Dauphin-Villemant C. et al. Independent elaboration of steroid hormone signaling pathways in metazoans. Proc. Natl. Acad. Sci. U.S.A, 2009; 106:11913–11918.

8. Nelson DR Cytochrome P-450 and the individuality of species. Arch. Biochem. Biophys.1999;369:1-10.

9. Qi X., Bakht S., Qin B. et al. A different function for a member of an ancient and highly conserved cytochrome P-450 family: from essential sterols to plant defense. Proc. Natl. Acad. Sci. U.S.A., 2006;103:18848–18853.

10. Feyereisen R. Arthropod CYPomes illustrate the tempo and mode in P-450 evolution. Biochim. Biophys. Acta, 2011;1814:19–28.

11. Zhi-Xu He, Xiao-Wu Chen, Zhi-Wei Zhou, Shu-Feng Zhou Impact of physiological, pathological and environmental factors on the expression and activity of human cytochrome P-450 2D6 and implications in precision medicine. Drug Metab Rev. 2015; 47(4):470-519.

12. Chen X., Wang H., Zhou G.et al. Molecular Population Genetics of Human CYP3A Locus: Signatures of Positive Selection and Implications for Evolutionary Environmental Medicine. Environmental Health Perspectives, 2009;117(10):1541-1548.

13. Neve EP, Ingelman-Sundberg M. Intracellular transport and localization of microsomal cytochrome P450. Anal Bioanal Chem. 2008; 392:1075–1084.

14. Hannemann F., Bichet A., Ewen KM, Bernhardt R. Cytochrome P-450 systems-biological variations of electron transport chains. Biochim. Biophys. Acta, 2007; 1770:330-344.

15. GoodwinT., Mercer E. Introduction to plant biochemistry. In 2 vols. M.: Mir, 1986. T.1. 392 p.

16. Koolman J. Ecdysteroides. Zool. Science, 1990;7:580-584.

17. Ahn T., Yun CH Molecular mechanisms regulating the mitochondrial targeting of microsomal cytochrome P-450 enzymes. CurrDrugMetab. 2010;11:830-838.

18. Anandatheerthavarada HK, Sepuri NB, Avadhani NG Mitochondrial targeting of cytochrome P-450 proteins containing NH2-terminal chimeric signals involves an unusual TOM20/TOM22 bypass mechanism. J Biol Chem. 2009; 284:17352-17363.

19. Avadhani NG, Sangar MC, Bansal S., Bajpai P. Bimodal targeting of cytochrome P450s to endoplasmic reticulum and mitochondria: The concept of chimeric signals. FEBS J. 2014; 278:4218-4229.

20. Neve EP, Ingelman-Sundberg M. Cytochrome P-450 proteins: Retention and distribution from the endoplasmic reticulum. CurrOpin Drug Discov Dev. 2010;13:78–85.

21. Nebert DW, Wikvall K., Miller WL Human cytochromes P-450 in health and disease. Philos Trans R SocLond B Biol Sci. 2013;19,368(1612): 20120431.

22. Xia C., Panda SP, Marohnic CC et al. Structural basis for human NADPH-cytochrome P-450 oxidoreductase deficiency. Proc. Natl Acad. Sci. USA, 2011;108(13): 486-413.

23. Xia C., Masters BS, Kim JJ et al. Conformational changes of NADPH-cytochrome P-450 oxidoreductase are essential for catalysis and cofactor binding. J. Biol. Chem. 2011; 286(16): 246-216.

24. Nelson DR Progress in tracing the evolutionary paths of cytochrome P-450. Biochim. Biophys. Acta, 2011;1814:14-18.

25. da Fonseca RR, Antunes A., Melo A., Ramos MJ. Structural divergence and adaptive evolution in mammalian cytochromes P-450 2C. Gene, 2007; 387: 58–66.

26. Gotoh O. Direct mapping and alignment of protein sequences onto genomic sequence. Bioinformatics, 2008;24: 2438–2444.

27. Gotoh O. Birth and death of P-450 genes in metazoan lineage. In the 16th International Conference on Cytochrome P-450. Nago, Okinawa, Medimond, Bologna, 2009.

28. Alder A., Bigler P, Werck-Reichhart D, Al-Babili S. In vitro characterization of Synechocystis CYP120A1 revealed the first nonanimal retinoic acid hydroxylase. FEBS J. 2009;276:5416-5431.

29. Yoshida Y, Aoyama Y., Noshiro M., Gotoh O. Sterol 14-demethylase P-450 (CYP51) provides a breakthrough for the discussion on the evolution of cytochrome P-450 gene superfamily. Biochem. Biophys. Res. Commun. 2000;273:799-804.

30. Yasukochi Y., Satta Y. Evolution of the CYP2D gene cluster in humans and four non-human primates. Genes Genet Syst. 2011;86:109-116.

31. Nelson DR, Zeldin DC, Hoffman SM et al. Comparison of cytochrome P-450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. Pharmacogenetics, 2004;14:1-18.

32. Gerhard DS. Wagner L., Feingold EA et al. The status, quality, and expansion of the NIH full-length cDNA project: The Mammalian Gene Collection (MGC). Genome Res. 2004;14:2121-2127.

33. Maeda N., Kasukawa T., Oyama R. et al. Transcript annotation in FANTOM3: Mouse gene catalog based on physical cDNAs. PLoS Genet. 2006; 2:e62.

34. Cooke BR, Bligh SW, Cybulski ZR et al. Debrisoquine metabolism and CYP2D expression in marmoset liver microsomes. Drug MetabDispos. 2012; 40:70-75.

35. Uno Y., Uehara S., Kohara S. et al. Cynomolgus monkey CYP2D44 newly identified in liver, metabolizes bufuralol, and dextromethorphan. DrugMetabDispos. 2010; 38:1486-1492.

36. Yasukochi Y., Satta Y. Molecular evolution of the CYP2D subfamily in primates: Purifying selection on substrate recognition sites without the frequent or long-tract gene conversion. Genome BiolEvol. 2015; 7:1053-1067.

37. Nebert DW, Dalton TP The role of cytochrome P-450 enzymes in endogenous signalling pathways and environmental carcinogenesis. Nat. Rev. Cancer, 2006;6:947-960.

38. Chiang EF, Yan YL, Guiguen Y. et al. Two Cyp19 (P-450 aromatase) genes on duplicated zebrafish chromosomes are expressed in ovary or brain. Mol. Biol. Evol. 2001; 18:542-550.

39. Corbin CJ, Berger T., Ford JJ et al. Porcine hypothalamic aromatase cytochrome P-450: isoform characterization, sexdependent activity, regional expression, and regulation by enzyme inhibition in neonatal boars. Biol. Reprod., 2009;81:388-395.

40. Martinez D., Larrondo LF, Putnam N. et al. Genome sequence of the lignocellulose degrading fungus Phanerochaetechrysosporiumstrain RP78. Nat. Biotechnol. 2004;22:695-700.

41. Gotoh O. Substrate recognition sites in cytochrome P-450 family 2 (CYP2) proteins inferred from comparative analyses of amino acid and coding nucleotide sequences. J. Biol. Chem. 1992;267:83-90.

42. Knudsen B., Miyamoto MMA likelihood ratio test for evolutionary rate shifts and functional divergence among proteins. Proc. Natl.Acad. Sci. U.S.A., 2001;98:14512-14517.

43. Woolley S., Johnson J., Smith MJ et al. TreeSAAP: selection on amino acid properties using phylogenetic trees. Bioinformatics, 2003;19: 671-672.

44. Yang Z. PAML 4: phylogenetic analysis by maximum likelihood. Mol. Biol. Evol. 2007;24:1586-1591.

45. Thomas JH Rapid birth-death evolution specific to xenobiotic cytochrome P-450 genes in vertebrates. PLoS Genet. 2007;3: e67.

46. DaFonseca RR, Antunes A., Melo A., Ramos MJ Structural divergence and adaptive evolution in mammalian cytochromes P-450 2C. Gene, 2007; 387:58-66.

47. Zawaira A., Matimba A., Masimirembwa C. Prediction of sites under adaptive evolution in cytochrome P450 sequences and their relationship to substrate recognition sites. Pharmacogenet. Genomics, 2008;18:467-476.

48. Gotoh O. Evolution and Differentiation of P-450 Genes, in Cytochrome P-450. (Omura T, Ishimura Y, Fujii-Kuriyama Y ed.) Kodansha, Tokyo, 1993;P.255-272.

49. Whalen KE, Starczak VR, Nelson DR et al. Cytochrome P-450 diversity and induction by gorgonian allelochemicals in the marine gastropod Cyphomagibbosum. BMC Ecol. 2010;10:24.

50. Ingelman-Sundberg M., Sim SC, Gomez A., Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmaco-epigenetic and clinical aspects. Pharmacol.Ther. 2007;116:496-526.

51. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P-450 enzymes and its clinical impact. Drug Metab. Rev. 2009;41:289-295.

52. Preissner S., Kroll K., Dunkel M. et al. SuperCYP: a comprehensive database on Cytochrome P-450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res. 2010;38 (Database issue), D237-D243.

53. Morita M. Verification of accelerated sequence diversification of substrate recognition sites of P-450 genes. Master Thesis. Department of Informatcis, Kyoto University, Kyoto, 2007; p. 37.

54. Markov GV, Paris M., Bertrand S., Laudet V. The evolution of the ligand/ receptor couple: a long road from comparative endocrinology to comparative genomics. Mol. Cell. Endocrinol. 2008; 293:5–16.

55. Tiwary B., Li WH Parallel evolution between aromatase and androgen receptor in the animal kingdom. Mol. Biol. Evol. 2009;26:123-129.

56. Baker ME Origin and diversification of steroids: co-evolution of enzymes and nuclear receptors. Mol. Cell. Endocrinol. 2011;334:14-20.

57. Reitzel AM, Tarrant AM Correlated evolution of androgen receptor and aromatase revisited. Mol. Biol. Evol.2010;27:2211-2215.

58. Callard GV, Tarrant AM, Novillo A. et al. Evolutionary origins of the estrogen signaling system: insights from amphioxus. J. Steroid Biochem. Mol. Biol. 2011;127: 176-188.

59. Eick GN, Thornton JW Evolution of steroid receptors from an estrogen-sensitive ancestral receptor. Mol. Cell. Endocrinol. 2011;334: 31-38.

60. Wu DD, Irwin DM, Zhang YP. Correlated evolution among six gene families in Drosophila revealed by parallel change of gene numbers. Genome Biol. Evol.2011;3: 396–400.

61. Gotoh O. Evolution of Cytochrome P-450 Genes from the Viewpoint of Genome Informatics Biol. Pharm. Bull. 2012;35(6):812–817.

62. Preissner SC, Hoffmann MF, Preissner R. et al. Polymorphic Cytochrome P-450 Enzymes (CYPs) and Their Role in Personalized Therapy. PLoS ONE, 2013;8(12): e82562. doi:10.1371/journal.pone.0082562

63. Nelson DR, Zeldin DC, Hoffman SMG et al. Comparison of cytochrome P-450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. Pharmaco-genetics, 2004;14:1-18.

64. Jorge-Nebert LF, Jiang Z., Chakraborty R. et al. Analysis of human CYP1A1 and CYP1A2 genes and their shared bidirectional promoter in eight world populations. Hum Mutat. 2010; 31: 27-40.

65. Kisselev P., Schunck W-H, Roots I., Schwarz D. Association of CYP1A1 polymorphisms with differential metabolic activation of 17-beta-estradiol and estrone. Cancer Res. 2005; 65: 2972-2978.

66. Zhou H., Josephy PD, Kim D., Guengerich FP Functional characterization of four allelic variants of human cytochrome P-450 1A2. Arch BiochemBiophys. 2004;422:23-30.

67. Palma BB, Silva E., Sousa M. et al. Functional characterization of eight human cytochrome P450 1A2 gene variants by recombinant protein expression. Pharmaco-genomics J. 2010;10:478-488.

68. Nakajima M., Yokoi T., Mizutani M. et al. Genetic polymorphism in the 5′-flanking region of human CYP1A2 gene: effect on the CYP1A2 inducibility in humans. J Biochem. 1999;125:803-808.

69. Ghotbi R., Christensen M., Roh H-K et al. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype–phenotype relationship in Swedes and Koreans. Eur J ClinPharmacol. 2007; 63:537–546.

70. Djordjevic N., Ghotbi R., Jankovic S., Aklillu E. Induction of CYP1A2 by heavy coffee consumption is associated with the CYP1A2–163C>A polymorphism. Eur J ClinPharmacol. 2010;66:697-703.

71. Han X-M, Ouyang D-S, Chen X-P et al. Inducibility of CYP1A2 by omeprazole in vivo related to the genetic polymorphism of CYP1A2. Br J ClinPharmacol. 2002;54: 540-543.

72. Browning SL, Tarekegn A., Bekele E. et al. CYP1A2 is more variable than previously thought: a genomic biography of the gene behind the human drug-metabolizing enzyme. Pharmacogenet Genomics, 2010;20:647-664.

73. Jiang Z., Dragin N., Jorge-Nebert LF et al. Search for an association between the human CYP1A2 genotype and CYP1A2 metabolic phenotype. Pharmacogenet Genomics, 2006;16:359-367.

74. Klein K., Winter S., Turpeinen M. et al. Pathway-targeted pharmacogenomics of CYP1A2 in human liver. FrontPharmacol. 2010;1.

75. Vasiliou V., Gonzalez FJ Role of CYP1B1 in glaucoma. Annu Rev PharmacolToxicol. 2008;48:333-358.

76. Chavarria-Soley G., Sticht H., Aklillu E. et al. Mutations in CYP1B1 cause primary congenital glaucoma by reduction of either activity or abundance of the enzyme. Hum Mutat. 2008;29:1147-1153.

77. Choudhary D., Jansson I., Sarfarazi M., Schenkman JB Characterization of the biochemical and structural phenotypes of four CYP1B1 mutations observed in individuals with primary congenital glaucoma. Pharmacogenet Genomics, 2008;18:665–676.

78. Li DN, Seidel A., Pritchard MP et al. Polymorphisms in P-450 CYP1B1 affect the conversion of estradiol to the potentially carcinogenic metabolite 4-hydroxyestradiol. Pharmacogenetics, 2000;10:343-353.

79. Aklillu E., Oscarson M., Hidestrand M. et al. Functional analysis of six different polymorphic CYP1B1 enzyme variants found in an Ethiopian population. MolPharmacol. 2002; 61: 586-594.

80. Napoli N., Rini GB, Serber D. et al. The Val432Leu polymorphism of the CYP1B1 gene is associated with differences in estrogen metabolism and bone density. Bone, 2009; 44:442–448.

81. Guengerich FP, Cheng Q. Orphans in the human cytochrome P-450 superfamily: approaches to discovering functions and relevance in pharmacology. Pharmacol Rev. 2011; 63: 684–699.

82. Hoffman SM, Nelson DR, Keeney DS Organization, structure and evolution of the CYP2 gene cluster on human chromosome 19. Pharmacogenetics, 2001;11:687–698.

83. Haberl M., Anwald B., Klein K. et al. Three haplotypes associated with CYP2A6 phenotypes in Caucasians. Pharmacogenet Genomics, 2005;15:609-624.

84. Mwenifumbo JC, Zhou Q., Benowitz NL et al. New CYP2A6 gene deletion and conversion variants in a population of Black African descent. Pharmacogenomics, 2010;11:189-198.

85. Von Richter O., Pitarque M., Rodriguez-Antona C. et al. Polymorphic NF-Y dependent regulation of human nicotine C-oxidase (CYP2A6). Pharmacogenetics, 2004; 14:369-379.

86. Fukami T., Nakajima M., Yamanaka H. et al. A novel duplication type of CYP2A6 gene in African-American population. Drug MetabDispos. 2007;35:515-520.

87. Wang H., Faucette S., Sueyoshi T. et al. A novel distal enhancer module regulated by pregnane X receptor/constitutive androstane receptor is essential for the maximal induction of CYP2B6 gene expression. J Biol Chem. 2003;278:14146-14152.

88. Lang T., Klein K., Fischer J. et al. Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. Pharmacogenetics, 2001;11:399-415.

89. Lamba V., Lamba J., Yasuda K. et al. Hepatic CYP2B6 expression: gender and ethnic differences and relationship to CYP2B6 genotype and CAR (constitutive androstane receptor) expression. J PharmacolExpTher. 2003;307:906-922.

90. Klein K., Lang T., Saussele T. et al. Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional variants, and possible implications for anti-HIV therapy with efavirenz. Pharmacogenet Genomics, 2005;15:861–873.

91. Zukunft J., Lang T., Richter T. et al. A natural CYP2B6 TATA box polymorphism (−82T–>C) leading to enhanced transcription and relocation of the transcriptional start site. MolPharmacol. 2005;67:1772-1782.

92. Desta Z., Saussele T., Ward B. et al. Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. Pharmacogenomics, 2007;8:547-558.

93. Hofmann MH, Blievernicht JK, Klein K. et al. Aberrant splicing caused by single nucleotide polymorphism c.516G>T [Q172H], a marker of CYP2B6*6, is responsible for decreased expression and activity of CYP2B6 in liver. J PharmacolExpTher. 2008;325: 284-292.

94. Zanger UM, Hofmann MH Polymorphic cytochromes P-450 CYP2B6 and CYP2D6: recent advances on single nucleotide polymorphisms affecting splicing. ActaChimSlov. 2008;55:38.

95. Sadee W., Wang D., Papp AC et al. Pharmacogenomics of the RNA world: structural RNA polymorphisms in drug therapy. ClinPharmacolTher. 2011;89:355-365.

96. Johnstone E., Benowitz N., Cargill A. et al. Determinants of the rate of nicotine metabolism and effects on smoking behavior. ClinPharmacolTher. 2006;80:319-330.

97. Rotger M., Tegude H., Colombo S. et al. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. ClinPharmacolTher. 2007;81:557-566.

98. Honda M., Muroi Y., Tamaki Y. et al. Functional characterization of CYP2B6 allelic variants in demethylation of antimalarial artemether. Drug MetabDispos. 2011;39: 1860-1865.

99. Watanabe T., Sakuyama K., Sasaki T. et al. Functional characterization of 26 CYP2B6 allelic variants (CYP2B6.2-CYP2B6.28, except CYP2B6.22). Pharmacogenet Genomics, 2010;20:459-462.

100. Bumpus NN, Hollenberg PF Investigation of the mechanisms underlying the differential effects of the K262R mutation of P-450 2B6 on catalytic activity. MolPharmacol. 2008;74:990-999.

101. Ariyoshi N., Ohara M., Kaneko M. et al. Q172H replacement overcomes effects on the metabolism of cyclophosphamide and efavirenz caused by CYP2B6 variant with Arg262. Drug MetabDispos. 2011;39:2045-2048.

102. Raccor BS, Claessens AJ, Dinh JC et al. Potential contribution of cytochrome P450 2B6 to hepatic 4-hydroxycyclophosphamide formation in vitro and in vivo. Drug MetabDispos. 2012;40:54-63.

103. Bumpus NN, Kent UM, Hollenberg PF Metabolism of efavirenz and 8-hydroxyefavirenz by P450 2B6 leads to inactivation by two distinct mechanisms. J PharmacolExpTher. 2006;318:345-351.

104. Talakad JC, Kumar S., Halpert JR Decreased susceptibility of the cytochrome P450 2B6 variant K262R to inhibition by several clinically important drugs. Drug MetabDispos. 2009;37:644-650.

105. Burger D., Van der Heiden I., La Porte C. et al. Interpatient variability in the pharmacocinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J ClinPharmacol. 2006;61:148-154.

106. Li H., Xiao D., Hu L., He T. Association of CYP1A1 polymorphisms with prostate cancer risk: an updated meta-analysis. MolBiol Rep. 2012;39:10273-10284.

107. Li H., Ferguson SS, Wang H. Synergistically enhanced CYP2B6 inducibility between a polymorphic mutation in CYP2B6 promoter and pregnane X receptor activation. MolPharmacol. 2010;78:704-713.

108. Zanger UM, Klein K., Saussele T. et al. Polymorphic CYP2B6: molecular mechanisms and emerging clinical significance. Pharmacogenomics, 2007;8:743-759.

109. Naraharisetti SB., Lin YS., Rieder MJ et al. Human liver expression of CYP2C8: gender, age, and genotype effects. Drug MetabDispos. 2010;38:889-893.

110. Ohtsuki S., Schaefer O., Kawakami H. et al. Simultaneous absolute protein quantification of transporters, cytochrome P-450s and UDP-glucuronosyl transferases as a novel approach for the characterization of individual human liver: comparison with mRNA levels and activities. Drug MetabDispos. 2012;40:83–92.

111. Kawashima S., Kobayashi K., Takama K. et al. Involvement of hepatocyte nuclear factor 4 alpha in the different expression level between CYP2C9 and CYP2C19 in the human liver. Drug MetabDispos. 2006;34:1012-1018.

112. Crespi CL, Miller VPThe R144C change in the *CYP2C9*2*allele alters interaction of the cytochrome P-450 with NADPH: cytochrome P-450 oxidoreductase. Pharmacogenetics,1997;7(3):203-210.

113. Niemi M., Cascorbi I., Timm R. et al. Glyburide and glimepiride pharmacocinetics in subjects with different *CYP2C9* genotypes. ClinPharmacol. Ther. 2002;72(3):326-332.

114. Kidd RS, Curry TB, Gallagher T. et al. Identification of a null allele of CYP2C9 in an African-American exhibiting toxicity to phenytoin. Pharmacogenetics, 2001;11(9): 803-808.

115. Delozier TC, Kissling GE, Coulter SJ et al. Detection of human CYP2C8, CYP2C9, and CYP2J2 in cardiovascular tissues. Drug MetabDispos. 2007;35:682-688.

116. Lai X-S, Yang L-P, Li X-T et al. Human CYP2C8: structure, substrate specificity, inhibitor selectivity, inducers and polymorphisms. Curr Drug Metab. 2009; 10:1009-1047.

117. Daily EB, Aquilante CL Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. Pharmacogenomics, 2009;10:1489-1510.

118. DeMorais SM,Wilkinson GR, Blaisdell J. et al. The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. J Biol Chem. 1994;269:15419-15422.

119. De Morais SM, Wilkinson GR, Blaisdell J. et al. Identification of a new genetic defect responsible for the polymorphism of (S)-mephenytoin metabolism in Japanese. MolPharmacol. 1994;46:594-598.

120. Sim SC, Risinger C., Dahl M-L et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. ClinPharmacolTher. 2006;79:103-113.

121. Kimura S., Umeno M., Skoda RC et al. The human debrisoquine 4-hydroxylase (CYP2D) locus: sequence and identification of the polymorphic CYP2D6 gene, a related gene, and a pseudogene. Am J Hum Genet. 1989;45:889-904.

122. Pai HV, Kommaddi RP, Chinta SJ et al. A frameshift mutation and alternate splicing in human brain generate a functional form of the pseudogene cytochrome P-4502D7 that demethylates codeine to morphine. J Biol Chem. 2004;279:27383–27389.

123. Gaedigk A., Gaedigk R., Leeder JS CYP2D7 splice variants in human liver and brain: does CYP2D7 encode functional protein? BiochemBiophys Res Commun. 2005; 336:1241-1250.

124. Zhang WY, Tu YB, Haining RL, Yu AM Expression and functional analysis of CYP2D6.24, CYP2D6.26, CYP2D6.27, and CYP2D7 isozymes. Drug MetabDispos. 2009;37:1-4.

125. Watanabe J., Hayashi S., Kawajiri K. Different regulation and expression of the human CYP2E1 gene due to RsaI polymorphism in the 5’ flanking region. J. Biochem. 1994;116(2):321-326.

126. Lucas D., Menez C., Floch F. et al. Cytochrome P-4502E1 and P-4501A1 genotypes and susceptibility to cirrhosis or upper aerodigestive tract cancer in alcoholic Caucasians. Alcohol ClinExp Res. 1996;20:1033-1037.

127. Savolainen VT, Pajarinen J., Perola M. et al. Polymorphism in the cytochrome P-4502E1 gene and risk of alcoholic liver disease. J Hepatol. 1997;26:55-61.

128. Carriere V., Berthou F., Baird S. et al. Human cytochrome P-4502E1 (CYP2E1): from genotype to phenotype. Pharmacogenetics, 1996;6:203–211.

129. Wong N., Rae F., Simpson KJ et al. Genetic polymorphisms of cytochrome P-4502E1 and susceptibility to alcoholic liver disease and hepatocellular carcinoma in a white population: a study and literature review, including meta-analysis. J ClinPathol:MolPathol. 2000;53:88–93.

130. King LM, Ma J., Srettabunjong S. et al. Cloning of CYP2J2 gene and identification of functional polymorphisms. MolPharmacol. 2002;61:840-852.

131. Spiecker M., Darius H., Hankeln T. et al. Risk of coronary artery disease associated with polymorphism of the cytochrome P-450 epoxygenase CYP2J2. Circulation, 2004;110: 2132-2136.

132. Chen X., Wang H., Zhou G. et al. Molecular Population Genetics of Human CYP3A Locus: Signatures of Positive Selection and Implications for Evolutionary Environmental Medicine. Environ Health Perspect. 2009;117:1541-1548.

133. Brooks BA, McBride OW, Dolphin CTet al. The gene CYP3 encoding P-450pcn1 (nifedipine oxidase) is tightly linked to the gene *COL1A2* encoding collagen type 1 alpha on 7q21–q22.1. Am J Hum Genet. 1988;43:280–284.

134. Hashimoto H., Toide K., Kitamura R.et al. Gene structure of *CYP3A4*, an adult specific form of cytochrome P-450 in human livers, and its transcriptional control. Eur J Biochem. 1993; 218:585–595.

135. Lamba JK, Lin YS, Thummel K.et al.Common allelic variants of cytochrome P4503A4 and their prevalence in different populations. Pharmacogenetics, 2002;12:121–132.

136. Eiselt R., Domanski TL, Zibat A.et al. Identification and functional characterization of eight CYP3A4 protein variants. Pharmacogenetics, 2001;11:447–458.

137. Westlind-Johnsson A., Hermann R., Huennemeyer A.et al. Identification and characterization of CYP3A4*20, a novel rare CYP3A4 allele without functional activity. ClinPharmacolTher. 2006;79:339–349.

138. Kuehl P., Zhang J., Lin Y.et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet. 2001;27:383–391.

139. Quaranta S., Chevalier D., Allorge D. et al. Ethnic differences in the distribution of CYP3A5 gene polymorphisms. Xenobiotica, 2006;36:1191-200.

140. Lee SJ, Usmani KA, Chanas B. et al. Genetic findings and functional studies of human CYP3A5 single nucleotide polymorphisms in different ethnic groups. Pharmacogenetics, 2003;13:461-472.

141. Xie HG, Wood AJ, Kim RB et al. Genetic variability in CYP3A5 and its possible consequences. Pharmacogenomics, 2004; 5:243–272.

142. Otto DME, Henderson CJ, Carrie D. et al. Identification of novel roles of the cytochrome P-450 system in early embryogenesis: effects on vasculogenesis and retinoic acid homeostasis. Mol Cell Biol. 2003; 23:6103–6116.

143. Finn RD, McLaren AW, Carrie D. et al. Conditional deletion of cytochrome P-450 oxidoreductase in the liver and gastrointestinal tract: a new model for studying the functions of the P-450 system. J PharmacolExpTher. 2007;322:40–47.

144. Gomes AM, Winter S., Klein K. et al. Pharmacogenomics of human liver cytochrome P-450 oxidoreductase: multifactorial analysis and impact on microsomal drug oxidation. Pharmacogenomics, 2009;10:579–599.

145. Backes WL, Kelley RW Organization of multiple cytochrome P-450s with NADPH-cytochrome P-450 reductase in membranes. PharmacolTher. 2003;98:221–233.

146. Tee MK, Huang N., Damm I., Miller WL Transcriptional regulation of the human P4-50 oxidoreductase gene: hormonal regulation and influence of promoter polymorphisms. MolEndocrinol. 2011;25:715–731.

147. Hart SN, Wang S., Nakamoto K. et al. Genetic polymorphisms in cytochrome P-450 oxidoreductase influence microsomal P-450-catalyzed drug metabolism. Pharmacogenet Genomics, 2008;18:11–24.

148. Fluck CE, Pandey AV, Huang N. et al. P-450 oxidoreductase deficiency - a new form of congenital adrenal hyperplasia. Endocr Dev. 2008;13:67–81.

149. Sim SC, Miller WL, Zhong X-B et al. Nomenclature for alleles of the cytochrome P-450 oxidoreductase gene. Pharmacogenet Genomics, 2009;19:565–566.

150. Fluck CE, Pandey AV Clinical and biochemical consequences of P-450 oxidoreductase deficiency. Endocr Dev. 2011;20:63–79.

151. Scott EE, Wolf CR, Otyepka M. et al. The Role of Protein-Protein and Protein-Membrane Interactions on P-450 Function. DrugMetabDispos.2016 Feb 5. pii: dmd.115.068569.

152. Li J., Cai J., Su H. et al. Effects of protein flexibility and active site water molecules on the prediction of sites of metabolism for cytochrome P-450 2C19 substrates. MolBiosyst. 2016;23;12(3):868-878.

153. Cederbaum AI Molecular mechanisms of the microsomal mixed function oxidases and biological and pathological implications. Redox Biology, 2015;4:60–73.

154. Otyepka M., Skopalík J., Anzenbacherová E., Anzenbacher P. What common structural features and variations of mammalian P-450s are known to date? Biochim. Biophys. Acta, 2007;770:376–389.

155. Williams PA, Cosme J., Ward A. et al. Crystal structure of human cytochrome P-4502C9 with bound warfarin. Nature, 2003;424:464–468.

156. Cruciani G., Aristei Y., Vianello R., Baroni M. GRID-derived molecular interaction fields for predicting the site of metabolism in human cytochromes. Methods Princ. Med. Chem. 2006;27:273–290.

157. Wilderman PR, Shah MB, Tong Liuetet al. Plasticity of Cytochrome P-450 2B4 as Investigated by Hydrogen-Deuterium Exchange Mass Spectrometry and X-ray Crystallography. J Biol Chem. 2010; 285(49): 38602–38611.

158. Rowland P., Blaney FE, Smyth MG et al. Crystal structure of human cytochrome P-450 2D6. J Biol Chem. 2006;281:7614–7622.

159. Strushkevich N, Usanov SA, Plotnikov AN et al. Structural analysis of CYP2R1 in complex with vitamin D3. J Mol Biol. 2008;380:95–106.

160. McIntosh JA, FarwellChC, Arnold FH Expanding P-450 catalytic reaction space through evolution and engineering. CurrOpinChem Biol. 2014; 50:126–134.

161. Colthart AM, Tietz DR, Ni Y. et al. Detection of substrate-dependent conformational changes in the P-450 fold by nuclear magnetic resonance.Sci Rep. 2016;6:22035. doi: 10.1038/srep22035.

162. Petrek M., Otyepka M., Banas P. et al. CAVER: A new tool to explore routes from protein clefts, pockets and cavities. BMC Bioinf. 2006;7:316.

163. Cojocaru V., Winn PJ, Wade RC The ins and outs of cytochrome P-450s. Biochim. Biophys. Acta, Gen. Subj. 2007;1770:390–401.

164. Shaik S., Cohen S., Wang Y. et al. P-450 enzymes: Their structure, reactivity, and selectivity-modeled by QM/MM calculations. Chem. Rev. 2010;110:949–1017.

165. Schöneboom JC, Lin H., Reuter N. et al. The elusive oxidant species of cytochrome P-450 enzymes: Characterization by combined quantum mechanical/ molecular mechanical (QM/MM) calculations. J. Am. Chem. Soc. 2002;124:8142–8151.

166. Ogliaro F., Cohen S., de Visser SP, Shaik S. Medium polarization and hydrogen bonding effects on compound I of cytochrome P-450: What kind of a radical is it really? J. Am. Chem. Soc. 2000;122:12892–12893.

167. Rittle J., Green MT Cytochrome P-450 Compound I: Capture, characterization, and C-H bond activation kinetics. Science, 2010;330:933–937.

168. Scott EE, Spatzenegger M., Halpert JRA truncation of 2B subfamily cytochromes P-450 yields increased expression levels, increased solubility, and decreased aggregation while retaining function. Arch BiochemBiophys. 2001;395:57–68.

169. Scott EE, He YA, Wester MR et al. An open conformation of mammalian cytochrome P-450 2B4 at 1.6-Å resolution. ProcNatlAcadSci USA, 2003;100:13196–13201.

170. Wester MR, Johnson EF, Marques-Soares C.et al. Structure of a substrate complex of mammalian cytochrome P-450 2C5 at 2.3-Å resolution: evidence for multiple substrate binding modes. Biochemistry, 2003;42:6370–6379.

171. Zhao Y., White MA, Muralidhara BK et al. Structure of microsomal cytochrome P-450 2B4 complexed with the antifungal drug bifonazole: insight into P-450 conformational plasticity and membrane interaction. JBiolChem. 2006;281:5973–5981.

172. Ivanov AS, Skvorzov VS, Archacov AI Computer modeling of cytochrome $b_5$3D structure. Voprosi Med.Khimii, 2000;6:25-34.

173. Borgese N., Gazzoni I., Barberi M. et al. Targeting of a tail-anchored protein to endoplasmic reticulum and mitochondrial outer membrane by independent but competing pathways. MolBiol Cell. 2001;12(8):2482-2496.

174. Ladda MA, GoralskiKBThe Effects of CKD on Cytochrome P-450–Mediated Drug Metabolism. Advances in Chronic Kidney Disease, 2016; 23(2): 67-75.

175. Guengerich FP Cytochrome P-450s and other enzymes in drug metabolism and toxicity, AAPS Journal, 2006, 8: E101–E111.

176. Zanger UM, Schwab M. Cytochrome P-450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. PharmacolTher. 2013;138:103–141.

177. Nishimura M., Yaguti H., Yoshitsugu H.et al. Tissue distribution of mRNA expression of human cytochrome P-450 isoforms assessed by high-sensitivity real-time reverse transcription PCR. Yakugaku Zasshi, 2003;123:369-375.

178. Kawakami H., Ohtsuki S., Kamiie J. et al. Simultaneous absolute quantification of 11 cytochrome P-450 isoforms in human liver microsomes by liquid chromatography tandem mass spectrometry with in silico target peptide selection. J Pharm Sci. 2011;100:341–352.

179. Bieche I., Narjoz C., Asselah T. et al. Reverse transcriptase-PCR quantification of mRNA levels from cytochrome (CYP)1, CYP2 and CYP3 families in 22 different human tissues. Pharmacogenet Genomics, 2007;17:731–742.

180. Dutheil F., Beaune P., Loriot M-A Xenobiotic metabolizing enzymes in the central nervous system: contribution of cytochrome P-450 enzymes in normal and pathological human brain. Biochimie, 2008;90:426–436.

181. Michaud V., Frappier M., Dumas M-C, Turgeon J. Metabolic activity and mRNA levels of human cardiac CYP450s involved in drug metabolism. PLoS One, 2010;5:e15666.

182. Leclerc J., Tournel G., Courcot-NgoubоNgangue E. et al. Profiling gene expression of whole cytochrome P-450 superfamily in human bronchial and peripheral lung tissues: differential expression in non-small cell lung cancers. Biochimie, 2010;92: 292–306.

183. Raunio H., Rahnasto-Rilla M. CYP2A6: genetics, structure, regulation, and function. Drug MetabolDrug Interact. 2012;27:73–88.

184. Miksys S., Lerman C., Shields PG et al. Smoking, alcoholism and genetic polymorphisms alter CYP2B6 levels in human brain. Neuropharmacology, 2003;45:122–132.

185. Aleksa K., Matsell D., Krausz K. et al. Cytochrome P-450 3A and 2B6 in the developing kidney: implications for ifosfamide nephrotoxicity. PediatrNephrol. 2005;20: 872–885.

186. Michaud V., Frappier M., Dumas M-C, Turgeon J. Metabolic activity and mRNA levels of human cardiac CY P-450 s involved in drug metabolism. PLoS One, 2010; 5:e15666.

187. Wang X., Abdelrahman DR, Zharikova OL et al. Bupropion metabolism by human placenta. BiochemPharmacol. 2010;79:1684–1690.

188. Ding X., Kaminsky LS Human extrahepatic cytochromes P-450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. Annu Rev PharmacolToxicol. 2003; 43: 149-173.

189. Du L., Neis MM, Ladd PA et al. Effects of the differentiated keratinocyte phenotype on expression levels of CYP1-4 family genes in human skin cells. ToxicolApplPharmacol. 2006;213:135–144.

190. Paine MF, Hart HL, Ludington SS et al. The human intestinal cytochrome P-450 "pie". DrugMetabDispos. 2006;34:880–886.

191. Delozier TC, Lee SC, Coulter SJ et al. Functional characterization of novel allelic variants of CYP2C9 recently discovered in Southeast Asians. J. Pharmacol. Exp. Ther. 2005;11:29-33.

192. Thelen K., Dressman JB., Cytochrome P-450-mediated metabolism in the human gut wall. J Pharm Pharmacol. 2009;61:541–558.

193. Carcillo JA, Parise RA, Adedoyin A. et al. CYP2D6 mRNA expression in circulating peripheral blood mononuclear cells correlates with in vivo debrisoquine hydroxylase activity in extensive metabolizers. Res CommunMolPatholPharmacol. 1996; 91:149–159.

194. Krovat BC, Tracy JH, Omiecinski CJ Fingerprinting of cytochrome P-450 and microsomal epoxide hydrolase gene expression in human blood cells. Toxicol Sci. 2000, 55:352–360.

195. Siest G., Jeannesson E., Marteau JB et al. Transcription factor and drug-metabolizing enzyme gene expression in lymphocytes from healthy human subjects. Drug MetabDispos. 2008; 36:182–189.

196. Haas CE, Brazeau D., Cloen D. et al. Cytochrome P-450 mRNA expression in peripheral blood lymphocytes as a predictor of enzyme induction. Eur J ClinPharmacol. 2005; 61:583–593.

197. Bahari A., Mehrzad J., Mahmoudi M. et al. Cytochrome P-450 isoforms are differently up-regulated in aflatoxin B1-exposed human lymphocytes and monocytes. Immunopharmacol Immunotoxicol. 2014;36:1–10.

198. Siegle I., Fritz P., Eckhardt K. et al. Cellular localization and regional distribution of CYP2D6 mRNA and protein expression in human brain. Pharmacogenetics, 2001;11:237–245.

199. Cheng J., Zhen Y., Miksys S. et al. Potential role of CYP2D6 in the central nervous system. Xenobiotica, 2013;43:973–984.

200. Wang X., Li J., Dong G., Yue J. The endogenous substrates of brain CYP2D. Eur J Pharmacol. 2014;724:211–218.

201. Yu AM, Indole alkylamines: Biotransformations and potential drug-drug interactions. AAPS J. 2008;10:242–253.

202. Yu AM, Idle JR, Herraiz T. et al. Screening for endogenous substrates reveals that CYP2D6 is a 5-methoxyindolethylamine O-demethylase. Pharmacogenetics, 2003;13:307–319.

203. Durand E., Petit O., Tremblay L. et al. Social behavioral changes in MPTP-treated monkey model of Parkinson's disease. FrontBehavNeurosci. 2015;9:42.

204. Kishimoto W., Hiroi T., Shiraishi M. et al. Cytochrome P-450 2D catalyze steroid 21-hydroxylation in the brain. Endocrinology, 2004; 145:699–705.

205. Ferguson CS, Tyndale RF Cytochrome P-450 enzymes in the brain: emerging evidence of biological significance. Trends Pharmacol Sci. 2011;32:708–714.

206. Gaedigk A., Baker DW, Totah RA et al. Variability of CYP2J2 expression in human fetal tissues. J PharmacolExpTher. 2006;319:523–532.

207. Klein K., Thomas M., Winter S. et al. PPARA: a novel genetic determinant of CYP3A4 in vitro and in vivo. ClinPharmacolTher. 2012;91:1044–1052.

208. Daly AK Significance of the minor cytochrome P-450 3A isoforms. ClinPharmacokinet. 2006;45:13–31.

209. Leeder JS, Gaedigk R., Marcucci KA et al. Variability of CYP3A7 expression in human fetal liver. J PharmacolExpTher. 2005;314:626–635.

210. Bolbrinker J., Seeberg S., Schostak M. et al. CYP3A5 genotype–phenotype analysis in the human kidney reveals a strong site-specific expression of CYP3A5 in the proximal tubule in carriers of the CYP3A5*1 allele. Drug MetabDispos. 2012;40:639–641.

211. Jounaidi Y., Chen CS, Veal GJ, Waxman DJ Enhanced antitumor activity of P-450 prodrug-based gene therapy using the low Km cyclophosphamide 4-hydroxylase P-450 2B11. Mol Cancer Ther. 2006;5:541-555.

212. Kim S., Jo CH, Park JS et al. The role of proximal nephron in cyclophosphamide-induced water retention: preliminary data. Electrolyte. BloodPress. 2011;9:7-15.

213. Halpert JR Structure and Function of Cytochromes P-4502B: From Mechanism-Based Inactivators to X-Ray Crystal Structures and Back. DrugMetabDispos. 2011;39(7):1113–1121.

HEAD II

MONOOXYGENASE SYSTEM REGULATION AND OPERATION

II.1. FEATURES OF MONOOXYGENASE SYSTEM OPERATION

It has known that in the liver and in many other organs during the operation of the microsomal monooxygenase lipidotrophin formed xenobiotic polar compounds having reactive groups. These metabolites can be both less and more toxic than the parent compounds, but they are acquired through reactive groups come into conjugation reaction to form non-toxic products, easily deduced from the organism with urine, feces and bile.

The transfer of electrons from the microsomal CYP nicotinamide adenine dinucleotide phosphate (NADP·H) is carried out by the cytochrome P-450 reductase to some extent and the reducing power of the system and may also contribute to cytochrome b_5, after reducing it happens via cytochrome b_5 reductase (Figure2.1) [1, 2, 3, 4].

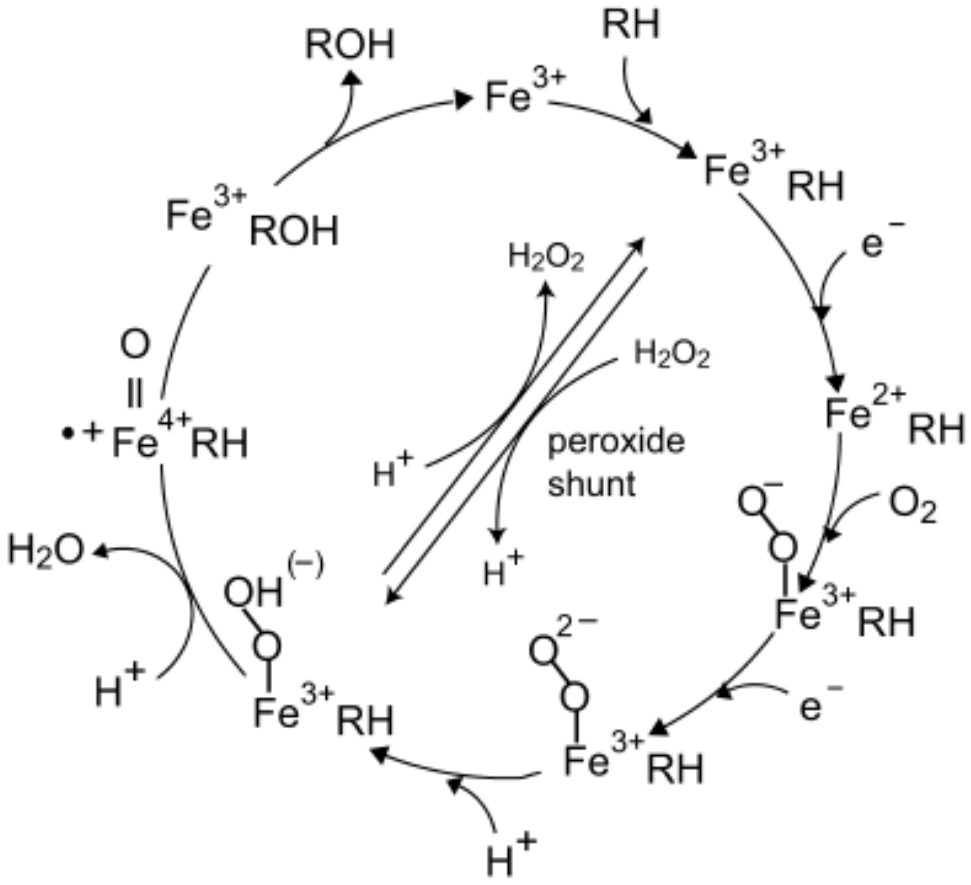


Figure 2.1. The catalytic cycle of the cytochrome P-450 oxidation reaction. RH and ROH respectively denote the substrate and the product [157].

NAD·H typically has about 10% efficiency relative NADP·H in promoting activity of microsomal P-450. NAD·H transfers electrons to FAD containing flavoprotein-cytochrome b_5 NAD·H reductase, which reduces cytochrome b_5 (Figure 2.2). Experiments

with inhibitors and antibodies using purified enzymes have provided clear evidence for a positive role NADP·H-P-450 reductase in reducing P-450 [5].

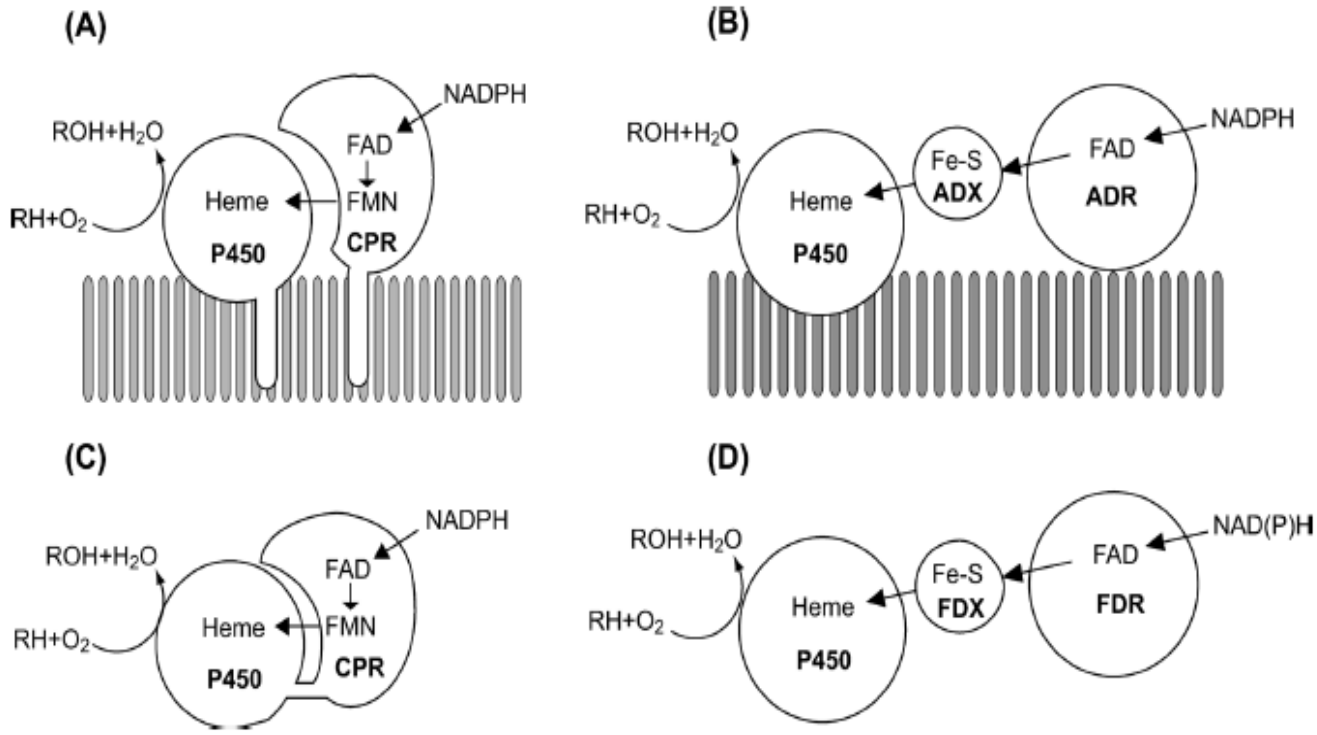


Figure 2.2. Schematic representation of the electron transport chains: (A) microsomal P-450, (B) mitochondrial P-450, Bacterial Class VIII P-450 (CYP102A1) (C) and Bacterial Class I P-450 (D); respectively by [5].

Note: CPR, ADX, ADR, FDX and FDR represent respectively NADPH -P-450 reductase, adrenodoxin, NADPH- adrenodoxin reductase, ferredoxin and NAD(P)H-ferrodoxin reductase. RH and ROH represents a substrate and product, respectively.

B_5 can reduce to some extent to reduce P-450. In some cases, can further NAD·H NADP·H-dependent increase the catalytic activity of P-450 by providing a second electron catalytic cycle required for P-450 (described below) NADP·H/NAD·H cytochrome b_5 system is normally involved in the transfer of electrons to the cyanide-sensitive factor required for fatty acid desaturation. Subtotal electronic transduction pathways involved in the P-450 catalyzing the reaction shown in scheme (Figure2.3) [6, 7, 8].

Mitochondrial CYP use adrenodoxin reductase and adrenodoxin (or ferrodoxin) to transmit electrons from NADP·H to CYP [9]. However, it was found that CYP5A1 (thromboxane X2 synthase), CYP8A1 (prostacyclin H2 synthase) and CYP74A (alleneoxide synthase) do not require protein partners for their catalysis [10].

In the group of membrane-bound, cytochrome b_5 isolated mitochondrial and microsomal forms that are associated with the respective cell organelles in various organs and tissues. It found that two different genes encode apoproteins of these cytochrome b_5 isoforms [11].

Along with monooxygenase, CYP may exhibit oxidase activity and reducing-O_2 to O_2, H_2O_2 and OH•, and also function as a true four-electron oxidase, generating water molecules in the reaction O_2 + 2NADP·H+ 2H+ → $2H_2O$ + 2NADP+ and even dioxygenase reactions catalyze [11]. Moreover, CYP capable of exhibiting peroxidase activity in the oxidation reaction using as co-substrate hydrogen peroxide or organic peroxide, instead NADP·H. Therefore, CYP also called the mixed function oxidases.

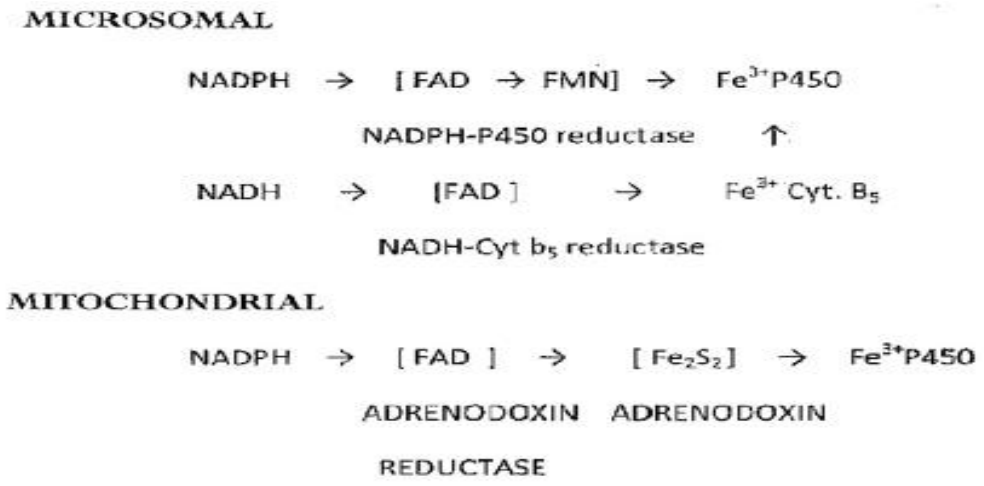


Figure 2.3. Scheme reactions catalyzed by microsomal and mitochondrial cytochrome P-450. The scheme presented respectively by [158].

The catalytic mechanism of all CYPs is stored, similar heme-thiolate functionality, but amino-acid variations in the substrate binding sites, provide regio- and stereo-selectivity of substrates metabolism [12].

Depending on origin, CYP differ significantly in substrate specificity. One of the most common reactions catalyzed by CYP is oxidative dealkylation that followed by oxidation of the alkyl group attached to the N-, O- or S-atoms. The second place on frequency belongs to the reactions of the hydroxylation cyclic, aromatic and heterocyclic hydrocarbons. CYP can also catalyze reactions of aliphatic compounds hydroxylation, S- and N-oxidation, N-hydroxylation, oxidative deamination, azo- and nitro- compounds reduction, saturated fatty acid oxidation, peroxidation of unsaturated fatty acids, biosynthesis of prostaglandins, hydroxylation of steroid hormones, bile acids and cholesterol.

Three families of human CYP, namely: CYP1, CYP2 and CYP3 are basic, contributing oxidative metabolism of more than 90% of the drugs used in the clinic, along with CYP from other families involved in the metabolism of endogenous components as steroids, fatty acids, bilirubin and arachidonic acid [13].

The study demonstrated that 110 of the tested drugs metabolized 66% of one or more enzymes CYP; of which 44% metabolized CYP3A4, 41% - 2D6, 26% - 2C19, 9% - 1A2 and 4% - 2C9 [14].

Of all CYP450 enzymes, CYP3A subfamily (CYP3A4, CYP3A5, CYP3A7 and CYP3A43), plays a central role in drug metabolism. CYP3A4 and CYP3A5 are involved in the metabolism of more than 50% of all known substrates of CYP450 [15].

CYP1A1 it takes the main rolein the biotransformation of certain pollutants and carcinogens including polycyclic amines and flavored hydrocarbons (PAH), which are significantly expressed CYP1A1 [16]. For example, benzopyrene - the main component of PAHs in coal tar, cigarette smoke, diesel exhaust gases and strongly burnt food that induces CYP1A isoforms and is metabolized to its ultimate carcinogenic metabolite, trans-7,8, diol-10-epoxide [17,18].

Substrates of CYP2A isoforms (CYP2A6, CYP2A7 and CYP2A13) include coumarin, nicotine (oxidation), cyclophosphamide, and aflatoxin B1 and nitrosamines, which are metabolized to carcinogenic derivatives [19, 20, 21]. Interestingly, CYP2A6 is not involved in the metabolism of endogenous substances in humans but CYP2A isoforms capable of catalyzing the hydroxylation of testosterone in the liver of rats [22, 23].

Substrate selectivity of CYP2B6 and CYP2B7 affects a wide variety of chemicals, including not only the clinically used drugs (approximately 25% of the drug), but also many chemical environment (Table 1.). Therapeutically important drugs these are metabolized, for mainly, by CYP2B6 include beta-blockers, tricyclic antidepressants, pro-drug cyclophosphamide, which is converted to a direct precursor of cytotoxic metabolites; antiretroviral drug, efavirenz; atypical antidepressive drug bupropion; antimalarial drug artemisinin; anesthetics propofol and ketamine; μ-opioid agonist is methadone, tamoxifen and others [24] (Figure 2.4.).

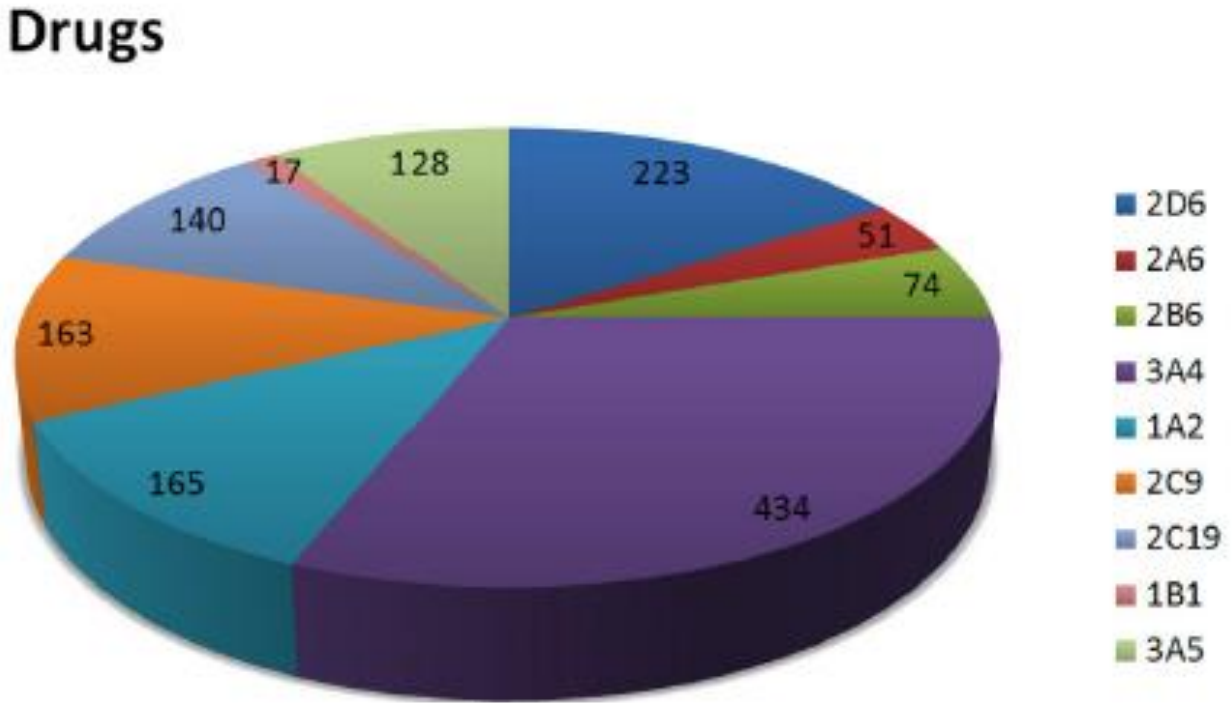


Figure 2.4. The number of drugs that are substrates of different isoforms of cytochrome P-450. Scheme represent respectively by [159].

Numerous studies have also confirmed the important role of CYP2B6 metabolism of pesticides and other chemical environmental substances environment and contaminants

[25], especially in the start-oxidation of organ phosphorus insecticides to their more toxic ozone metabolites and procarcinogens agents aflatoxin B1 and dibenzanthracene [26,27].

Other isoform is CYP2D6 that is active in the metabolism of drug compounds (metabolized beta-blockers, tricyclic antidepressants, and many other drugs) (see. Table 2 in the Attachment).

CYP2C9 (which substrates are S-warfarin, non-steroidal anti-inflammatory drugs such as ibuprofen, oral anti-diabetic products), CYP2C19 (substrate diazepam, tricyclic antidepressant such as amitriptyline, imipramine, anti-ulcer drugs omeprazole and lansoprazole), CYP2E1 (typical substrate of which is paracetamol inhalation anesthetic halothane and organic solvents such as ethanol, acetone, acetonitrile, nitrosamines).

The complexity of metabolism of drug compounds is not only the problem of a sufficiently large number of cytochrome, but also the fact that most drugs metabolized in several ways, which take several CYP isoforms involved. A good example of this can be warfarin as S-warfarin metabolized of CYP2C9, while the less active form - R-warfarin metabolized by isoforms with CYP3A4 and CYP1A2. The consequence of this fact is that the inhibition or induction of CYP2C9 will have a greater effect on the metabolism of warfarin than those that affect CYP3A4 and CYP1A2 level. In turn, one-isoform substrates may also interact in a complex way. It also shown that inhibition of CYP3A4 substrates relative may be a partial inhibition of the interaction and activation of testosterone - terfenadine, testosterone - and terfenadine, midazolam - midazolam, respectively [28].

Table 1

The substrates for the human hepatic CYP isoforms

Isoforms	Structural and functional properties of the substrates
CYP1A2	Planar aromatic; poly aromatic and heterocyclic amines and amides
CYP2A6	No planar molecules of low molecular weight typically two acceptors by hydrogen bonds; and ketones include nitrosamines
CYP2B6	Neutral or slightly basic generally no planar lipophilic molecule one or two hydrogen bond acceptors on; anesthetics include, herbicides and insecticides
CYP2C8	Relatively large molecules and weakly acidic; They include anti-malarial drugs and oral anti-diabetic
CYP2C9	Low-acid molecule to an acceptor for hydrogen bond; They include ketones; They include most drugs NSAIDs
CYP2C19	Neutral or weakly basic amides molecule or with two or three of the hydrogen bond acceptor on; Most include proton pump inhibitors
CYP2D6	Lead molecules with the ability to protonate the nitrogen atom at the distance of 4-7 Å metabolizing site; It includes many plant alkaloids and antidepressants
CYP2E1	Small, common neutral and hydrophilic planar molecules; They include aliphatic alcohols and halogenated alkanes

CYP2J2	Active point can accommodate the large substrates of CYP3A4 like, but have a catalytic function restrictive
CYP3A4/5	Large and lipophilic molecules are very diverse structure; They comprise over 50% of all drugs used in clinic

It has known that one isoform of the cytochrome P-450 may catalyze biotransformation reactions of various substrates, and cytochrome b_5 affects the rate of reaction depending on both isoforms and species of the reaction (substrate). In its presence, the catalytic activity of CYP increases, decreases or does not change, and change the profile of metabolites synthesized and the amount of generated reactive oxygen species [29]. It is also possible that the presence of cytochrome b_5 changes the direction of the reaction catalyzed by the enzyme. For example, cytochrome P-450s 17 depending on a number of factors, including the presence of cytochrome b5 functions as 17-alpha-hydroxylase and 17, 20-lyase [30].

Recently, using humanized mice, it has found that the cytochrome b_5 is a major determinant of the human CYP2D6 activity and 3A4 in vivo, which has performed with the participation of metabolism of xenobiotic about half entering the body [31]. According Guengerich FP [32], the catalytic activity of CYP3A4 expressed in significant amounts in human liver, has shown only in the presence of cytochrome b_5. However, with respect to this obtained contradictory data in the reactions of biotransformation of various substrates. It is shown that the presence of cytochrome b_5 necessary for 6β-hydroxylation of steroids and N-hydroxylation of nifedipine and erythromycin metabolism (N-demethylation) and benzphetamine possible in its absence [33]. When studying the activity of cytochrome P-4503A4 human liver in the reconstituted system showed that the optimum molar ratio of components monooxygenase cycle displays catalytic activity of the enzyme is the ratio of cytochrome P-4503A4 to cytochrome b_5 NADP·H to cytochrome P-450 reductase to 1: 3: 20. In the absence of the enzyme cytochrome b_5 not metabolize cortisol, erythromycin and (R) -warfarin [34].

There are several possible mechanisms for stimulating effect on cytochrome b_5 isoform of cytochrome P-450 [35, 36]:

1. direct transmission of an electron in a monooxygenase reaction, without the involvement of NADP·H cytochrome P-450 reductase;

2. formation of more reactive oxygen radicalsby monooxygenase cycle occurs in the case of the second electron from the cytochrome b_5, which in turn has accompanied by a rapid formation of the metabolite;

3. cytochrome b_5 interact with cytochrome P-450 hemoprotein complex formation of two and the subsequent transfer of two electrons from NADP·H cytochrome P-450 reductase, which increases the rate of formation of active oxygen and eliminates the need for repeated interaction of cytochrome P-450 and NADP·H cytochrome P-450 reductase;

4. allosteric stimulation of cytochrome P-450 without the electron transport, for example, in the second step of catalytic cycle;

5. cytochrome b_5 may have a protective effect on the molecule terminal oxygenase, not connected with the reactions of the redox cycle, which prevents its destruction.

At the same time, the mechanism of the inhibitory effect on cytochrome b_5 reactions catalyzed by cytochrome P-450 is still unclear.

Accumulating evidence suggests that:

- In the presence of cytochrome b_5, metabolic rate most endogenous compounds and xenobiotic increases,

- The effect of cytochrome b_5 in the biotransformation of the same compound, such as androstenedione, in different animal species differently - in rabbits (CYP 2V5) increases, and the dogs (CYP 2V11) reduces steroid metabolism; increasing the a-and dogs (CYP 2V11) reduces steroid metabolism;

- cytochrome$b_5$in different species (human and hamster) may be indispensable component for oxidation of the compound (nitrosamine) or stimulated action;

- Presence of cytochrome $b_5$alters metabolites spectrum formed during the metabolism of compounds by same isoform of the cytochrome P-450, such as CYP B1 (tetrachlorobiphenyl);

- In the presence of cytochrome b_5, reduced the formation of reactive oxygen species,overproduction of that has a negative effect on the cells of organism;

- Metabolism of biologically active compounds (arachidonic acid, leukotrienes) occurs only in the presence of cytochrome b_5.

II.2. INDUCTION AND INHIBITION OF THE MONOOXYGENASE ENZYMES ACTIVITY

The activity of microsomal oxygenases that catalyze biotransformation processes in the first detoxification phase, as the activity of enzymes involved in the conjugation reaction is not strictly constant.

The most pronounced effect on the functioning of the biochemical systems responsible for detoxification processes, provide chemical substances that can be has divided into two groups: the inductors and inhibitors of microsomal monooxygenase. Analysis of published data shows that the widespread nature of the phenomenon in the induction and inhibition of enzyme activity in the regulation of enzymatic processes, probably the most pronounced is in the CYP system.

Induction and inhibition of CYP, potentially responsible for many adverse drug interactions, as a modification of the CYP enzyme activity can dramatically alter metabolism and clearance of drugs. For example, in cases where one drug acts as an inhibitor of CYP metabolic intermediate second drug accumulation result should be the second drug to toxic levels in the body. In contrast, in cases where the patient is receiving the combination treatment, which includes an inductor CYP metabolic intermediate of the second drug, is the resulting in low plasma concentrations of the drug and the second failed drug therapy [37, 38].

Where in the drug compound can act as an inhibitor or inducer of certain isoforms even if the substrate is not these isoforms. Thus, guanidine, being a potent inhibitor of CYP2D6, CYP3A4 metabolized itself, so it is able to interfere with the metabolism of compounds desipramine type or codeine are metabolized by CYP2D6, but itself is not subjected to transformations involving this isoform. Whereas erythromycin is the substrate, and CYP3A4 inhibitor [39, 40].

Inhibition of P-450 isoform is the most common reason for the decline of metabolism and hepatic clearance of substrates of these isoforms, as well as responsible for the majority of drug-drug interactions, life-threatening. Although the drug compounds are able to inhibit several different isoforms (amiodarone), in most cases, the inhibition is

specific isoform (e.g., inhibited CYP3A4, but not CYP2D6). In addition, the inhibitor may be metabolized isoform that it inhibits or may not. For example, whereas erythromycin is both substrate and inhibitor of CYP3A4, guanidine (as mentioned above) is a potent inhibitor of CYP2D6, but it has metabolized by CYP3A4.

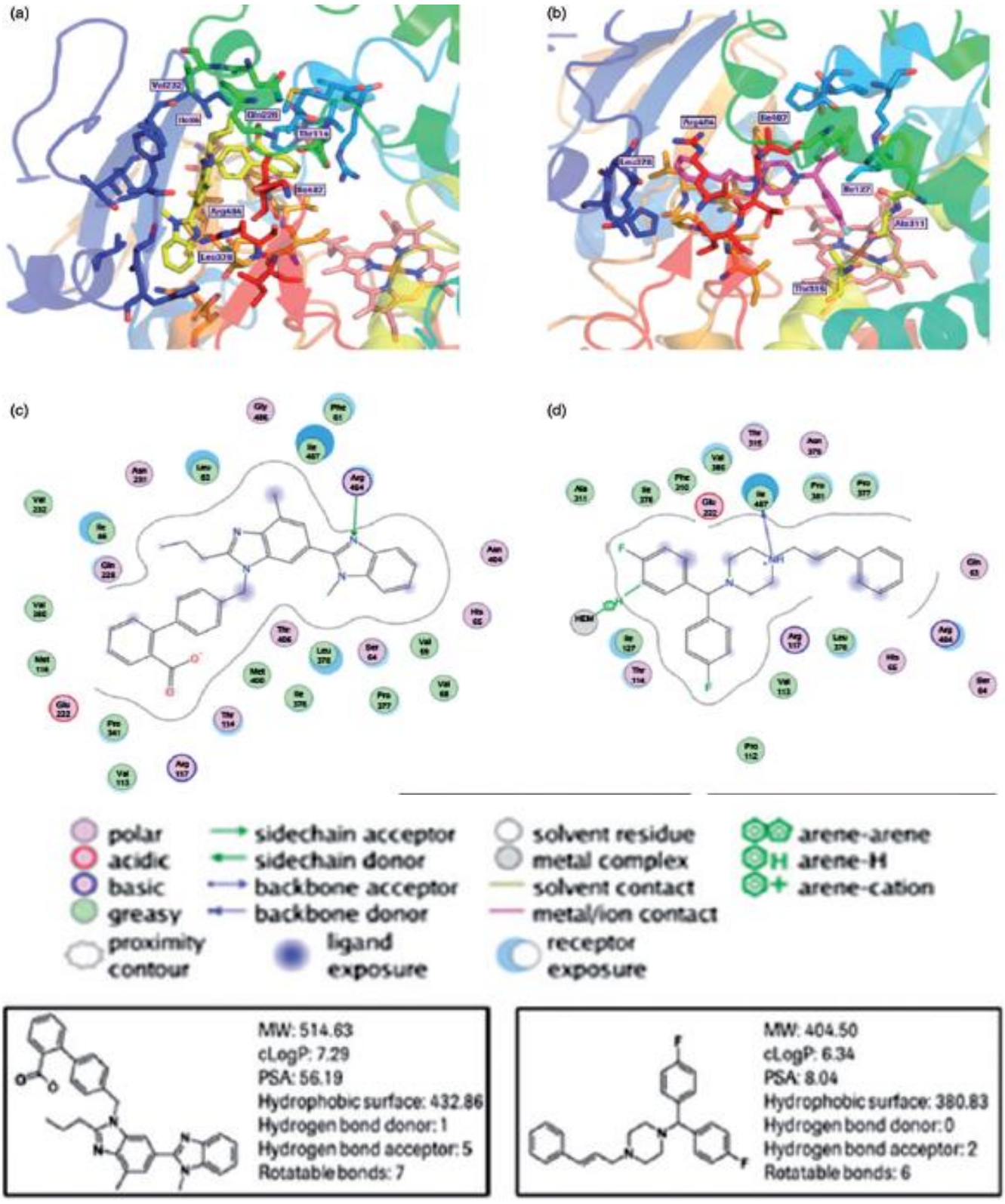


Figure 2.5. CYP2J2 inhibitor-binding pocket at the end of the 2ns MD simulation for telmisartan (A) and flunarizine (B).

Note: The pocket for telmisartan (A, C), is mainly formed from the residues of a hydrophobic nature, mainly of N-terminal loop and helix A (Val59, Phe61, Ser64, His65, and Val68), sheet b1 and binding loops (Leu83, Ile86, and Met400), helix K (Asn404 and Thr406), sheet b4 and associated loop (Arg484, Gly486, and Ile487), K/b1-4 segment (Ile376, Pro377, Leu378, Val380, and Pro381), B/C segment (Val113, Thr114, Met116, and Arg117), helix F (Glu222) and F/G segment (Gln228, Asn231, and Val232). The binding pocket for flunarizine (B, D), is formed primarily by hydrophobic residues, mainly N-terminal loop and helix A (Gln63, Ser64, and His65), sheet b4 and associated loop (Arg484 and Ile487), K/ b1-4 segment (Ile376, Pro377, Leu378, Asn379, Val380, and Pro381), B/C segment (Pro112, Val113, Thr114, Arg117, and Ile127), helix F (Glu222), helix I (Phe310, Ala311, and Thr315) and hemeporphyrin ring. CYP2J2 protein - represented in the figure, colored in rainbow spectrum (respectively by Ren et al. [44]).

Among the inhibitors of microsomal monooxygenase are numerous compounds of different chemical nature, which can be has divided into several groups [41]. The first group consists of reversible inhibitors of direct action. This group consists of esters, lactones, isocyanates, oxygenated steroids, phenols, quinones and others. The second group includes the reversible inhibitors of indirect action affecting the microsomal enzymes through intermediate products of their metabolism, which form complexes with cytochrome P-450. This group includes benzene derivatives, aromatic amines, hydrazines, alkyl amines, and others. The third group includes irreversible inhibitors disrupting cytochrome P-450. Among them belong polyhalogenic alkanes, derivatives of olefins, oleines, sulfur compounds, and others. The fourth group consists of inhibitors which inhibit the synthesis and (or) the accelerating disintegration of the cytochrome P-450. These metal ions, organic compounds that affect heme synthesis and inhibit protein synthesis.

Some drugs and components identified as CYP2J2 inhibitors are substrates CYP2J2, but some of them - no. Type CYP2J2 inhibition may be reversible (competitive, uncompetitive or mixed type), or be reversible (machine-based).

It is shown that the substrates CYP2J2, AA, terfenadine, and ebastine, can be competitive inhibitors of O-demethylation of astemizole to a human microsomes and rabbit small intestine, and liver concentration-dependent manner [42]. O-demethylation of astemizole reduced by 25% and 60% (AA 50 mmol), 22% and 49% (terfenadine 50 mM), and 12% and 72% (ebastine 50 mM) versus control by adding these inhibitors in the microsome of the small intestine and rabbit liver. Activity has reduced respectively by 31% and 25% of control levels by addition ebastine (100 mM) and terfenadine (50 mmol) in human intestinal microsomes. These components are also hampered O-demethylation of astemizole in human liver microsomes; Nevertheless inhibiting force were weaker than in the small intestine.

After comparing the IC50 values of the synthesized components, Lafite et al. [43] summarized three important structural characteristics for the good identification of CYP2J2: (1) the presence of short-chain hydrophobic alkyl group at one end of the molecule, (2) the presence of the keto group in this chain alkyl terminally aryl group, and (3) the presence of hydrophobic diaryl-methyl constituting at position 4 of the central piperidine ring (Figure 2.5.).

In order to identify a specific inhibitor CYP2J2, Lee et al. [45] 138 drugs screened using both terfenadine and astemizole test substrates for recombinant CYP2J2. Forty-two demonstrated inhibitory drug effect CYP2J2 activity, whereas eight components (danazol, ketoconazole, lapsoprazol, loratadine, miconazole, nicardipine, verapamil and orphenadrine) significantly reduced activity CYP2J2. Of these, danazol inhibits hydroxylation of terfenadine competitive with IC50 value of 77 nM, and O-demethylation of astemizole with a Ki value of 20 nM, whereas IC50 value of the drug for CYP2C9, 2C8 and 2D6 were respectively 1.44, 1.95 and 2.74 mM. As CYP2J2 substrate, danazol is also a potent and selective competitive inhibitor CYP2J2 [46]. Preferably, however, the specific inhibitory agent should not be a substrate CYP2J2; otherwise, it may be difficult when it has used in experimental studies and in analyzing the data obtained.

Accordingly, Ren et al. [44] screened 69 known drugs for the inhibition CYP2J2, and a number of them have been identified as potent and selective inhibitors CYP2J2. Among them, telmisartan and flyunarizin have proven as selective inhibitors CYP2J2, which acts, at least 10-fold more selective against all other intensively metabolizing CYP. Furthermore, they are not CYP2J2 substrates and show no time-dependent inhibition of the process changes with respect to this enzyme CYP (Figure 2.5).

Other chemical agents including α-naphthoflavone (inhibitor CYP1A2,2C9, 50 mmol), ketoconazole (an inhibitor of CYP1A2, 2C9, 2D6 and 3A4, 10 mmol) troglitazol (an inhibitor of CYP2C8, 2C9 and 3A4, 10 mmol) and tranylcypromine (CYP2A6 inhibitor and 2C, 50 mM) also showed the inhibitory effect of different (11-56%) for the O-demethylation of astemizole in microsomes from recombinant CYP2J2 [42]. Azamulin (14-O- (5- (2-amino-1 March: 4-triazolyl) thioacetyl) - dihydromutilin), a strong and selective inhibitor of CYP3A, was also CYP2J2 inhibitor with the value of Ki 6.6 mM in microsomes with CYP2J2 [47].

Quinidine - a selective inhibitor of CYP2D6, but it - is not a substrate for this enzyme. Many CYP2D6 substrates and other components reversibly inhibit CYP2D6. In particular, certain drugs and other chemicals are mechanism-based inhibitors of CYP2D6, including paroxetine, cimetidine, metoclopramide, pimozide, desethylamiodaron, the SCH 66712 [5-fluoro-2-[4 -[(2-phenyl-1H-imidazol-5-yl) methyl]-1-piperazinyl] pyrimidine], 1 -[(2-ethyl-4-methyl-1Himidazol-5-yl)-methyl]-4-[4-(trifluoromethyl)-2-pyridinyl] piperazine MDMA [48]. Joint prescribing these inhibitors may cause serious drug-drug interactions that have observed in clinical practice. In development of drugs, if it turns out that the new candidate on drugs would be a strong or a mechanism-based inhibitor of CYP2D6, further development will be stop as long as the substance has a high potential for adverse drug-drug interaction.

Induction of P-450 isoform is the result of an increase in their synthesis, which leads to an increase in the hepatic clearance and metabolism of substrates involved in this pathway. This process is more complex than inhibition, and more ambiguous to predict the consequences.

Xenobiotic-mediated induction of CYP is often tissue-specific, dose-dependent and reversible with the removal of the inductor. In contrast to the inhibition of hepatic enzymes,the induction requires time (hours or days) and is a function of chronic exposure. CYP inducers can be divided into five classes: (a) prototypal-/phenobarbital-like inducers (e.g., phenobarbital, phenytoin); (B) polycyclic aromatic hydrocarbon - such inducers (e.g. omeprazole and cigarette smoke); (C) pregnenolone and 16-carbonyl glucocorticoid

type inducers (e.g., dexamethasone, rifampin and erythromycin); (D) ethanol-like (e.g. ethanol and isoniazid); and (e) type peroxisome proliferators - (e.g. clofibrate and phthalates used in plasticizers) [49, 50].

Table 3 (see appendix) includes classical inducer of hepatic P-450: polycyclic flavored hydrocarbons and barbiturates such as phenobarbital have been initially among certain inducers of CYP1A1 and CYP2B1/2B2 respectively, whereas corticosteroids such as dexamethasone, enhance CYP3A4 and ethanol raises CYP2E1. Not all forms of P-450 are inducible, especially P-450 with steroid metabolized characteristics of the 26 families (11, 17, 19, 2). Not all P-450 even in a particular family are inducible, for example, CYP 2B and 2E are inducible (phenobarbital or ethanol, respectively), but CYP 2A, 2C and 2D are not inducible. Thus, CYP2D6 is not generally inducible by known typical CYP inducers that indicated on regulating differences from others CYP.

Induction of most (but not all) P-450 includes the activation of the gene and increase de novo protein synthesis. In some cases, specific cellular receptors that interact with inducing agent, have identified, for example, induction of CYP1A1 flavored polycyclic hydrocarbons, such as 3-methylcholanthrene-primary inductor and include communication with Ah receptor nuclear translocation and activation of potential CYP1A1 gene. Induction of CYP2E1 ethanol is complex and involves both transcriptional and posttranscriptional mechanisms [51]. CYP2E1 gene is under the transcriptional regulation during development in rats is activated immediately after birth. Because of diabetes or fasting, CYP2E1 mRNA increased several times due to post-transcriptional stability of mRNA [52]. Increasing CYP2E1 many low molecular weight chemicals, including ethanol, acetone, and pyrazole, provided mainly for protein stabilization and increasing the half-life of the protein [51, 53].

During the in vitro and in vivo studies on the regulation of human CYP, several prototype inducers commonly used including rifampin, phenobarbital, β-naphthoflavone and dexamethasone [54, 55]. Inductors of phenobarbital type activate transcription CYP2A, 2B, 2C and 3A. Dexamethasone/rifampicin type inductors induce such CYPs, but CYP3A more efficiently is induced than CYP2C and CYP2B. Inductive effect of drugs is not limited to the regulation of CYP, other drug-metabolizing enzymes or transporters of drugs, but involves major pleiotropic response, including the stimulation or suppression of multiple genes and physiological activity. For example, the latest advanced gene-analysis showed that rifampin could regulate multiple genes in human hepatocytes through a link with the newly identified corresponding to the drug-regulatory elements [56].

In another genomic study found that the target gene was hypomethylated CAR Cyp2b10 activated transcriptional and tissue-specific processin the liver after treatment with phenobarbital [57].

In addition, analysis of active and repressive histone modification, chromatin immunoprecipitation using, revealed strong phenobarbital - mediated epigenetic regulator Cyp2b10 promoter. The effects of dexamethasone on the expression of CYP in human hepatocytes are complex, partly caused by the physiological role of glucocorticoids in maintaining constitutive expression of PXR and CAR.

Rifampin is an effective antimicrobial agent against gram-negative bacteria and is widely used mainly in the treatment of tuberculosis and other infections such as Legionella pneumophila pneumonia [58, 59]. It has known that it increases the elimination of a long

list of drugs with important clinical consequences in terms of loss of or decrease the effectiveness of drugs or increased toxicity [60, 61]. Rifampin has recognized as a pleiotropic, but a specific inducer that alters the activity of CYP-specific, and other medication-metabolizing enzymes and transporters of drugs, which creates a rational basis for a vast interaction between drugs [60].

While CYP inhibition processes have well detected when performing experiments on human hepatic microsomes or cDNA, expressing CYP, cultured human hepatocytes are extensively use for the CYP induction studies [62, 63]. Using cultured human hepatocytes was detected induction CYP1A, 2A, 2B, 2C, 2E and 3A subfamilies prior art inductors, such as rifampin, phenobarbital, β-naphthoflavone and dexamethasone [64]. In contrast to these CYP enzymes, in none of the experimental models inductors effect did not increase levels of CYP2D6, 2E1 and 4A11, except for sections of cultured human liver [65]. For CYP2D6, studies have shown that the most stable CYP induction to other known inducers subfamilies CYP [64]. The cultured primary human hepatocytes, rifampin, rifabutin and rifampentin induce CYP3A, but not CYP2D6. Phenobarbital and rifampin induce CYP1A and 3A4, but not CYP2C9, 2C19, P-gp/MDR-1 and MRP-1 in human hepatocytes [66]. Phenobarbital and rifampin significantly induce CYP2B6, 2C8, 2C9, 2C19, 2E1, and 3A4, but does not induce CYP2D6 activity in human hepatocytes [67]. In human hepatocytes clotrimazole, phenobarbital, rifampin and ritonavir strongly induce CYP2B6 and activated PXR. Dexamethasone and sulfinpyrazone weakly induce CYP2B6 and moderately activate PXR; paclitaxel strongly activates PXR, but does not increase the expression of CYP2B6; carbamazepine and phenytoin are moderately or severely increase the expression of CYP2B6, but weakly activates PXR; and dexamethasone, methotrexate, probenecid, sulfadimidine and troleandomycin have weak or insignificant effects on CYP2B6 and PXR [68]. Using human enterocytes derived from six healthy subjects before and after a 10-day oral administration of rifampicin at 600 mg/day, it revealed that CYP2D6 has not induced, whereas CYP2C8, 2C9 and 3A4 undergo significant induction [69].

Rifampicin dose-dependently induces CYP3A4, but inhibits the expression of SHP mRNA levels in primary human hepatocytes [70]. Rifampicin strongly stimulates interaction PXR and HNF-4α, and reporter activity CYP3A4, which further stimulated the co-activator PPARgco-1a (PGC-1a) and co-activator-one steroid receptor (SRC-1), but inhibited SHP [70]. These results indicate that PXR SHP inhibits transcription of the gene increases and PXR-mediated induction of CYP3A4 gene in the human liver. Ritonavir and nelfinavir do not affect the CYP2D6 in cultured human hepatocytes, but significantly induce CYP1A2, 2B6, 2C9, 2C19 and 3A4 [71]. In cultured human hepatocytes, rifampin induces expression of CYP3A4/5, 2B6, 2C8, 2C9 and 2A6, but inhibits CYP2E1, 2J2 and 4A11 [64]. It is a small but significant increase in the expression at the same time observed for CYP2D6, 2C19, and 1A2.

Introduction patient rifampicin (600 and 1200 mg daily) for 7 day's period increases the sparteine metabolic clearance of up to 30% for EMs, but not PMs. In PMs healthy male volunteers treated with rifampicin at a dose of 600 mg/day for 8 days, showed a significant decrease in MR debrisoquine and induction of CYP1A2 activity, 2C9 and 2D6 to time-dependent manner using caffeine mephenytoin and debrisoquine as appropriate drugs test [72]. Older CYP2D6 EMs (age, 70.5±3.5 years), 600 mg rifampin daily intake for 9 days induced Phase I (mainly related of CYP2D6) and Phase II of propafenone

metabolism [73]. In healthy subjects, the use of nelfinavir, ritonavir or rifampin for 2 weeks induces CYP1A2, 2B6 and 2C9, but did not CYP2D6 [74]. The seven-day administration of rifampicin induces CYP2C19 and 3A4, but CYP2D6 and 1A2 in healthy Japanese volunteers [75]. Introduction rifampin healthy subjects in the 600 mg daily for 9 days improves as the P-gp, and MRP2, but not CYP2D6; while rifampin decreases the AUC of carvedilol to a degree independent of the genotype CYP2D6 [76].

Nuclear receptors are key mediators drug-induced increase in the expression of monooxygenase enzymes. Species differences in the activation of nuclear receptors make forecasting inducing medicine-metabolizing enzymes in humans according to the data obtained from animal models is very problematic.

CYP1A1 and CYP1A2 highly inducible multiple xenobiotics which act as AhR ligands, such as: methylcholanthrene and other polycyclic aromatic hydrocarbons, dioxins, β-naphthoflavone [77], as well as atypical inductors comprising omeprazole and primaquine that regulate transcription through the same corresponding elements, but not binding to AhR [78]. Typical sources of exogenous AhR activators are natural combustion products, dietary components (e.g. in broccoli), and by-products of chemical production (e.g. Dioxins). Well established as the induction of CYP1A2 by smoking and confirmed in in vivo studies [79,80].

CYP3A4 and several other CYP isoforms, such as, CYP2B6 [81] and CYP2C [82, 83], through induced PXR activation in response to a myriad of natural and synthetic components [84, 85]. In humans, the most important CYP3A4 enzyme CYP, involved in drug metabolism. There are two main reasons: (i) CYP3A4 abundantly expressed in the liver and intestine, which - the main bodies involved in the metabolism of xenobiotics; (Ii) it has a broad substrate specificity is responsible for biotransformation of more than 50% of clinically used drugs [86-88]. In addition to the regulatory phase I DMEs, PXR regulates the expression of several enzymes of phase II DME and conveyors for detoxify and elimination of xenobiotics [89]. These facts distinguish PXR protective role against potentially toxic components, endangering the body. However, PXR also constitutes the molecular basis for potential drug-drug interactions, drug-grass and food-drug when patients use a combination of chemicals. PXR activator may, for example, to increase the expression of the target CYP, which then alters clearance of other parallel input lead to drugs and therapeutic failure patients. For this reason, drug interactions involve significant barriers in the development of new drug candidates, and it is necessary to characterize them in the early stages of pre-clinical development [84, 90, 91].

II.3. INFLUENCE OF FOOD FACTORS ON FUNCTION AND EXPRESSION OF THE CYP ISOFORMS

Diet can significantly affect the metabolism of drugs by modulating the activity of CYP [92, 93].

CYP levels can vary with relatively normal fasting food; for example, CYP2E1 levels increase after 24 hours of fasting. It has found that in healthy subjects, short-term fasting (36 hours) has increased the oral clearance of caffeine and 20% reduction of this index for S-warfarin by 25%. However, short-term fasting is not changed CYP2D6-, 2C19- and 3A4- mediated metabolism of drugs. In the short-term fasting in rats was observed an

increase in mRNA expression of orthologs of the human CYP1A2, 2C19, 2D6 and 3A4 and the decrease in mRNA expression of orthologs CYP2C9 [94].

Poor nutrition may reduce P-450-catalyzed oxidation of drugs, decreasing the synthesis and induction of CYP, influencing the biosynthesis of heme and thus altering the degree and CYP modulating cofactor availability. Various components of the diet can influence the oxidation hepatic drugs such as CYP inhibition and induction [95]. This is particularly remarkable for the components in grapefruit juice, such as naringin, which is a strong inhibitor of CYP3A4. The isothiocyanates of cruciferous vegetables are present, and in the garlic - diallyl sulphydes having the ability to inhibit the catalytic activity of CYP2E1. Alcohol increases the levels of CYP2E1. Burnt food or smoke can induce CYP1A2, which is able to activate many carcinogens.

Dietary factors have a significant impact on the fate of drug compounds in the body. In particular, about 18% of the US adult population uses drugs in conjunction with dietary or vitamin products. Carried [96] the study of influence 116 herbal supplements are commercially used for food purposes or for controlling body weight, for the expression of isoform CYP1A2, 2C11, 2D6, 2E1 and 3a1, showed that 75% of additives has modulated the expression of at least one isoform and only 25% has not influence on this process. In most inhibited CYP2C11 isoform (51%), whereas the most frequently induced (21%) CYP1A2 isoform. As the number of interactions between drugs and plant, products are increasing in recent years, a systematic screening system in vitro and subsequent clinical studies required for the identification of such interaction in the development of plant health products or nutritional supplements.

Diverse food and phytonutrients can significantly change the activity of CYP. For example, cruciferous vegetables may act as an inducer of human CYP1A1 and 1A2, and the animals can stimulate CYP1B1 [97-100]. At the same time, the most well established inductive effect of cruciferous on CYP1A2.

Clinical studies have also shown that resveratrol and containing his food are stimulants CYP1A1 [101].

Conversely, berries and isolated from their polyphenol ellagic acid, can reduce the increased activity of CYP1A1 [102], and pointed vegetables and quercetin can inhibit the excessive activity of CYP1A2 [98, 103]. Cruciferous vegetables and berries have believed to be potential modulators of estrogenic metabolites: by reducing the activity of CYP1A1 berry [102] and a strong induction on CYP1A enzymes 1B1 cruciferous vegetables [99, 100, 104]. Cryzoeriol presented in «rooibos» tea and celery, able to inhibit selectivelyCYP1B1 in vitro conditions [105] that can be very useful for patients with hyperactivity CYP1B1. However, to confirm a detected need for further research.

On the other hand, many foods appear to act also as inducers and as enzyme inhibitors CYP1, effects which may be dose-dependent or changed in the allocation of food derived bioactive compounds. For example, a diet containing 0.1% curcumin induced CYP1A1 [106] and a diet with a 1% turmeric, on the contrary, inhibited [107]. Black tea in 54 ml/day induced both CYP1A1, and CYP1A2 [108], while the tea flavonoid concentration of 20 mg/kg, exerted an inhibitory effect on CYP1A1 [109]. Consumption of soy beans in an amount of 100 mg/kg stimulated CYP1A1 activity [110], but at the same time receiving 1 g/kg of black soybean extract [111] and 200 mg daidzein twice daily [112], the opposite effect is created. Since this revealed the data, of course, they require further research in humans to confirm the effects of various doses.

II.3.1. Role of food components in the CYP2A-Eisoforms regulation

Big CYP2 family of enzymes involved in the metabolism of drugs, xenobiotics, hormones, and other endogenous components, such as ketones, fatty acids and glycerol [113, 114]. Some notable polymorphisms found in CYP2C and subgroups CYP2D, leading to patients classified as "poor metabolizers" of various pharmaceutical drugs such as warfarin for CYP2C9, antiarrhythmic agents, and metoprolol and propafenone for CYP2D6, phenytoin, cyclobarbital and omeprazole for CYP2C19 [113, 115]. CYP2D polymorphisms may be associated with Parkinson's disease and lung cancer [113]. Clinical evidence exists for the induction of CYP2A6 quercetin and broccoli [97, 103]. It was revealed that in animals induces enzymes chicory CYP2A [116], and rosemary and garlic can stimulate the activity of CYP2B [117, 118]. Clinical studies using resveratrol and garden cress, established inhibition of CYP2D6 [101, 119]. Ellagic acid, green and black tea and cruciferous vegetables also inhibit various enzymes CYP2.

CYP2E1 enzymes have also attracted attention for their role in the development of various diseases. CYP2E1 metabolizes a number of drugs that affect the nervous system, such as halothane, isoflurane, chlorzoxazone and ethanol, it makes bioactivation procarcinogenic nitrosamines and aflatoxin B1 [113, 120]. It produces free radicals regardless of substrate [113] and CYP2E1 polymorphisms associated with an increased risk of coronary heart disease [121] and stomach cancer [122]. It has also shown that CYP2E1 induced oxidative stress leads to disruption of insulin action through the inhibition of the expression of GLUT4 [123]. Consequently, the weakening of activity 2E1 may be important in the prevention of high-risk patients.

Watercress salad and garlic are CYP2E1 inhibitors in humans [124,125]. Based on the results of in vivo studies also found that N-acetyl cysteine, ellagic acid, green tea, black tea, dandelion, chrysene and medium-chain triglycerides (MCT) can inhibit CYP2E1 [108, 114, 126-129]. MCT oil can specifically inhibit ethanol-induced stimulation of CYP2E1 and mitochondrial production of 4-HNE, a marker of oxidative stress [129].

II.3.2. Nutritional components in the regulation of CYP3A and CYP4 families

The detection of different CYP3A isoforms - a tissue-specific [113]. Tea «Rooibos», garlic and fish oil have an inducing effect on CYP3A activity, 3A1 and 3A2 [130-133]. Presumably, inhibiting enzymes foods include green tea, black tea and quercetin [108, 134-136]. Most of the clinically important enzyme is CYP3A4, which has expressed primarily in liver and to a lesser extent in the kidneys [137]. Caffeine, testosterone, progesterone, and androstendione are substrates CYP3A4enzyme system, as well as various procarcinogens including PAHs and afflatoxin B1 [113]. To date, CYP3A4 was the most "favorite" object of research because of its role in the metabolism of more than 50 percent of all pharmaceuticals [138]. The potential for drug interactions with this enzyme only associated with wide inter-individual differences in enzyme activity creates a certain risk level at high doses and multiple drugs as well as the interaction of drug and food-drug-grass. Grapefruit juice - probably the most famous food an inhibitor of this enzyme [139], although resveratrol and garden cress, a member of the cruciferous plants exhibit similar effects in humans, despite the fact that consumed higher than would be

expected in the absence of high-supplementation [101, 119]. Curcumin may stimulate the activity of 3A4 [140].

There are signs that the biphasic effect may occur because of the dietary bioactive components; Davenport and Wargovich [130] found that transient or lower dosing garlic organosulfur components produces potentially anticarcinogenic effects, but longer periods of consumption of the higher dose (200mg/kg) of allyl sulfides lead to minor hepatic toxicity. A garlic head comprises only 2.5-4.5 mg of allisin - allyl sulfide precursor [141], so that a higher dose could be significantly greater that that usually absorbeda typical human diet. In another example, the two components of cruciferous vegetables - sulforafens and indole-3-carbinol, and inhibits the activity increases, respectively [142, 143], creating the potential need studies in humans, in cases of using whole food consumption to evaluate the outcome.

Regarding family CYP4 little has known, it has believed that they play a minor role in the metabolism of drugs. However, it is known that they are being primarily extrahepatic family of cytochromes, clofibrate and ciprofibrate inducible (hypolipidemic drugs), NSAIDs, prostaglandins and toxicants such as phthalate esters [113, 144]. CYP4B1 isoform is involved in the metabolism of MCT (medium chain triglycerides) and it makes bioactivation pneumotoxic and carcinogenic components [145]. Polymorphism and over expression of this subgroup may be associated with the development of gallbladder cancer [113] and colitis [146]. According to Ye et al. [146] who studied the relationship between colitis and CYP4B1activity, found that an increase in its activity by caffeine acid (found in caffeine-containing food) consistent with a decrease in inflammation and disease severity. Green tea can induce CYP4A1, as explained in the experimental animal studies [147]. However, to more accurately determine the effect of food on this enzymatic family need to continue research.

II.3.3. Clinical applications

With the accumulation of data, confirming the role of toxins in the development of chronic disease, clinicians becomes extremely necessary to understand how to provide a therapeutic modality to reduce toxins in the patient load. The information below provides some key concepts for its translation into clinical concepts.

1. ***Non-clinical against clinical studies***. One of the limitations that are at the forefront of this research is the system information, which in many cases is limited to original research on cells or animals. It remains debated - have similar effects should be identified in people with moderate and reasonable doses. In studies on cells, it is difficult to assume the attention caused by lack of pleiotropic activities that take place in the complex, in a living system with multiple operating systems at the same time detoxifying. Similarly, animal studies are often difficult to extrapolate to humans (individuals) due to the high degree of variability in the genotype and phenotype of environmental, detectable in various human populations. Therefore, in such cases it is best to take precautionary measures, and the justification of food effects or essential nutrients, which are consuming only cells or animals, using them as supporting evidence. It is best to rely on clinical studies, which have published today for the implementation of more reliable recommendations.

2. ***The only agent against lifestyle***. If you focus on isolated nutrients and foods that contain these nutrients, then it would probably be best for the clinical perspective, consider the situation - as in, the whole lifestyle can induce or inhibit an array of detoxifying enzymes. On the other hand, the modern clinician, along with this, it is necessary to weigh and compare with each other and even variables such factors as smoking, physical activity and stress. Yet, science cannot fully demonstrate the individual effect of all these indicators, taken together. Therefore, in this case, the preferred solid Dietary pattern, with raw products, food based on plants and removing or reducing the amount of toxic substances in the environment, which is a two-way approach, which might have been the best direction for the construction of a scientific foundation.

3. ***Modulation of anti-inhibiting/inducing effects***. In several examples, certain foods are particularly enzyme activity, whereas at higher doses they have detected another opposite effect. As such, many kinds of food serve as what has commonly referred to as "bifunctional modulators" having the ability to induce or inhibit efficient detoxifying enzyme activity based on the dose-response reactions. Consequently, the resulting clinically selected path should be encouraged to comply with a variety of mixed diet, whole foods, has based entirely on the plants. Smaller amounts of many of the components can be more therapeutic and support for the biochemical pathways, rather than cancellation of signals derived from the high concentration of nutrients through supplements or the dose highly repetitive techniques, daily consumption of large quantities of the same food.

4. ***Polypharmation***. For patients who are taking multiple pharmaceuticals, it is important to know which detoxifying system under the influence of nutrients and food will act so that the side effects would be minimized or canceled.

5. ***Dietary supplements against food***. While there are potential effects on food nutrients detoxifying path for the average patient will be best to follow the way described above, mixed and complex whole food diet. In addition, dietary supplements adjunct may be useful for patients on which the practitioner has knowledge of the genetic variability to fit respectively could nutrients. Without a full understanding of the SNP patients (the only nucleotide polymorphisms), it becomes difficult to make accurate estimates of nutrients and dosing.

6. ***Period of dosing***. Another indicator for the optimal solutions for therapeutic intervention is the synchronization and the duration of dosing nutrient or food. Some of the studies presented here, the effects on detoxifying enzymes were visible only after a few days of food intake or supplements, while in other cases, and the induction of enzymes could be quite fast, accompanied by effective adaptability. This variability should be taken into account in further clinical studies with the need to closed audits in clinical practice.

7. ***Food that affects the detoxification***. Some foods demonstrate their influence on detoxifying the system. Many of them have recognized as part of naturopathic medicine. It would therefore be useful to have a knowledge base on these sets of cumulative food as detoxifying agents in the protocols for patients. There has been confirmation of the clinical effects of cruciferous vegetables (in combination and separately in the watercress, garden cress, and broccoli), top-flowering vegetables, grapefruit, resveratrol, fish oil, quercetin, lycopene and daidzein. As in vivo modulators, detoxifying enzymes and they have presented in a variety of other kinds of food, beverage, nutritional components and bioactive substances.

In the last decade, number of studies on nutriogenomics and epigenetic influence of food components for chronic diseases have increased [148, 149]. Similar studies have found that exposure and accumulation of toxins plays an important role in cardiovascular disease, diabetes type 2 and obesity [150-154]. Thus, dietary intake, and effect the environment can have a big impact on the incidence of chronic diseases. In fact, these effects can be significant not only for the individual, but also for several generations thanks to the inheritance of epigenetic changes [155, 156].

Of course, created, currently, clinical nutrition recommendations expand and reduce the impact effects of toxins. However, this should not occur without caution and critical thinking, and detoxifying protocols for patients to be collected by trained clinicians, as are many unresolved questions about the information - as well as what foods to modulate detoxifying path.

REFERENCES

1. Locuson CW, Wienkers LC, Jones JP, Tracy TS. CYP2C9 protein interactions with cytochrome b_5: Effects on the coupling of catalysis. DrugMetabDispos. 2007;35:1174–1181.

2. Iyanagi T, Xia C, Kim JJ NADPH-cytochrome P-450 oxidoreductase: Prototypic member of the diflavinreductase family. Arch BiochemBiophys. 2012;528:72–89.

3. Pandey AV, Fluck CE. NADPH P450oxidoreductase: Structure, function, and pathology of diseases. PharmacolTher. 2013;138:229–254.

4. Henderson CJ, McLaughlin LA, Scheer N. et al. Cytochrome b5 is a major determinant of human cytochrome P-450 CYP2D6 and CYP3A4 activity in vivo. MolPharmacol. 2015;87:733–739.

5. Hannemann F., Bichet A., Ewen KM, Bernhardt R. Cytochrome P-450 systems-biological variations of electron transport chains. Biochim. Biophys. Acta, 2007;1770: 330–344.

6. Ahn T., Yun CH. Molecular mechanisms regulating themitochondrial targeting of microsomal cytochrome P-450 enzymes. Curr Drug Metab. 2010;11:830–838.

7. Coon MJ Cytochrome P-450: nature's most versatile biological catalyst. Annual Review of Pharmacology and Toxicology, 2005;45:1–25.

8. Koymans L., Donne-OpDenKelder GM., KoppeleTe JM., Vermeulen NP Cytochromes P450: their active-site structure and mechanism of oxidation. Drug Metabolism Reviews, 1993;25(3):325–387.

9. Neve EP, Ingelman-Sundberg M. Cytochrome P-450 proteins: Retention and distribution from the endoplasmic reticulum. CurrOpin Drug Discov Dev. 2010;13:78–85.

10. Brash AR. Mechanistic aspects of CYP74 allene oxide synthases and related cytochrome P-450 enzymes. Phytochemistry, 2009;70:1522–1531.

11. Chen Q., Zhang T., Wang JF, Wei DQ. Advances in human cytochrome P-450 and personalized medicine. Current Drug Metabolism,2011;12(5):436–444.

12. Werck-Reichhart D., Feyereisen R. Cytochromes P-450: A success story. Genome Biol, 2000;1:REVIEWS3003.

13. Nebert DW, Wikvall K, Miller WL Human cytochromes P-450 in health and disease. Philos Trans R SocLond B Biol Sci. 2013;368:20120431.

14. Stringer RA, Strain-Damerell C., Nicklin P., Houston JB Evaluation of recombinant cytochrome P-450 enzymes as an in vitro system for metabolic clearance predictions. Drug MetabDispos. 2009;37:1025–1034.

15. Guengerich FP. Cytochrome P-450s and other enzymes in drug metabolism and toxicity, AAPS Journal, 2006;8:E101–E111.

16. Kawajiri K. Chapter 15. CYP1A1. Volume 148 IARC Sci Publications, Chichester, UK;1999, 159-172.

17. Cheng PY, Morgan ET Hepatic cytochrome P-450 regulation in diseasestates. Curr Drug Metab. 2001;2(2):165-183.

18. Shimada T., Fujii-Kuriyama Y. Metabolic activation of polycyclic romatichydrocarbons to carcinogens by cytochromes P-450 1A1 and 1B1. Cancer Sci. 2004;95(1):1-6.

19. Gonzalez FJ, Gelboin HV Role of human cytochromes P-450 in the metabolic activation of chemical carcinogens and toxins. Drug Metab Rev. 1994;26:165-183.

20. Honkakoski P., Negishi M. The structure, function, and regulation ofcytochrome P450 2A enzymes. Drug Metab Rev. 1997;29(4):977-996.

21. Pelkonen O., Rautio A., Raunio H., Pasanen M. CYP2A6: a human coumarin 7-hydroxylase. Toxicology, 2000;144:139-147.

22. Haduch A., Wojcikowski J., Daniel WA Effect of short- and long-term treatment with antidepressant drugs on the activity of rat CYP2A in the liver.Pharmacol Rep. 2005;57:774-781.

23.Robottom-Ferreira AB, Aquino SR, Queiroga R. et al. Expression of CYP2A3 mRNA and its regulation by 3-methylcholanthrene, pyrazole, andbeta-ionone in rat tissues. Braz J Med Biol Res. 2003;36:839-844.

24. Turpeinen M., Zanger UM. Cytochrome P-450 2B6: function, genetics, and clinical relevance. Drug Metabol Drug Interact. 2012;1–13.

25. Hodgson E., Rose RL The importance of cytochrome P-450 2B6 in the human metabolism of environmental chemicals. PharmacolTher. 2007;113:420–428.

26. Martignoni M., de Kanter R., Grossi P. et al. An in vivo and in vitro comparison of CYP induction in rat liver and intestine using slices and quantitative RT-PCR. ChemBiol Interact. 2004;151:1-11.

27. Xie W., Evans RM Orphan nuclear receptors: the exotics of xenobiotics. J Biol Chem. 2001;276:37739-37742.

28. Zanger UM, Schwab M. Cytochrome P-450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology & Therapeutics, 2013;138:103–141.

29. Peterson J., Prough R. Cytochrome P-450 reductase and cytochrome b5* in cytochrome P-450 catalysis.//Cytochrome P-450: structure, mechanism, and biochemistry. /Ed. Ortiz de Montellano P.- Plenum Press, New York, 1985;P.89-117.

30. Brock BJ, Waterman MR. Biochemical differences between rat and human cytochrome P-450c 17 support the different steroidogenic needs of these two species. Biochemistry, 1999;38(5):1598-1606.

31. Henderson CJ, McLaughlin LA, Scheer N. et al. Cytochrome b5 is a major determinant of human cytochrome P-450 CYP2D6 and CYP3A4 activity in vivo. MolPharmacol. 2015;87:733–739.

32. Guengerich FP. Cytochrome P-450 3A4: regulation and role in drug metabolism. Annu Rev PharmacolToxicol. 1999;39: 1-17.

33. Shiraga T., Matsuda H., Nagase K. et al.Metabolism of FK506, a potent immunosuppressive agent, by cytochrome P-450 3A enzymes in rat, dog and human liver microsomes. BiochemPharmacol. 1994;47(4):727-735.

34. Buters JT, Korzekwa KR, Kunze KL et al.cDNA-directed expression of human cytochrome P-450 CYP3A4 using baculovirus. Drug MetabDispos. 1994;22(5):688-692.

35. Porter TD. The roles of cytochrome b5 in cytochrome P-450 reactions. J BiochemMolToxicol. 2002;16(6):311-316.

36. Schenkman JB, Jansson I. The many roles of cytochrome b5. PharmacolTher. 2003;97(2):139-152.

37. Zhou SF, Liu JP, Lai XS Substrate specificity, inhibitors and regulation of human cytochrome P-450 2D6 and implications in drug development. Curr Med Chem 2009;16(21):2661-2805.

38. Zhou SF, Zhou ZW, Yang LP, Cai JP. Substrates, inducers, inhibitors and structure-activity relationships of human cytochrome P-450 2C9 and implications in drug development. Curr Med Chem. 2009;16(27):3480-3675.

39. Guengerich FP. Cytochrome P-450 and chemical toxicology. Chem Res Toxicol 2008;21(1):70-83.

40. Hollenberg PF. Mechanisms of cytochrome P-450 and peroxidase catalyzed xenobiotic metabolism. FASEB J. 1992;6(2):686-694.

41. Lin JH, Lu AY. Inhibition and induction of cytochrome P-450 and the clinical implications. ClinPharmacokinet. 1998;35:361–390.

42. Matsumoto S., Hirama T., Matsubara T. et al. Involvement of CYP2J2 on the intestinal first-pass metabolism of antihistamine drug, astemizole. Drug MetabDispos. 2002;30:1240–1245.

43. Lafite P., Dijols S., Zeldin DCet al. Selective, competitive and mechanism-based inhibitors of human cytochrome P-450 2J2. ArchBiochemBiophys. 2007;464:155–168.

44. Ren S., Zeng J., Mei Y. et al. Discovery and Characterization of Novel, Potent, and Selective Cytochrome P-450 2J2 Inhibitors. DrugMetabDispos. 2013;41:60–71.

45. Lee CA, Jones JP, Katayama J. et al. Identifying a selective substrate and inhibitor pair for the evaluation of CYP2J2 activity. Drug MetabDispos. 2012;40:943–951.

46. Lee CA, Neul D, Clouser-Roche A et al. Identification of novelsubstrates for human cytochrome P450 2J2. Drug MetabDispos. 2010;38:347–356.

47. Stresser DM, Broudy MI, Ho T. et al. Highly selective inhibitionof human CYP3Aa in vitro by azamulin and evidence that inhibition is irreversible. Drug MetabDispos. 2004;32:105–112.

48. Zhi-Xu He, Xiao-Wu Chen, Zhi-Wei Zhou, Shu-Feng Zhou Impact of physiological, pathological and environmental factors on the expression and activity of human cytochrome P-450 2D6 and implications in precision medicine. Drug Metab Rev. 2015;47(4):470–519.

49. Lin JH, Lu AY. Interindividual variability in inhibition and induction of cytochrome P-450 enzymes. Annu Rev PharmacolToxicol. 2001;41:535–567.

50. Zhu BT On the general mechanism of selective induction of cytochrome P-450 enzymes by chemicals: Some theoretical considerations. Expert Opin Drug MetabToxicol. 2010;6:483-494.

51. Koop DR, Tierney DJ Multiple mechanisms in the regulation of ethanol-inducible cytochrome P-450 IIE1.BioEssays, 1990;12:429–435.

52. Song BJ, Matsunaga T., Hardwick JP et al. Stabilization of cytochrome P-450j messenger ribonucleic acid in the diabetic rat. Molecular Endocrinology, 1987; 1: 542–547.

53. Song BJ, Veech RL, Park SS et al. Induction of rat hepatic N-nitrosodimethylaminedemethylase by acetone is due to protein stabilization, Journal of Biological Chemistry, 1989;264(6):3568–3572.

54. Donato MT, Castell JV. Strategies and molecular probes to investigate the role of cytochrome P-450 in drug metabolism: Focus on in vitro studies. ClinPharmacokinet. 2003;42:153–178.

55. Hewitt NJ, Lecluyse EL, Ferguson SS Induction of hepatic cytochrome P-450 enzymes: Methods, mechanisms, recommendations, and in vitro-in vivo correlations. Xenobiotica, 2007;37:1196–1224.

56. Smith RP, Eckalbar WL, Morrissey KM et al. Genome-wide discovery of drug-dependent human liver regulatory elements. PLoSGenet. 2014;10:e1004648.

57. Lempiainen H., Muller A., Brasa S. et al. Phenobarbital mediatesan epigenetic switch at the constitutive androstane receptor (CAR)target gene Cyp2b10 in the liver of B6C3F1 mice. PLoS One,2011;6:e18216.

58. Aristoff PA, Garcia GA, Kirchhoff PD, Showalter HD Rifamycins-Obstacles and opportunities. Tuberculosis (Edinb), 2010;90:94–118.

59. Varner TR, Bookstaver PB, Rudisill CN, Albrecht H. Role ofrifampin-based combination therapy for severe community-acquired Legionella pneumophila pneumonia. Ann Pharmacother. 2011;45:967–976.

60. Baciewicz AM, Chrisman CR, Finch CK, SelfTH Update onrifampin, rifabutin, and rifapentine drug interactions. Curr Med ResOpin. 2013;29:1–12.

61. Sousa M., Pozniak A., Boffito M. Pharmacokinetics and pharmacodynamics of drug interactions involving rifampicin, rifabutin and antimalarial drugs. J AntimicrobChemother. 2008;62:872–878.

62. Sahi J, Grepper S, Smith C. Hepatocytes as a tool in drug metabolism, transport and safety evaluations in drug discovery. CurrDrug Discov Technol. 2010; 7:188–198.

63. Sinz M., Wallace G., Sahi J. Current industrial practices in assessing CYP450 enzyme induction: Preclinical and clinical. AAPS J. 2008;10:391–400.

64. Ramamoorthy A., Liu Y., Philips S. et al. Regulation of microRNA expression by rifampin in human hepatocytes. DrugMetabDispos. 2013;41:1763–1768.

65. Martin H., Sarsat JP, de Waziers I. et al. Induction of cytochrome P-450 2B6 and 3A4 expression by phenobarbital and cyclophosphamide in cultured human liver slices. Pharm Res. 2003;20:557–568.

66. Runge D., Kohler C., Kostrubsky VE et al. Induction ofcytochrome P-450 (CYP)1A1, CYP1A2, and CYP3A4 but not ofCYP2C9, CYP2C19, multidrug resistance (MDR-1) and multidrug resistance associated protein (MRP-1) by prototypical inducers inhuman hepatocytes. BiochemBiophys Res Commun. 2000;273:333–341.

67. Madan A., Graham RA, Carroll KM et al. Effects of prototypical microsomal enzyme inducers on cytochrome P-450 expression incultured human hepatocytes. Drug MetabDispos. 2003;31:421–431.

68. Faucette SR, Wang H., Hamilton GA et al. Regulation of CYP2B6 in primary human hepatocytes by prototypical inducers. DrugMetabDispos. 2004;32:348–358.

69. Glaeser H., Drescher S., Eichelbaum M., Fromm MF Influence ofrifampicin on the expression and function of human intestinal cytochrome P-450 enzymes. BrJClinPharmacol. 2005;59:199–206.

70. Li T., Chiang JY Rifampicin induction of CYP3A4 requires pregnane X receptor cross talk with hepatocyte nuclear factor 4a and coactivators, and suppression of small heterodimer partner gene expression. Drug MetabDispos. 2006;34:756–764.

71. Dixit V., Hariparsad N., Li F. et al. Cytochrome P-450 enzymes and transporters induced by anti-human immunodeficiency virus protease inhibitors in human hepatocytes: Implications for predicting clinical drug interactions. Drug MetabDispos, 2007;35:1853–1859.

72. Branch RA, Adedoyin A., Frye RF et al. In vivo modulation of CYP enzymes by quinidine and rifampin. ClinPharmacolTher. 2000;68:401–411.

73. Dilger K., Hofmann U., Klotz U. Enzyme induction in the elderly: Effect of rifampin on the pharmacokinetics and pharmacodynamics of propafenone. ClinPharmacolTher. 2000;67:512–520.

74. Kirby BJ, Collier AC, Kharasch ED et al. Complex drug interactions of HIV protease inhibitors 2: In vivo induction andin vitro to in vivo correlation of induction of cytochrome P-450 1A2,2B6, and 2C9 by ritonavir or nelfinavir. DrugMetabDispos. 2011;39:2329–2337.

75. Inui N., Akamatsu T., Uchida S. et al. Chronological effects ofrifampicin discontinuation on cytochrome P450 activity in healthyJapanese volunteers, using the cocktail method. ClinPharmacolTher. 2013;94:702–708.

76. Giessmann T., Modess C., Hecker U. et al. CYP2D6 genotype and induction of intestinal drug transporters by rifampin predict presystemic clearance of carvedilol in healthy subjects. ClinPharmacolTher. 2004;75:213–222.

77. Nebert DW, Dalton TP, Okey AB, Gonzalez FJ Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. J Biol Chem. 2004;279:23847–23850.

78. Yoshinari K., Ueda R., Kusano K.et al. Omeprazole transactivates human CYP1A1 and CYP1A2 expression through the common regulatory region containing multiple xenobiotic-responsive elements. BiochemPharmacol. 2008;76:139–145.

79. Ghotbi R., Christensen M., Roh H.-K.et al. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype–phenotype relationship in Swedes and Koreans. Eur J ClinPharmacol. 2007;63:537–546.

80. Dobrinas M., Cornuz J., Oneda B.et al. Impact of smoking, smoking cessation, and genetic polymorphisms on CYP1A2 activity and inducibility. ClinPharmacolTher. 2011;90:117–125.

81. Goodwin B., Moore LB, Stoltz CM et al. Regulation of the human cyp2b6 gene by the nuclear pregnaneX receptor. MolPharmacol. 2001;60(3):427–431.

82. Synold TW, Dussault I., Forman BM The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux. Nat Med. 2001; 7(5):584–590.

83.Gerbal-Chaloin S., Pascussi JM, Pichard-Garcia L.et al. Induction of cyp2c genes in human hepatocytes in primary culture. Drug MetabDispos.2001;29(3):242–251.

84. Staudinger JL, Ding X., Lichti K. Pregnane X receptor and natural products: Beyond drug-drug interactions. Expert Opin Drug MetabToxicol. 2006;2(6):847–857.

85. Sinz M., Kim S., Zhu Z.et al.Evaluation of 170 xenobiotics as transactivators of human pregnane X receptor (HPXR) and correlation to known cyp3a4 drug interactions. Curr Drug Metab. 2006;7(4):375–388.

86. Li AP, Kaminski DL, Rasmussen A. Substrates of human hepatic cytochrome p450 3a4. Toxicology, 1995;104(1–3):1–8.

87. Martinez-Jimenez CP, Jover R., Donato MT et al. Transcriptional regulation and expression of cyp3a4 in hepatocytes. Curr Drug Metab. 2007;8(2):185–194.

88. Plant N. Use of reporter genes to measure xenobiotic-mediated activation of CYP gene transcription. Methods Mol Biol. 2006;320:343–354.

89. Wang YM, Ong SS, Chai SC, Chen T. Role of CAR and PXR in xenobiotic sensing and metabolism. Expert Opin Drug MetabToxicol. 2012;8(7):803–817.

90. Ma X., Idle JR, Gonzalez FJ The pregnane X receptor: From bench to bedside. Expert Opin Drug MetabToxicol. 2008;4(7):895–908.

91. Lin JH Cyp induction-mediated drug interactions: *In vitro* assessment and clinical implications. Pharm Res. 2006;23(6):1089–1116.

92. Ioannides C. Effect of diet and nutrition on the expression of cytochromes P-450. Xenobiotica, 1999;29(2):109–154.

93. Guengerich FP Influence of nutrients and other dietary materials on cytochrome P-450 enzymes. American Journal of Clinical Nutrition, 1995;61(Suppl.3):651S–658S.

94. Lammers LA, Achterbergh R., de Vries EM et al. Short-term fasting alters cytochrome P-450-mediated drug metabolism in humans. DrugMetabDispos. 2015;43:819–828.

95. Jang EH, Park YC, Chung WG. Effects of dietary supplements on induction and inhibition of cytochrome P-450s protein expression in rats. Food and Chemical Toxicology, 2004;42(11):1749–1756.

96. Hodges RE, Minich DM Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. J NutrMetab. 2015;760689.

97. Hakooz N., Hamdan I. Effects of dietary broccoli on human in vivo caffeine metabolism: a pilot study on a group of Jordanian volunteers. Current Drug Metabolism.2007;8(1):9–15.

98. Peterson S., Schwarz Y., Li SS et al. *CYP1A2*, *GSTM1*, and *GSTT1* polymorphisms and diet effects on CYP1A2 activity in a crossover feeding trial. Cancer Epidemiology Biomarkers and Prevention. 2009;18(11):3118–3125.

99. Walters DG, Young PJ, Agus C. et al. Cruciferous vegetable consumption alters the metabolism of the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP) in humans. Carcinogenesis. 2004;25(9):1659–1669.

100. Horn TL, Reichert MA, Bliss RL, Malejka-Giganti D. Modulations of P-450 mRNA in liver and mammary gland and P-450 activities and metabolism of estrogen in liver by treatment of rats with indole-3-carbinol. Biochemical Pharmacology, 2002;64(3):393–404.

101. Chow HHS, Garland LL, Hsu CH et al. Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. Cancer Prevention Research. 2010;3(9):1168–1175.

102. Aiyer HS, Gupta RC Berries and ellagic acid prevent estrogen-induced mammary tumorigenesis by modulating enzymes of estrogen metabolism. Cancer Prevention Research. 2010;3(6):727–737.

103. Chen Y., Xiao P., Ou-Yang DS et al. Simultaneous action of the flavonoid quercetin on cytochrome P-450 (CYP) 1a2, cyp2a6, n-acetyltransferase and xanthine oxidase activity in healthy volunteers. Clinical and Experimental Pharmacology and Physiology, 2009;36(8):828–833.

104. Lord RS, Bongiovanni B., Bralley JA Estrogen metabolism and the diet-cancer connection: rationale for assessing the ratio of urinary hydroxylated estrogen metabolites. Alternative Medicine Review, 2002;7(2):112–129.

105. Takemura H., Sakakibara H., Yamazaki S., Shimoi K. Breast cancer and flavonoids-a role in prevention. Current Pharmaceutical Design. 2013;19(34):6125–6132.

106. Bansal S.S., Kausar H., Vadhanam M.V. et al. Curcumin implants, not curcumin diet, inhibit estrogen-induced mammary carcinogenesis in ACI rats. Cancer Prevention Research, 2014;7(4):456–465.

107. Thapliyal R., Maru GB Inhibition of cytochrome P-450 isozymes by curcumins in vitro and in vivo. Food and Chemical Toxicology, 2001;39(6):541–547.

108. Yao HT, Hsu YR, Lii CK et al. Effect of commercially available green and black tea beverages on drug-metabolizing enzymes and oxidative stress in Wistar rats. Food and Chemical Toxicology, 2014;70:120–127.

109. Catterall F., McArdle NJ, Mitchell L. et al. Hepatic and intestinal cytochrome P-450 and conjugase activities in rats treated with black tea the a fulvins and the a flavins. Food and Chemical Toxicology, 2003;41(8):1141–1147.

110. Bogacz A., Mikołajczak PŁ, Mikołajczak PŁ et al. The influence of soybean extract on the expression level of selected drug transporters, transcription factors and cytochrome P-450 genes encoding phase I drug-metabolizing enzymes. GinekologiaPolska, 2014;85(5):348–353.

111. Zhang T., Jiang S., He C. et al. Black soybean seed coat polyphenols prevent B(a)P-induced DNA damage through modulating drug-metabolizing enzymes in HepG2 cells and ICR mice. Mutation Research, 2013;752(1-2):34–41.

112. Peng WX, Li HD, Zhou HH Effect of daidzein on CYP1A2 activity and pharmacokinetics of theophylline in healthy volunteers. European Journal of Clinical Pharmacology,2003;59(3):237–241.

113. Danielson PB The cytochrome P-450 superfamily: biochemistry, evolution and drug metabolism in humans. Current Drug Metabolism,2002;3(6):561–597.

114. Nissar AU, Farrukh MR, Kaiser PJet al. Effect of N-acetyl cysteine (NAC), an organosulfur compound from Allium plants, on experimentally induced hepatic prefibrogenic events in wistar rat. Phytomedicine, 2013;20(10):828–833.

115. Chen Q., Zhang T., Wang JF, Wei DQ Advances in human cytochrome P-450 and personalized medicine. Current Drug Metabolism,2011;12(5):436–444.

116. Rasmussen MK, Brunius C., Zamaratskaia G., Ekstrand B. Feeding dried chicory root to pigs decrease androstenone accumulation in fat by increasing hepatic 3β-hydroxysteroid dehydrogenase expression. Journal of SteroidBiochemistry and Molecular Biology,2012;130(1-2):90–95.

117. Lii CK, Tsai CW, Wu CC Garlic allyl sulfides display differential modulation of rat cytochrome P-450 2B1 and the placental form glutathione S-transferase in various organs. Journal of Agricultural and Food Chemistry,2006;54(14):5191–5196.

118. Debersac P., Heydel JM, Amiot MJ et al. Induction of cytochrome P-450 and/or detoxication enzymes by various extracts of rosemary: Description of specific patterns. Food and Chemical Toxicology,2001;39(9):907–918.

119. Al-Jenoobi FI, Al-Thukair AA, Alam MA et al. Effect of garden cress seeds powder and its alcoholic extract on the metabolic activity of CYP2D6 and CYP3A4. Evidence-Based Complementary and Alternative Medicine, 2014;2014:6.

120. Sheweita SA Drug-metabolizing enzymes: mechanisms and functions. Current Drug Metabolism, 2000;1(2):107–132.

121. Zgheib NK, Mitri Z., Geryess E., Noutsi P. Cytochrome P-450 2E1 (CYP2E1) genetic polymorphisms in a Lebanese population: frequency distribution and association with morbid diseases. Genetic Testing and Molecular Biomarkers, 2010;14(3):393–397.

122. González CA, Sala N., Capellá G. Genetic susceptibility and gastric cancer risk. International Journal of Cancer, 2002;100(3):249–260.

123. Armoni M., Harel C., Ramdas M., Karnieli E. CYP2E1 impairs GLUT4 gene expression and function: NRF2 as a possible mediator. Hormone and Metabolic Research, 2014;46(7):477–483.

124. Leclercq I., Desager JP, Horsmans Y. Inhibition of chlorzoxazone metabolism, a clinical probe for CYP2E1, by a single ingestion of watercress. Clinical Pharmacology and Therapeutics, 1998;64(2):144–149.

125. Loizou GD, Cocker J. The effects of alcohol and diallylsulphide on CYP2E1 activity in humans: a phenotyping study using chlorzoxazone. Human and Experimental Toxicology, 2001;20(7):321–327.

126. Celik G., Semiz A., Karakurt S. et al. A comparative study for the evaluation of two doses of ellagic acid on hepatic drug metabolizing and antioxidant enzymes in the rat. BioMed Research International, 2013;2013:9.

127. Park KA, Kweon S., Choi H. Anticarcinogenic effect and modification of cytochrome P450 2E1 by dietary garlic powder in diethylnitrosamine-initiated rat hepatocarcinogenesis. Journal of Biochemistry and Molecular Biology, 2002;35(6):615–622.

128. Tahir M., Sultana S. Chrysin modulates ethanol metabolism in Wistar rats: a promising role against organ toxicities. Alcohol and Alcoholism, 2011;46(4):383–392.

129. Lieber CS, Cao Q., Decarli LM et al. Role of medium-chain triglycerides in the alcohol-mediated cytochrome P-450 2E1 induction of mitochondria. Alcoholism: Clinical and Experimental Research, 2007;31(10):1660–1668.

130. Davenport D.M., Wargovich M.J. Modulation of cytochrome P-450 enzymes by organosulfur compounds from garlic. Food and Chemical Toxicology,2005;43(12):1753–1762.

131. Chen H.W., Tsai C.W., Yang J.J. et al. The combined effects of garlic oil and fish oil on the hepatic antioxidant and drug-metabolizing enzymes of rats. British Journal of Nutrition,2003;89(2):189–200.

132. Matsuda K., Nishimura Y., Kurata N. et al. Effects of continuous ingestion of herbal teas on intestinal CYP3A in the rat. Journal of Pharmacological Sciences, 2007;103(2):214–221.

133. Wu CC, Sheen LY, Chen HW et al. Differential effects of garlic oil and its three major organosulfur components on the hepatic detoxification system in rats. Journal of Agricultural and Food Chemistry,2002;50(2):378–383.

134. Park D., Jeon JH, Shin S. et al. Green tea extract increases cyclophosphamide-induced teratogenesis by modulating the expression of cytochrome P-450 mRNA. Reproductive Toxicology,2009;27(1):79–84.

135. Misaka S., Kawabe K., Onoue S. et al. Green tea extract affects the cytochrome P-450 3A activity and pharmacokinetics of simvastatin in rats. Drug Metabolism and Pharmacokinetics, 2013;28(6):514–518.

136. Umathe SN, Dixit PV, Kumar V. et al. Quercetin pretreatment increases the bioavailability of pioglitazone in rats: involvement of CYP3A inhibition. Biochemical Pharmacology, 2008;75(8):1670–1676.

137. Institute for Functional Medicine. Textbook of Functional Medicine. Boulder, Colo, USA: Johnston Printing; 2006.

138. Liu J., Tawa GJ, Wallqvist A. Identifying cytochrome P-450 functional networks and their allosteric regulatory elements. PLoS ONE, 2013;8(12) doi:10.1371/journal.pone.0081980.e81980.

139. Tanaka S., Uchida S., Miyakawa S. et al. Comparison of inhibitory duration of grapefruit juice on organic anion-transporting polypeptide and cytochrome P-450 3A4. Biological and Pharmaceutical Bulletin, 2013;36(12):1936–1941.

140. Hsieh YW, Huang CY, Yang SY et al. Oral intake of curcumin markedly activated CYP 3A4: in vivo and ex-vivo studies. Scientific Reports,2014;4(article 6587)

141. Linus Pauling Institute. Garlic and Organosulfur Compounds. Corvallis, Ore, USA: Micronutrient Information Center; 2008. http://lpi.oregonstate.edu/infocenter/phytochemicals/garlic/

142. Yoxall V., Kentish P., Coldham N.et al. Modulation of hepatic cytochromes P-450 and phase II enzymes by dietary doses of sulforaphane in rats: implications for its chemopreventive activity. International Journal of Cancer,2005;117(3):356–362.

143. Leibelt DA, Hedstrom OR, Fisher KA et al. Evaluation of chronic dietary exposure to indole-3-carbinol and absorption-enhanced 3,3′-diidolylmethane in Sprague-Dawley rats. Toxicological Sciences, 2003;74(1):10–21.

144. Ioannides C. Effect of diet and nutrition on the expression of cytochromes P-450. Xenobiotica, 1999;29(2):109–154.

145. Baer B., Rettie A. CYP4B1: an enigmatic P-450 at the interface between xenobiotic and endobiotic metabolism. Drug Metabolism Reviews, 2006;38(3):451–476.

146. Ye Z., Liu Z., Henderson A. et al. Increased CYP4B1 mRNA is associated with the inhibition of dextran sulfate sodium-induced colitis by caffeic acid in mice. Experimental Biology and Medicine (Maywood), 2009;234(6):606–616.

147. Bu-Abbas A., Clifford MN, Walker R., Ioannides C. Selective induction of rat hepatic CYP1 and CYP4 proteins and of peroxisomal proliferation by green tea. Carcinogenesis, 1994;15(11):2575–2579.

148. Sales NMR, Pelegrini PB, Goersch MC Nutrigenomics: definitions and advances of this new science. Journal of Nutrition and Metabolism, 2014;2014:6. doi: 10.1155/2014/202759.202759

149. Lim U., Song MA Dietary and lifestyle factors of DNA methylation. Methods in Molecular Biology, 2012;863:359–376.

150. Lang IA, Galloway TS, Scarlett A. et al. Association of urinary bisphenola concentration with medical disorders and laboratory abnormalities in adults. The Journal of the American Medical Association, 2008;300(11):1303–1310.

151. Rezg R., El-Fazaa S., Gharbi N., Mornagui B. Bisphenol A and human chronic diseases: current evidences, possible mechanisms, and future perspectives. Environment International, 2014;64:83–90.

152. Mostafalou S., Abdollahi M. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. Toxicology and Applied Pharmacology, 2013;268(2):157–177.

153. Magliano DJ, Loh VHY, Harding JL et al. Persistent organic pollutants and diabetes: a review of the epidemiological evidence. Diabetes & Metabolism, 2014;40(1):1–14.

154. Agarwal S., Zaman T., Tuzcu EM, Kapadia SR Heavy metals and cardiovascular disease: results from the National Health and Nutrition Examination Survey (NHANES) 1999–2006. Angiology, 2011;62(5):422–429.

155. Rissman EF, Adli M. Mini review: transgenerational epigenetic inheritance: focus on endocrine disrupting compounds. Endocrinology, 2014;155(8):2770–2780.

156. Walker DM, Gore AC Transgenerational neuroendocrine disruption of reproduction. Nature Reviews Endocrinology, 2011;7(4):197–207.

157. Toshiyuki Sakaki Practical Application of Cytochrome P-450. Biol. Pharm. Bull. 2012;35(6):844–849.

158. Cederbaum AI Molecular mechanisms of the microsomal mixed function oxidases and biological and pathological implications. Redox Biology, 2015;4:60–73.

159. Preissner SC, Hoffmann MF, Preissner R. et al. Polymorphic Cytochrome P-450 Enzymes (CYPs) and Their Role in Personalized Therapy. PLoS ONE, 2013;8(12): e82562. doi:10.1371/journal.pone.0082562.

HEAD III. THE WAYS OF MONOOXYGENASE ENZYMES REGULATION

Monooxygenase system, as an involved part of the body in the protection process by exogenous toxic substances and excess endogenous compounds, is one of the regulators of homeostasis, but at the same time and highly exposed to the regulation. In addition, this regulation has carried out in different ways. Under normal physiological conditions, the *de novo* of CYP synthesis index must be equal to decomposition parameter, but this parametric index *in vivo* in humans is usually absent. The back half-life of CYP has generally considered as a derivative of the induction of the enzyme or mechanism-based inhibition in *in vivo* studies [1, 2]. Thus, the estimated half-life in humans CYP2D6 has calculated as - 46.6-51 h [2, 3]. For of CYP3A4, the estimated half-life is negotiable 26-106 h [2], and CYP2C9, 2D6, 3A4 and 4A11 - 70-104 hours and CYP1A2, 2A6, 2B6, 2C8, 2C19, 2E1 and 3A5 - 23-36 hours [4]. Any impact that will change the stability and degradation of human CYP, change, and their half-life and thus alter drug metabolism. Genetic and epigenetic regulation of this process has carried out using a number of factors and receptors (Fig. 3.1), which ultimately lead to both an increase and a decrease in the activity of CYP.

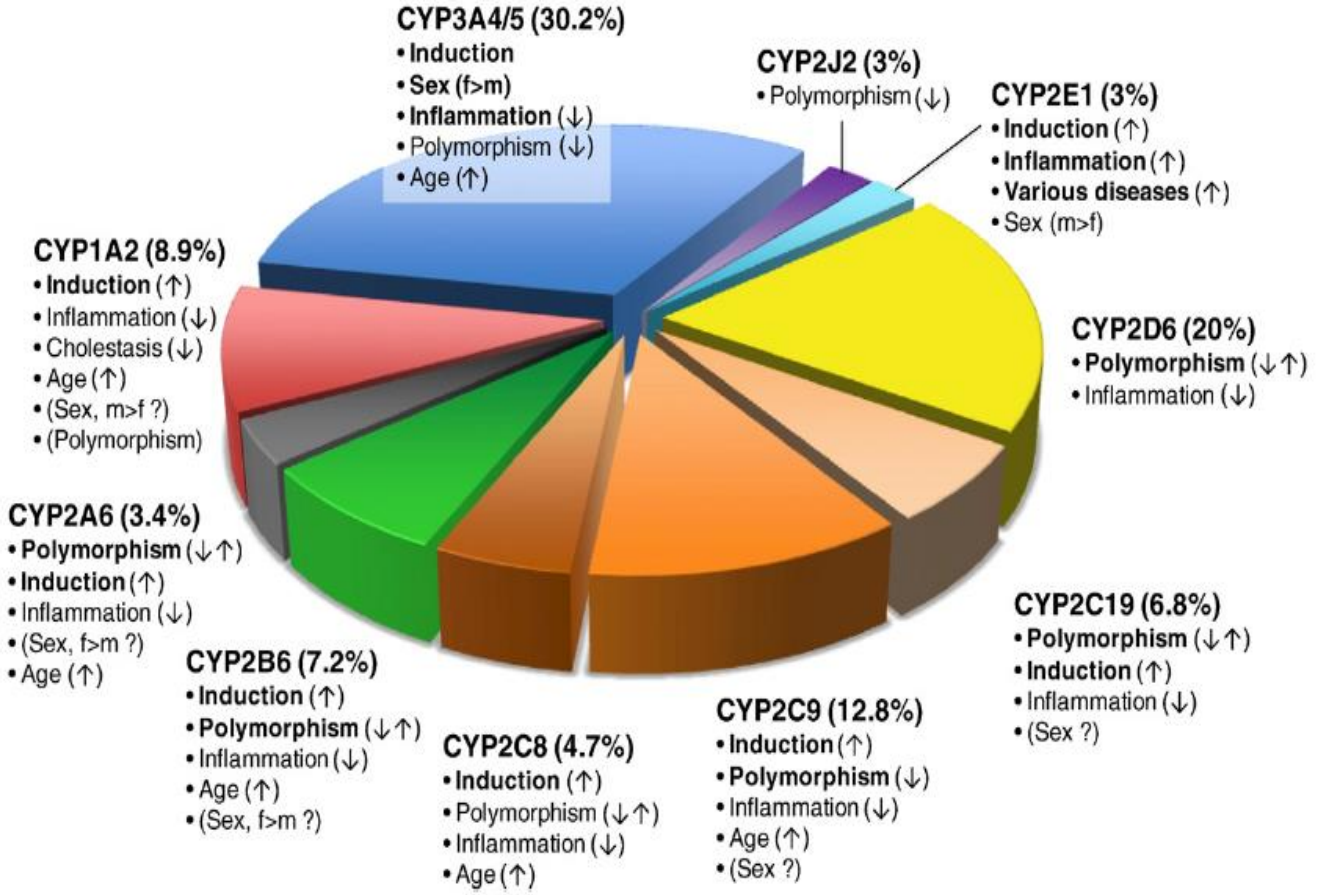


Figure 3.1 Possible changes in the activity of various CYP isoforms under the influence of physiological and non-physiological factors (scheme presented, respectively by [5]).

Nuclear receptors are ligand-dependent transcription factors that regulate the expression of genes involved in virtually all aspects of physiology and disease. Most members CYP1 families, CYP2, CYP3 and CYP4 regulated at transcriptional, post transcriptional and epigenetical levels [6].

Besides nuclear receptors, other indicators, such as cis- and trans-acting transcriptional factors, alternate splicing, RNA and protein stability, expression by regulatory RNA (e.g. mi RNA), such epigenetics as DNA methylation and histone modification can regulate phenotypic variation of human CYP genes [7].

Members of human subfamilies CYP1A, 2B, 2C, 3A and 4A - highly inducible by some xenobiotic, including drugs and some components of the environment, contributing to the development of large individual differences in the activity of these enzymes and interactions during medicals [5].

III.1. EPIGENETIC REGULATION OF CYP EXPRESSION AND ACTIVITY

III.1.1. Epigenetic regulation types of CYP expression

Expression of human CYP genes in the process of ontogenetic development and adult life undergoes epigenetic regulation pertaining to genome modifications that may affect gene expression and cellular phenotypes, but does not change the DNA sequence [8, 9, 10, 11].

DNA methylation and histone modification involved in the regulation of human CYP genes and they have mainly observed in cancers [12]. DNA methylation is associated with changes in gene expression levels in during the development period between human fetal and adult liver [13]. This analysis identified 657 differentially methylated genes only in adult liver, which were enriched binding sites for the transcription factor, HNF-1α and HNF-4α. Most drug-metabolizing CYP genes, such as, CYP1A2, 2D6 and 3A4, not expressed during the differentiation of human embryonic stem cells into hepatocytes *in vitro* [14].

Thus, CYP2D6 inhibitory epigenetic regulation of hepatocyte occurred from human embryonic stem cells is associated with transcriptional inactivation of the gene because of hypermethylated CpG islands and permissive histone modifications. Combinatorial inhibition of DNA methyltransferases and histone deacetylases increased copy number of CYP2D6 [14]. These data suggest the possibility that epigenetic modifications such as DNA methylation and histone modification can modulate the expression of CYP2D6.

Several studies point to the miRNAs involved in the regulation of human CYP enzymes [8, 15, 16, 17, 18]. Example, Tsuchiya et al. [19] reported that CYP1B1 are post-transcriptional regulated by miR-27b. CYP2E1 is regulated by miR-378 [20], miR-892a regulates of CYP1A1 [21], a miR-130b suppresses of CYP2C9 [22]. Different programs have can be used to predict the target miRNAs or miRNAs, which could regulate specific gene. Using the program Target Scan 6.2 (http: //www.targetscan.org/), revealed that miR-140-3p, miR-149, miR-1321, miR-3191, miR-4505, miR-4700-5p and the like may be regulate CYP2D6. However, the predicted data have confirmed by functional experiments.

Expression levels of mRNA and CYP2D6 activity in good agreement with each other in in vitro and in vivo conditions [23, 24], the fluctuation of the correlation coefficient of 0.71 to 0.91. This high correlation between mRNA levels and enzyme activity was typical for CYP3A4, 1A2, 2B6 and 2C9 [25] whose activity levels have controlled by transcriptional regulation of genes. These the results suggest that different transcriptional regulation of CYP2D6 may contribute to high individual variability in their activity. Hepatocyte nuclear factor (HNF-4α) - a member of the nuclear receptor

superfamily and has expressed in limited quantities, mostly in the liver, intestine, kidney and pancreas [26]. It plays an important role in the regulation of many liver-specific genes, such as encoding apolipoprotein, blood clotting parameters and CYP, which are involved in lipid transport and metabolism of glucose metabolism of drugs and blood clotting. HNF-4α is required for PXR and CAR-mediated transcriptional activation of CYP3A4 [27]. Transcriptional activation of CYP2C9, 1A1 and 1A2 HNF-4α requires PGC-1a and SRC-1 [28]. PGC-1a also shows a moderate effect in the activation of CYP3A4, 3A5 and 2D6.

Binding element of HNF-4α stored in the proximal promoter regions more than 20 CYP2 genes. Jover et al. [29] demonstrated on human hepatocytes that HNF-4α play-based role in the regulation of the P-450 genes, including CYP3A4, 3A5, 2A6, 2B6, 2C9 and 2D6. Kamiyama et al. [30] found that HNF-4α inhibition causes a decrease in the levels of mRNA CYP2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4; UGT1A1 and 1A9, and PXR and CAR. Furthermore, removal of HNF-4α reduces debrisoquine 4-hydroxylase activity of CYP2D6 in humanized mice by more than 50% [31]. These data indicate that HNF-4α can act as a common regulator of liver-specific transcription of many genes P-450.

CYP2D6 gene is inhibited by nitric oxide at transcriptional level in HepG2 cells and the donor of nitric oxide (±) -N-[(E)-4-ethyl-2-[(Z)-hydroxyimino]-5-nitro-3-hexene-l-yl]-3-pyridine carboxamide (NOR4), reduces the expression of mRNA CYP2D6 concentration-dependent manner [32]. Further studies indicate that the DNA-binding activity of HNF-4α directly inhibited nitric oxide donors: S-nitrosoglutathione and S-nitroso-N-acetyl-penicillamine in a concentration-dependent manner [32]; mutation of HNF-4α-binding sites in the promoter CYP2D6 partially restores activity of promoter inhibition of nitric oxide donors. An inhibitor of guanylic cyclase does not prevent suppression of activity CYP2D6S nitrosoglutathione promoter, indicating that inhibition of CYP2D6 activity through the promoter of nitrogen oxide guanylate cyclase-independent pathway [32].

Down regulation of cytochrome P-450 with involving active oxygen (AO) in conditions of oxidative stress may occur at the transcriptional level through the inactivation of nuclear factor NF1 (nuclear factor 1), or by strengthening the proteasome enzyme degradation. Glucocorticoids, pro-inflammatory cytokines (tumor necrosis factor-α, interferon-γ, interleukins 1, 6, 11), growth factors, bacterial lipopolysaccharides inhibit gene expression of many isoforms of cytochrome P450 - CYP1A, CYP3A, CYP2B, CYP2E. This action can have realized through strengthening of AO production and inactivation of the redox-sensitive factor NF1 [33].

In regulation of gene expression of different P-450 isoforms the NF1 transcription factor acts synergistically with polycyclic aromatic carbohydrates receptor (AhR); in its structure it contains a cysteine residue Cys427, which upon oxidation reduced the binding NF1 with regulatory DNA site [34]. Accordingly, the addition H_2O_2 or an inhibitor of catalase 3-amino-1,2,4-triazole to primary rat hepatocytes in phenobarbital-containing medium causes a decrease in the mRNA level of cytochrome CYP2B1, and the addition of N-acetyl cysteine at a concentration of greater than 5 mM - increase in 5-10 fold [35]. AO production by microsomal monooxygenase cause oxidative modification and degradation of proteins, including cytochrome P-450 [36, 37].

Cytochrome P-450 2E1 has characterized by the shortest lifetime in cells compared to the other P-450 isoforms (CYP1A1, CYP1A2, CYP2B1, CYP2B2 and CYP3A). In the

absence of oxidation substrate CYP2E1 degradation in rat hepatic microsomes occurs on biphasic variant and are characterized by a twofold reduction of cytochrome content of 6-7 hours, the presence of ethanol increases the time of cytochrome 50% destruction rate to 37 hours [38]. CYP2E1 is highly sensitive to the damaging action of the AO then in similar conditions; the albumin structure did not change [36]. The presence of NADPH (1 mM), increases the rate of CYP2E1 degradation in human hepatic microsomal fractions; antioxidant Trolox (50 mcM) and α-tocopherol (20 mcM) and iron ions chelators - deferoxamine (40 mcM) and EDTA (100 mcM) inhibit of CYP2E1 destruction [37]. In addition to the action by NF1 transcription factor and increased proteasome degradation, AO can reduce the expression of cytochrome P450 and other enzymes. The transcriptional activity its genes checked at AhR participation or via activation of NF-kB transcription factor [39].

Most of xenobiotics/drugs, environmental chemicals, and many endobiotics are metabolized by detoxification ways controlled xenobiotic receptors.

III.1.2. Role of pregnane X receptor in CYP enzymes regulation

In mammals, the main receptors of xenobiotic are pregnane X receptor (PXR), constitutive androstane receptor (CAR) and the aryl hydrocarbon receptor (AhR). Ligand-dependent, orthologous human PXR and CAR, DHR has been identified in Drosophila [40], suggesting evolutionary conservation of xenobiotic receptor to interact with harmful xenobiotic. PXR - xenobiotic primary receptor ligands that cover a wide variety of structural components rank of endogenous and exogenous sources, which include drugs, chemicals and environmental bile acids [41]. PXR adjustment cytochrome P-450 3A4 (CYP3A4) plays an important role in the metabolism of more than 50% of clinical drugs [42]. Many PXR regulate such genes are CYP3A, CYP2C and UGT1A, which are well known for their importance in drug metabolism and adverse effects (Figure 3.2.).

In addition to the direct connection and activation of PXR, many xenobiotic change multiple kinase pathways, included in the post-translational modification PXR, thus leading to changes in the PXR-transcriptional activity and contributing to drug interactions [43].

In addition to its pivotal role in the regulation of xenobiotics metabolism, PXR also interacts with the metabolism of endogenous components and inflammation processes [45-47]. It has shown that PXR is also involved in the modulation of hepatic glucose and lipid metabolism [48-50], bone homeostasis [51], endocrine homeostasis [52] and other processes [50, 51, 53, 54].

It is believed that PXR gene is pleiotropic regulator and, in addition, the well-established role in the regulation of xenobiotics metabolism, provides regulation of physiological and pathophysiological processes, including cell proliferation, carcinogenesis, inflammatory responses, homeostasis of cholesterol, lipids and energy [41, 53]. These first discovered PXR functions, combined with a wide variety of its ligand, PXR make an attractive therapeutic target for the treatment of diseases [55, 56].

The cloning and initial characterization of PXR had performed in 1998 [57]. Identification of critical sensor xenobiotic facilitated the study of the regulatory mechanism of critical drug-metabolizing enzymes and transporters. Distal regulatory module (-8 kb from start site of the transcription; TSS) CYP3A4 gene proved critical for the regulation of PXR [58].

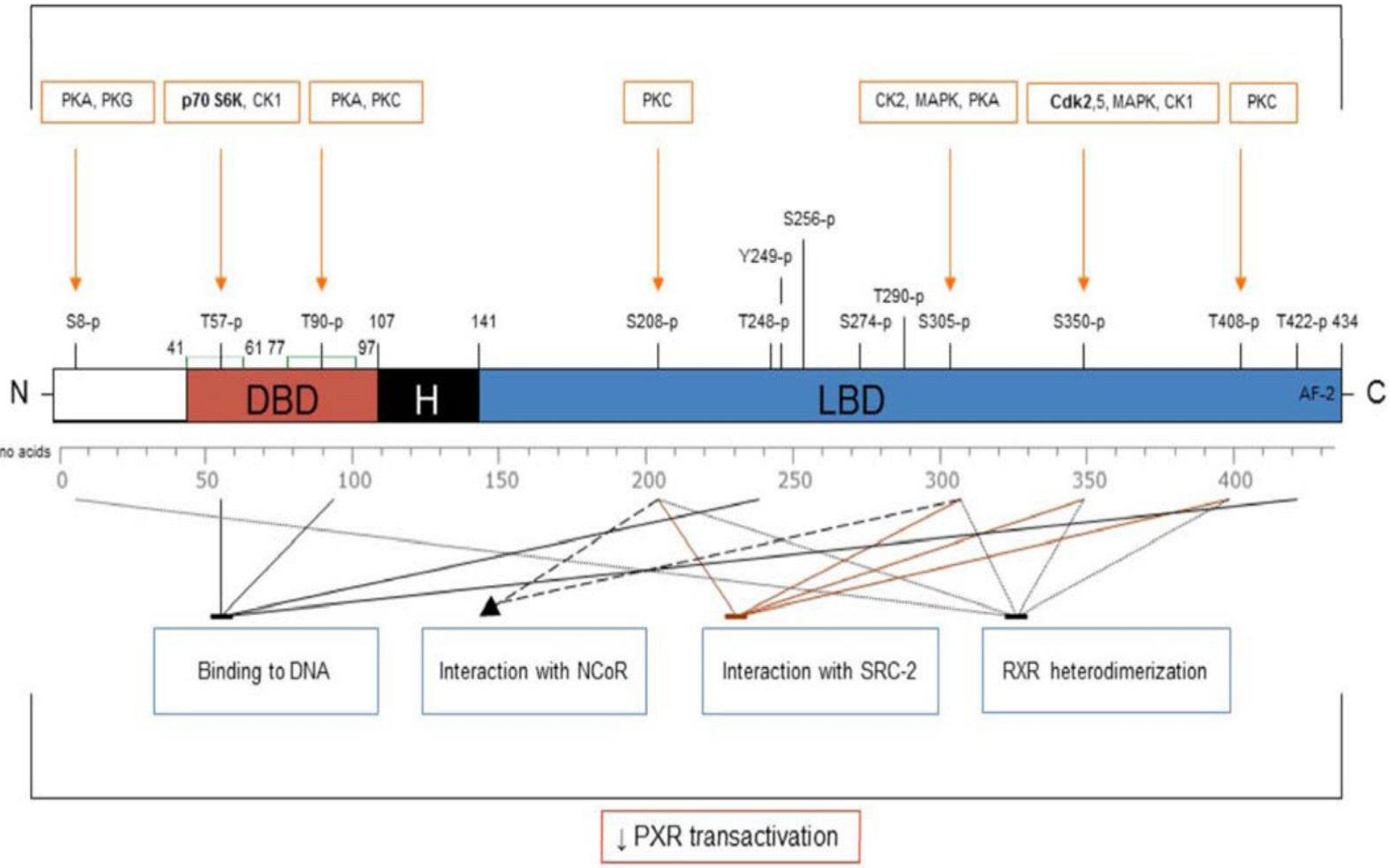


Figure 3.2. Way of pregnane X receptor functioning

Note: N-terminal region of human PXR includes DNA-associated domain (DBD), which is attached to the ligand-binding domain (LBD) and activates the hinge region (H) functions 2 (AF2), located on the C-terminal respectively region. Presented appropriately by [41].

Evolutionary preserved motifs of zinc finger lighted by green color; orange arrows [44] indicate predictive phosphorylation sites for protein kinases (orange squares) in the human PXR. Protein kinases, by which phosphorylation specific sites within human PXR were important for their effect on PXR-mediated transcriptional activity, are in bold.

Effects of site-specific phosphorylation of human PXR such as, DNA, binding, RXR dimerization and co-regulator interaction are depicted as blue squares; an arrow indicates the activation; stop bar means suppression.

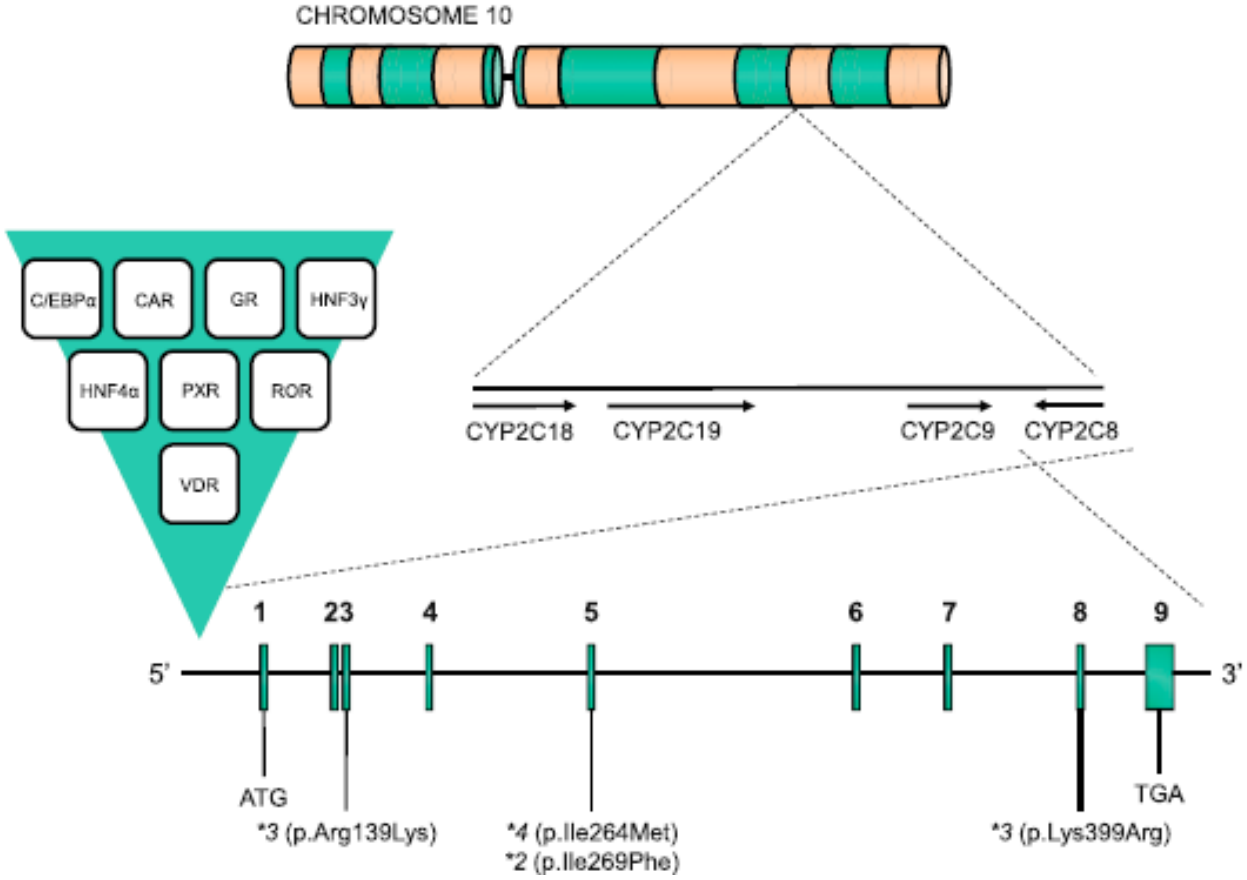


Figure 3.3. Localization of regulatory region of CYP2C8 gene.

Note: The CYP2C8 gene is located to the CYP2C gene cluster on chromosome 10. C/EBPα, CCAAT/enhancer binding protein α; CAR, constitutive androstane receptor; GR, glucocorticoid receptor; HNF, hepatic nuclear factor; PXR, pregnane X receptor; ROR, retinoic acid-related orphan receptor; VDR, receptor of vitamin D. Presented respectively by [63].

Further characterization of CYP3A4 on PXR-related places has led to the identification of additional distally linked module (between -10.5 and -11.4 kb from TSS) as a constitutive hepatic enhancer module [59]. These PXR-connected modules can

differentially affect the expression of genes regulated through interaction with a preferential correlates, such as hepatocyte nuclear factor 4 alpha (HNF-4α) [60]. A recent study, based on a set of experiments with chromatin immune-precipitation (ChIP)-seq and ChIP-chip showed that (NR)-binding nuclear receptor regulatory modules places often located approximately – in 10 kb from TSS places; therefore, the existence of remote modules NRs, in fact, quite common [61]. In addition to rising regulatory regions, ChIP-seq analysis of mouse hepatic tissue also indicates the binding site, which is on the descending sequences, as well as in the intergenic regions [62].

In general, the transcriptional regulation of P-450 cytochromes, especially CYP2C8, has mediated through several transcriptional factors and certain nuclear receptors that may activate the appropriate responsive elements within the five '-flanking promoter region of the gene (Figure 3.3) [64-66]. Such factors/receptors include constitutive androstane receptor (CAR), pregnane X receptor (PXR), vitamin D receptor (VDR), glucocorticoid receptor (GR), hepatic nuclear factor-4α (HNF4α), HNF3g, CCAAT/enhancer binding protein α (C/EBPα), and retinoic acid-related orphan receptors (RORs).

Epigenome, the central stage of the adaptive responses to environmental change and gene-environment interaction is a driving force for the evolution of all organisms and this interaction requires that living organisms be very adaptable to the constantly changing environment. Adaptability depends on the plasticity of the epigenome, which has regulated by reversible changes in chromatin modifications and DNA methylation. The term epigenetics here related to the study of heritable changes in phenotype or gene expression caused by mechanisms other than changes in the basing DNA sequence and the epigenome refers to the states of potentially heritable epigenetic modifications of the genome. ”The composition of the epigenome within a given cell is a function of genetic determinants, lineage, and environment” [67]. If the genome is the hard-wired in primary sequences of DNA and relatively static, epigenome is the high ductiled and may be modified in steps of body development, cell medium and stimulus signaling through DNA methylation, chromatin modification and non-coding RNAs, including micro-RNA (mi RNA), which play an important role in regulating translation. Changes in the epigenome can be manifested itself through cellular mitotic division and become the basis for "epigenetic memory", and when the changes persist through meiotic phase, they subsequently become trans-generative.

Epigenome of PXR regulated genes can take several different epigenetic states. For example, the gene expression of CYP3A4, CYP3A5 and CYP3A7 in humans is regulated during organism development and in mice turns out that Cyp3a16 (neonatal isoform) and Cyp3a11 (adult isoform) genes are regulated through H3k27 (marker repression) and H3K4 (activation marker) histones triple methylation although the promoter methylation of DNA is apparently not included [68].

Epigenetically modulating agents, such as 5-aza-20- deoxycitidine that inhibit of DNA methylation and trichostatine A (TSA; inhibiting histone deacetylation) capable of changing the expression of CYP3A in the human hepatic cell line HepG2 [69]. Nuclear factors of kappa B is invoked (NF-kB) inflammatory cytokines can strongly suppress the expression of human CYP3A4 [45], and, reciprocally, PXR activation suppresses the inflammatory response through interaction with the NF-kB pathways [46]. It has established that PXR simulation also plays a role in suppressing the inflammatory

response [70]. PXR regulated genes, for example, of CYP3A4, in a given tissue or cell type may become unresponsive, responsive or sensitive (very responsive) to epigenetic regulation. With increasing age, people change and the levels of PXR and CYP3A4; amount of RNA (mRNA) PXR messengers and protein in the liver and intestine reach maximum levels in young adults (15-38 years) and then gradually decrease with age to less than half their maximum levels [71].

The mechanism of age-related decrease in the expression of PXR is not clear. It was revealed that a reversible methylation of CpG island in the PXR promoter controls the PXR levels in colon cells lines [72]; but to establish the role of CpG islands methylation in the process of age-related changes in the PXR level necessary to investigate further. Understanding of epigenetic mechanisms PXR-controlled drug metabolism network becomes important to put targeted pharmacologically questions. For example, does change the epigenomes by preliminary drugs exposition or cellular stimuluses (e.g., cytokines and growth hormone) to effect on the responses to following drug exposition? Does play role of genome epigenetic changes in the drug idiosyncrasy reaction?

III.1.3. Complexity of receptor regulation of CYP enzymes

Farnezoid X receptors (FXRs) are nuclear hormone receptors expressed in large amounts in the tissues of the body that are involved in the metabolism of bilirubin in the liver, intestines and kidneys [73-75]. Chenodeoxycholic acid and other bile acids are natural ligands of FXRs. FXRs inhibits expression of the gene encoding CYP7A1 (i.e. cholesterol 7α-hydroxylase), which is level-limiting enzyme in the biosynthesis of bile acids [74]. FXRs induce the expression of the SHP, which then operates to inhibit the transcription of the CYP7A1 gene. Like other nuclear receptors, FXR translocate to the cell nucleus to activate ligand binding and a dimer forming (heterodimer with RXR) and binds to hormone response element on DNA, which regulates the expression of its target genes [73]. Furthermore, FXRs plays a critical role in carbohydrate and lipid metabolism and regulation of insulin sensitivity [76]. FXRs also modulate the growth and regeneration processes on liver damage [77].

SHP is a typical target gene of FXRs, which serves as a bile-acid sensor in the liver [78, 79]. When hepatic bile-acid level is high in such pathological conditions as cirrhosis and cholestasis, the ligand-starting FXRs transactivate SHP promoter. SHP in turn suppresses the expression of its target genes, including in the homeostasis of bile acids in the liver and thus protects the liver from toxicity of bile acids excess [79]. SHP and FXRs role in bile acid homeostasis widely characterized by using selective agonists FXRs, such as, GW4064 (3- (2,6-dichloro-phenyl) -4- (30-carboxy-2-chlorostilben-4-yl) oxymethyl-5-isopropylisoxazole) and 6-ethyl-chenodeoxycholic acid (6-ECDCA; obethicholate acid or INT-747) [80].

Many FXR agonists are in development for the treatment of various liver or metabolic diseases, including primary biliary cirrhosis, NASH and diabetes type II. For example, obethicholate acid (i.e. the INT-747), a strong selective FXR agonist passed phase III trials for the treatment of non-cirrhotic, non-alcoholic steatohepatitis [81]. In this connection, FXR may be a useful therapeutic target for the treatment of non-alcoholic fatty and cholestasis liver diseases, but requires more clinical trials to establish its safety and effectiveness profiles.

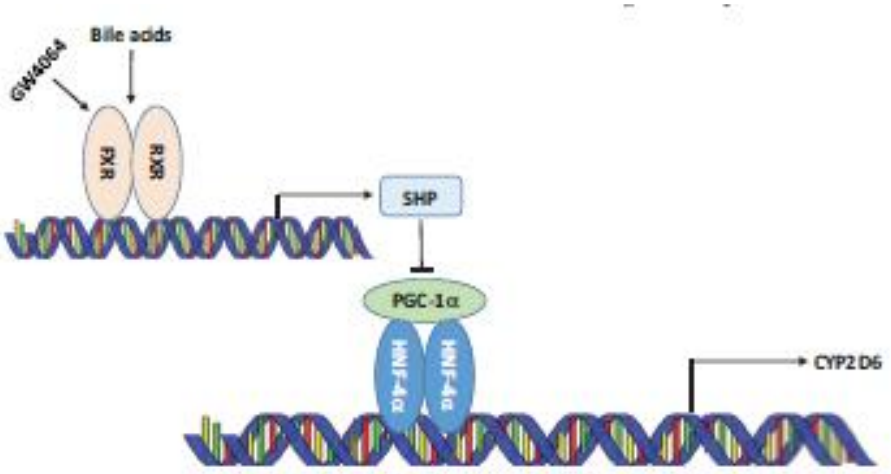


Figure 3.4. Regulation of CYP2D6 in human hepatocytes by HNF-4α, FXR and SHP (by Backman et al. [63])

After activation by endobiotic or xenobiotic, CAR, PXR and VDR form heterodimers with the retinoid X receptor while GR forms homodimers (Fig. 3.5.) [82]. These dimers have recognized by specific response elements within the promoter CYP2C8.

Highlights of FXR in the regulation of the functioning CYP can be demonstrated on the example of CYP2D6 (Fig. 3.4). Immediately regulatory element (DR) with a single nucleotide spacer disposed proximal promoter CYP2D6 gene region, plays an important role in the expression modulating CYP2D6, and HNF-4α is reacted with this binding element. PGC-1α is also showing moderate activating effect on CYP2D6. Trans-located to FXR agonists for FXR activation of the cell nucleus, for example, GW4064 and bile acid forms a heterodimer with RXR and binds to a hormone responsible for elements of DNA that stimulate expression of their target gene SHP, unique Orphan nuclear receptor. SHP inhibits HNF-4α-mediated transactivation CYP2D6 promoter and thus inhibits expression of hepatic CYP2D6 [63].

After activation, an orphan nuclear receptor HNF4α as a homodimer binds with a DR1 type element, and with Hep-G2 motif of specific P450 factor-1 [84], as HNF3g binds to DNA as a monomer [85]. At least two Hep-G2 specific P450 factor-1 motifs and several supposed HNF3g binding sites identified within the CYP2C8 promoter [64, 82, 85]. RORs - constitutively active orphan nuclear receptors, which are natural ligands, such as all-trans retinoid acid capable of affect their activity. In addition, RORs, apparently involved in the regulation of constitutive CYP2C8 and at least two ROR responsive elements identified in the promoter of the gene [86].

Evidence is accumulating that PXR functions have regulated by genetic/epigenetic mechanisms both at the level of transcription and translation. The model has deployed as a transcriptional and translational regulation of PXR has schematically illustrated in Figure 3.5. It showing that the static level of the transcriptase has achieved through balancing action genesis and degradation of RNA, which has actively regulated by PXR increase the understanding of genomic/epigenetic regulation of gene expression includes the identification of new drug-minded goal, which are regulatory components of the epigenome to treat diseases.

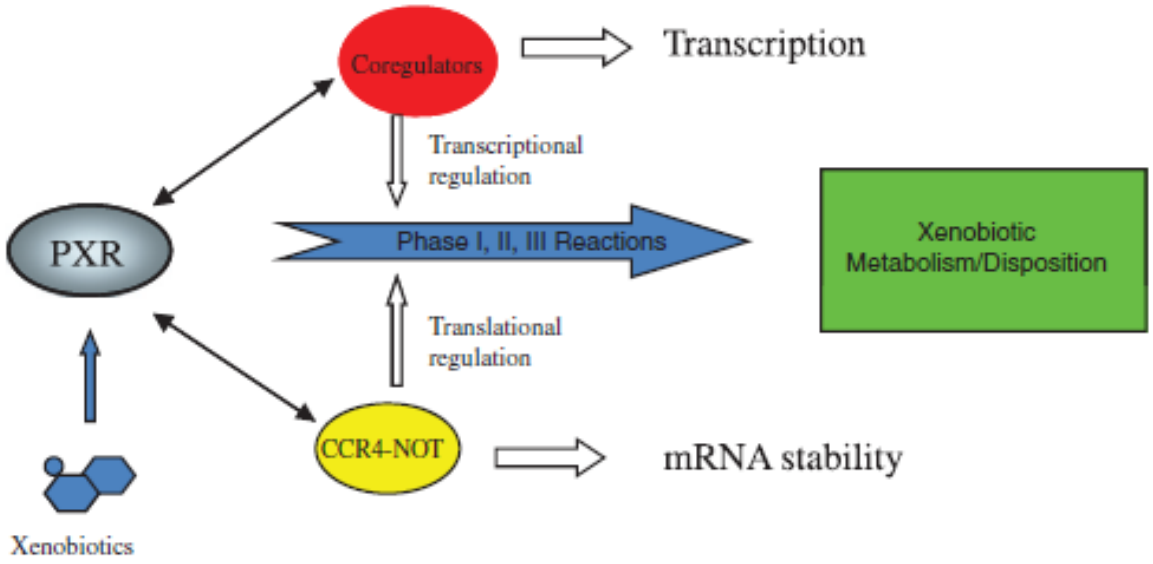


Figure 3.5. Model of coordinated transcriptional and translational regulation of gene expression by PXR (by Tian [83])

Note: Ligand-activated PXR/RXR complex interacts with the co-regulators and chromatin modification enzymes, such as, PRMT1, SRC1,2 and P300/CBP for transcriptional regulation, which generates mRNA. In the cytoplasm, PXR interacts with CCR4-NOT complex and regulates its deadenylase activity, which determines the stability of mRNA for PXR-regulated genes.

Post-translational modifications (PTMs) of proteins increase the functional diversity of the proteome covalent addition of functional groups or proteins, proteolysis cleavage of regulatory sub-blocks or expansion of the entire protein molecule [87-89]. These PTMs include phosphorylation, glycosylation, ubiquitination, nitrosylation, methylation, acetylation, proteolysis and lipidation. In fact, it has estimated that 5% of the proteome includes enzymes that perform more than 200 types of PTMs [87]. These enzymes include kinases, phosphatases, transferases and ligases that add or remove functional groups, proteins, lipids or sugar or amino acid side chains and proteases. Reversible protein phosphorylation, particularly serine, threonine or tyrosine are the most important and well-studied PTMs [87]. Phosphorylation plays a critical role in the regulation of many cellular processes including cell cycle, growth, differentiation and apoptosis [90-94]. Protein phosphorylation is the reversible PTM, which associated with kinases and phosphatases, respectively phosphorylated and dephosphorylated substrate. These two families of enzymes facilitate the dynamic nature of the phosphorylated proteins in a cell. Protein kinases have grouped into a subfamily, which show specificity for distinct catalytic domains, and include the tyrosine kinases or serine/threonine kinases [90, 91].

Research space orientation Cyp19α mutagenesis showed that Ser118 - as a potential site of phosphorylation and mutation reduces the stability and activity of the enzyme. Poor saved place N-glycosylation does not show any effect in the CYP19A1 activity [95], but saved place phosphorylation may result in reduced activity of the enzyme. In contrast, phosphorylation of serine and CYP11A1 threonine via PKC and CYP17A1 - PKA results in an increase of both enzymes activity [96].

With these, human liver samples obtained by surgery, it was found that CYP1A2 (Ser82), 2A6 (Ser131 and Thr488), 2B6 (Ser128), 2E1 (Ser129), 2C8 (Ser127), 2D6 (Ser135), 3A4 (Ser134), 3A7 (Ser135) and 8B1 (Ser127), were phosphorylated in vivo [97]. It turns out that the largest drug-metabolizing CYP already phosphorylated to some extent. Nevertheless, the functional effects of phosphorylation have not yet known.

In addition to the genetic regulation of the CYP family are subject to and influenced by many other endogenous and exogenous factors responsible for the regulation and non-genetic ways.

III.2. NON-GENETIC REGULATION OF MONOOXYGENASE ENZYMES ACTIVITY -PHYSIOLOGICAL FACTORS

III.2.1. Sexual activity determinism of monooxygenase enzymes

Gender effect on a number of important pharmacokinetic parameters, including body weight; body fat distribution, hepatic blood flow, as well as the expression of drug-metabolizing enzymes and transporters [98]. Sexual-specific expression of cytochrome P-450 is a common for laboratory animal, including rats and mice, and it was found that it is governed by different profiles of secretion of growth hormone (GH) in males and females [99, 100]. In humans, the differences were more subtle and their relevance in pharmacotherapy - material constant worry [98, 100, 101].

Most clinical studies indicate that women metabolize medications more quickly than men do. It is notably in cases of substrates essential drugs metabolized by cytochrome P-450, CYP3A4 (e.g. antipyrine, alfentanile, erythromycin, midazolam, verapamil [102]). Analysis of CYP3A4 in human liver actually showed about 2-fold higher protein levels in women compared to men's hepatic tissue [103-105].

It also revealed a significant difference at the level of mRNA and translated into the substrate obviously -dependent pharmacokinetic differences in the order of 20% - 50%. For other CYP, facts biased sexual expression has not found explanations and somewhat conflicting data published in the literature.

GH considered as a known endogenous factor in maintenance of sexually dimorphic expression of hepatic CYPs [106, 107]. Moreover, in all studied species, including humans [108, 109], GH has secreted in a somewhat sexually dimorphic pattern where the male profile characteristic of "episodic" and the female - "continuous" release of the hormone [106, 110]. For the most studied species - rats, GH secretion in males as occasional explosions about every 3-4 hours, with undetectable levels of GH in inotropic periods characterized. In female rats the hormone pulses are more frequent and irregular, and have a lower value than that of males, because the concentration of GH inotropic always measurable. GH exposition in continuous or female secretory profile "constants" produces a characteristic pattern of expression of CYP isoforms in females. Conversely, occasional or "pulsating" rhythm of GH secretion is responsible for the expression of CYP, observed in male rats [111].

In humans, these studies typically using GH-deficient subjects have shown that GH replacement can restore the activity of drug-metabolizing enzymes to the normal level [112]. Later, in vivo markers enzyme CYP3A4 to study even inductive effects of GH therapy had found in GH-deficient individuals. In one case, the inductive effects of daily injections sc-GH on CYP3A4-dependent activity was assessed separately on GH-deficient

boys and girls [113]. In another, differentiated effects of recovery of sexual-dependent profiles of GH (i.e., episodic and continuous) on of CYP3A4, estimated by erythromycin breath test, were found in the combined cohort of GH-deficient men and women [114]. While in vitro analysis, where we measured mRNA, protein, and the specific catalytic activity of CYP3A4 in a culture of hepatocytes, preferably from floors combination found that the constant exposure to GH pharmacological dose results in an inductive effect [115]. It was also studied the effect of such exposure physiologically occasional or continuous doses of human GH (hGH) to the expression levels of some CYP, including CYP3A4, in hepatocyte cultures isolated from donor [116] men and women. The presence or absence of dexamethasone (positive control for all members of the family of CYP3A) [115, 116] and regardless of sex, like the profile of a male episodic GH are suppressed the expression of CYP3A4, whereas such a continuous female profile provided GH inductive effect.

In addition to the observed differential effect of the male and female profiles of GH on the expression of CYP3A4, had marked by a clear significant sexually dimorphic answer some isoforms of CYP, in which episodic profile of GH was more overwhelming in hepatocytes men than women, while the continuous profile GH had more induction in hepatocytes women than men. In this respect, the same daily GH replacement regime was much more overwhelming for CYP3A4 enzyme activity in boys than girls [113]. Similar sexually- dimorphic inherent responses in humans for the same identified episodic GH mode were identified for IGF-I, bone mineralization and lipid metabolism, growth tempus and growth hormone - related protein, moreover much more in men than in women [117, 118].

Human CYP3A4 gene promoter is regulated especially mobile transactivation ability to directly or indirectly, more than a dozen nuclear receptors /transcription factors. Different ligands (e.g. xenobiotic, chemicals, environment, hormones and pathophysiological disorders), in varying degrees, induce the expression of CYP3A4 by activating a number of transcriptional networks, as well as some overlap action components range capable of transactivation various ensembles connecting elements on the promoter of CYP3A4 [59, 60, 119, 120]. Because CYP3A4, major CYP isoform representing advantageous detoxification and metabolic pathways, it has assumed that the functional redundancy and network synergies authorized promoter transactivation different modules in order to consistently guarantee a certain level of CYP3A4 induction to meet different needs [120]. It is noteworthy that all the identified transcriptional way, it turns out; contain binding nuclear receptor PXR, functioning as a heterodimer PXR RXRα and invariably HNF-4α [59, 60, 119, 120].

Cytochrome P450 - dependent aromatase (CYP19A1) is responsible for the finite-step conversion catalysis of androgens to estrogens [121]. The importance of this enzyme in the regulation of blood pressure observed in animal studies. Aromatase inhibitors have an antihypertensive effect in rats with genetic and experimental forms of hypertension [122, 123].

It is shown that the prevalence of polymorphisms of CYP19A1 gene (rs11575899 and rs10046), related to the level of estradiol and androgens in the serum of pre- and post-menopausal women [124-127]. Moreover, the effect of these genetic variants of CYP19A1 appeared dependent on fat accumulation in the body of women [127, 128]. In men and postmenopausal women, when estrogen synthesis in the ovaries was completed,

adipose tissue becomes the main source of estrogen and hence circulating estrogen levels have correlated with body mass index [128, 129].

It has found that there are statistically significant associations between markers in the gene CYP19A1 and blood pressure in women. At the same time, it did not show any evidence of communication CYP19A1 gene variants with the risk of hypertension in men [130]. According to one of the Framingham study (Framingham Heart Study), it confirms sexually specific contribution CYP19A1 gene polymorphism in blood pressure changes in women [131].

GnRH analogues (GnRH) can indirectly modify the total and 24-hour profile of secretion of growth hormone (GH). As a result, changes in GH levels can modify sexual-dependent fusion mechanism of cytochrome P-450 (CYP450), including transcriptional expression indices [132]. It found that setrorelix causes changes in the circadian pattern GH secretion and increases the concentration of GH in the blood. These changes, in turn, can cause increased expression of a specific "female» CYP450 (particularly CYP3A9), and indicators HNF4α/HNF6 transcription factors. Reducing the concentration of GH in the blood because of dalarelin effect may contribute to the inhibition of specific «female» CYP2C12 and CYP3A9 isoform and activator of transcription STAT5b. There were also slight changes in the sexual-independent protein expression of CYP3A1, caused analogs of GnRH. Apparently, in adult female rats HNF4α/HNF6 STAT5b and are critical for the regulation of GnRH antagonists, respectively/GH- and GnRH agonists/GH- dependent CYP450 expression patterns.

Wang et al. [133] found that women have a higher risk of medication-induced hepatotoxicity during antituberculosis therapy (HATT), than men. It has suggested that the only nucleotide polymorphism (SNP) genotypes and the resulting gene haplotype pregnane X receptor (PXR), which regulates the expression of cytochrome P-450 (CYP) 3A4, have sex-specific effects on HATT development risk. Logistic regression analysis found that the risk increased with HATT Women's AA genotype at rs2461823 and decreased when the female genotype AA at rs7643645 PXR gene. Haplotype analysis showed that female h001101 h000110 and haplotypes were associated with an increased risk of HATT. Identified predictors were significantly associated risk HATT female among 182 patients in the cohort confirm. On this basis, it has found that the two genotype and haplotype SNP PXR 2 affect only HATT risk women. This SNP PXR showed sexually specific effect, which contributes to an increased risk in women HATT.

It has known that an increase in the concentration of sex steroids during pregnancy or use of oral contraceptive steroids inhibits the oxidative metabolism of drugs [134]. Exogenous female sex steroid hormones used in oral contraceptive drugs significantly inhibit CYP2C19 activity [125-127, 130]. However, the effect of changes in the concentration of endogenous sex steroids during the menstrual cycle on CYP2C19 activity had not detected.

III.2.2. Pregnancy as a factor influencing on the activity of monooxygenase enzymes

Pregnancy has regarded as a physiological condition associated with changes in metabolism and distribution of drugs used in the clinic [135]. The activities of CYP3A4, 2D6, 2C9, 2B7 and UGT1A4 increase during gestation, whereas CYP1A2 and 2C19 activity decreased [135]. Like the liver, the placenta is also involved in drug metabolism

and CYP1A1, 2E1, 2F1, 3A4/3A5 and 4B1 has expressed in the placenta at significantly lower levels than in the liver [136, 137].

It has known that pregnancy induces hepatic CYP2D6 mediated metabolism of medications [138]. For example, the plasma clearance of metoprolol increased from two to 13 times during the pregnancy, regarding postnatal period. However, there was no induction of gene Cyp2d [139] in pregnant rats, whereas the expression and activity of murine Cyp2d11, 2d22, 2d26, and 2d40 were significantly increased [140]. Estimated charge element of RA has identified within the Cyp2d40 promoter, and CYP2d40 mRNA is consistent with Cyp26a1 and Rarb [140]. This probably reflects the large differences between mice, rats and humans in the authorized sequences of regulatory regions of genes encoding CYP enzymes.

In CYP2D6 humanized transgenic mice whose genome a 2.5-kb band above its regulatory region embedded human CYP2D6 gene, CYP2D6 expression during pregnancy increases almost 4 times [141]. This has accompanied by increasing in use of HNF-4α in the CYP2D6 promoter. Increased activity of HNF-4α during pregnancy has partially accompanied by a decrease in the expression of SHP [141], co-repressor capable inhibit HNF-4α activity through physical interaction. Suppression of SHP expression during pregnancy is associated with a decrease in RA level in the liver, which has can be correlated, with an increase in the hepatic expression of CYP26A1.

In mice with hepatic Hnf-4α knockdown is prevented pregnancy mediated increase in Cyp2d40 expression. Data from transient transfection, estimated by reporter's promoter and shifts in electrophoretic mobility indicate that Hnf-4α has trans-activated Cyp2d40 promoter through direct communication with the -117/-105 of the gene. Chromatin immunoprecipitation has shown by means of a 2.3-fold increase in Hnf-4α attraction to the Cyp2d40 promoter during pregnancy [142]. These data indicate that the expression of human CYP2D6 and mouse Cyp2d40 increased during pregnancy due to transactivation of HNF-4α. CYP2D40 highly homologous (i.e. 81%) by CYP2D6, and this suggests that CYP2D40 can play a similar role of CYP2D6, participating in drug detoxification in the liver and modulating the function of the brain.

Further microarray studies with humanized CYP2D6 transgenic mice have shown that the levels of seven transcription factors, namely: activating transcription factor 5 (ATF5), early growth response 1 (EGR1), FOXA3, JUNB, KLF9, KLF10 and REV-ERBα, increase in liver of mice during pregnancy [143]. KLF9 itself is a weak trans-activator of CYP2D6 promoter, but significantly increases the CYP2D6 promoter transactivation by HNF-4α - a known transcriptional activator of CYP2D6 expression. The results of the deletion and mutations analysis of CYP2D6 promoter activity allowed to identify the supposed link KLF9 motif with -22/-14 region to be critical in the potentiation of HNF-4α-induced transactivation of CYP2D6 [143]. KLF9, a member of the KLF family of transcription factors, zinc finger DNA-bound proteins can either activate or inhibit the expression of the target gene promoter in the specific context. KLF9 is involved in cell differentiation of B-cells, keratinocytes and neurons. Biological action KLF9 mediated through a direct connection with the promoters of its target genes, such as, either of CYP1A1 or via co-activation of other transcription factors [144]. KLF9 is as a key transcriptional regulator for proliferation of the uterus endometrium cell, adhesion and differentiation of all factors which essential during pregnancy and switched in the

process of carcinogenesis [145, 146]. The endometrial cells, KLF9 bind to progesterone receptor and increase the transcriptional activation of target genes [147].

Increasing the HNF-4α CYP2D6 promoter transactivation in part triggered the decrease and increase of SHP KLF9v expression during pregnancy, but neither SHP, no KLF9 does not play an important role in modulating HNF-4α transactivation Cyp2d40 promoter in mice. This is due to potential differences in the promoter of sequence between CYP2D6 and mouse Cyp2d40, the resulting changes in the binding affinity SHP, KLF9 and HNF-4α. CYP2D6 promoter has binding sites for a plurality KLF9, which increases transactivation HNF-4α promoter, unlike Cyp2d40 mice [142]. To identify the molecular mechanisms underlying the regulation of CYP during pregnancy, further research has needed.

III.2.3. Age-related aspects of the monooxygenase enzymes activity regulation

There are significant changes in hepatic CYP expression and activity in ontogeny [148]. Differences metabolism of xenobiotic appear to due to age, most clearly seen in infants and the elderly.

Age is a well established an influential figure for the possibility of drug metabolism, especially in early life, which is pretty much low as possible drug metabolism. Because of the ethical and logical constraints on the implementation of studies in the pediatric population, studies have mainly performed on the expression and activity of CYP in the early development of the body of people since the birth of the child or to the fetus killed by abortion or malformations incompatible with life.

It has known that about 3% of all babies are born with one or more large birth defects [149, 150]. Although the risk of exposure "high-risk" teratogens, such as thalidomide or isotretinoin, is low, at present it is not clear that predisposes certain embryos to the harmful effects usually frequently used "moderate-risk" medications, such as anticonvulsants and delaying blood-clotting substances [151]. In the US, 7% of children identify developmental disorders to the age of one year, at 12-14% - to the beginning of the school period and from 17% to 18 years of age; see in this role, in utero exposure to drugs [152].

It is important to note that the same enzyme which is currently assumed that participate in the metabolic processes in complications of pregnancy (e.g., androgens, cholesterol, eicosanoids, estrogens, progestin, retinoid acid, thyroxin, vitamin D, etc.) is also performed critical role in the synthesis and catabolism of endogenous components important for the growth and development of the fetus [151]. Therefore, medications prescribed with therapeutic intentions may have the potential to disrupt normal cellular function through the competition with endogenous substrates and ligands.

In the neonatal period, it is the result of the immaturity of some enzyme systems, including cytochrome P-450 [153-155], which has fully developed only in the first year of life. It has shown that the system of cytochrome P-450 begins to appear at 3 months of fetal development alongside with appearance of the smooth endoplasmic reticulum. Its neonatal activity is generally lower than in adults. And besides, there is some specificity in the expression of specific isoforms, e.g.: CYP3A7 - originally expressed fetal form subfamilies of CYP3A, CYP1A2 and generally not expressed in newborns, making them susceptible to the toxic effects of such funds, as caffeine.

In newborns, the liver samples up to 7 days of age the expression of CYP2D6 exceed those in the first two trimesters, but was slightly higher than the samples of the third trimester of pregnancy [155], and further increases significantly with increasing age. Based on their data no difference in activity and expression of CYP2D6 in the period between the first weeks after birth, and third trimester of pregnancy, as well as the identification of a positive correlation between age and postnatal increase in its activity. Treluyer et al. [156] have suggested that there is a birth-dependent mechanism that regulates the expression of CYP2D6.

In another study, Blake et al. [157], using dextromethorphan as the test drug, reported CYP2D6 activity changes from 193 healthy infants during the first year of life. Activity dextromethorphan O-demethylation was detectable in infants aged 2 weeks and was associated with genotype of CYP2D6, and later, up to one year of age, there were no significant changes in its level. Apparently, a small sample of the object (for all seven groups with different age) representing early childhood and lack of ethnic data still does not allow to carry out an exhaustive analysis of the data to understand the key indicators that determine the ontogeny of CYP2D6.

There are no published data on changes in the metabolic activity of CYP3A in early childhood children. Since the enzymatic activity can substantially change during the ontogeny of short lengths, a study age activity can also lead to the identification of the important factors in the regulation of CYP3A.

The expression of this form of CYP in the fetal liver is considerably low down to undetectable levels in 36% of liver samples [158]. Subsequently CYP2B6 level is increases about 2-fold during the first month of life.

In assessing the role of pharmacogenomics in the fruit, identify the causes of birth defects, it is important to analyze the number of fetal tissue to changes in gene expression. Although the CYP genes have expressed mainly in the hepatic tissues, extrahepatic expression occurs in kidney, lung, heart, and in many other tissues, to date, it has not performed regularly.

For example, Bieche et al. [159] who studied the mRNA CYP 1, 2 and 3 in various human tissues, including fetal liver, showed that in contrast to adult liver, which expressed several CYP enzymes, CYP3A7 prevalent in fetal liver and has been almost exclusively in this tissue, although other fetal tissue have not been evaluated. Conversely, Gaedigk et al. [160] compared the expression of mRNA CYP2J2 in several fetal tissues and its comparable levels found in heart and fetal liver.

MOS system study in the antenatal period and carried out by us in the Tashkent Medical Institute. Because these studies have undertaken with a view to finding means and opportunities to prevent child deaths from respiratory distress syndrome and the effects of fetal growth retardation, attention had focused on the functional state of the liver and lungs in the pre- and postnatal development of the fetus. At the same time, along with the MOS, studied and surfactant-synthesizing condition of the lungs, since the main cause of death in premature infants was the morphological and functional immaturity of the lung tissue, causes the surfactant deficiency. It had found that the MOS inductors groups 1 and 3 (and glucocorticoid phenobarbital group) were able to stimulate the synthesis of the surfactant in the lungs, which proven in the experiment [161, 162]. However, for clinical use classical representatives of these groups were not suitable inducers, for a number of adverse effects. Therefore, it was tested and suggested for the purpose of drug

phenobarbital group - benzonal for which did not reveal any adverse effects, but has full inductive power for MOC and for the surfactant system [161, 162].

In particular, research in the conditions of the experiment on rats it was found that the ISO fetal lung in the last stages of pregnancy has a higher functional activity than MOS his liver and activity is comparable to ISO lung mother. However, in the lungs of the fetus in the pregnancy was detected surfactant deficiency. In the antenatal benzonal treatment, it found the increased MOS activity in liver tissue and fetal lung, and liver, lung and placenta parent organism. Simultaneously, the drug exerted a pronounced surfactant stimulating effect on the lungs of the fetus that has proven to change the phospholipid spectrum of light surfactant system [161].

These experimental results then had confirmed in a clinical setting in the development of respiratory distress syndrome and pulmonary atelectasis in infants and children born to pregnant women suffering from late toxicoses as the introduction of a single MOS inductor, and when it has combined with antioxidants [163, 164, 165].

The investigations of benzonal properties continued in postnatal infants with malnutrition. It had found that in animals with malnutrition postnatal depression marked monooxygenase enzymes in the liver that fails to address proper nutrition, but had restored to the control level with the additional use of benzonal and phytin [166, 167].

It has known that the elderly constitute a high-risk human populations and their drug therapy requires careful individualization of dosing. Now it becomes especially important due to the rapid aging of the population in developed countries. For people aged 65 and older account for 13% of the US population, but consume more than 30% of drugs prescribed by doctors, and more than 40% taken independently and in addition, more than half of them consume as many as five or more drugs simultaneously [168, 169].

In the elderly population, the ability to metabolize the drugs clearly decreases. This is particularly important for drugs with a narrow therapeutic window, including antidepressant and antipsychotic agents, blood coagulation inhibiting agents, and beta-blockers. The paracetamol and benzodiazepines clearance also becomes lower in older men. However, this can be not a consequence of a lower expression or activity of drug metabolizing enzymes.

The human liver investigations found a modest increase in the expression and activity of most CYP throughout life, especially of CYP2C9, which remained significant after adjustment for multiple factors, whereas the effect of age on CYP 1A2, 2A6, 2B6, 2C8, and 3A4 partially interacted with gender [105]. However, in the experiment, age-related changes in expression of genes involved in the metabolism of xenobiotics, had found in rats [170] and the long-lived mutant mice [171].

Other reasons for limiting the clearance of drugs in the elderly is polypharmacy, i.e. inhibition of enzymes due to co-administration of multiple potentially interacting drugs and reduction of hepatic blood flow and renal function [102]. The elderly are more likely to use age groups of 3 or more drugs at the same time, which leads to an increase in adverse events associated with taking the drug. For example, side effects and adverse drug reactions in the United States is 10 to 17% of calls to the older doctor.

Thus, age is an important factor in the change CYP enzyme activity. Underdeveloped system metabolism of foreign compounds in young children makes them particularly susceptible to a number of toxins. Such changes can have a profound effect in the therapeutic efficacy, as well as the risk of adverse drug actions in the fetus and child.

III.2.4. Stress as a major factor regulating the activity of monooxygenase enzymes

Among the factors that play a role in regulating cytochromes leading place takes stress [172-176]. Numerous investigations reported that the level of stress and emotional state could affect the health and development of the disease [177], because in the process of stress, homeostasis (stable state) of the organism subjected to threat. Under the influence of psychological or physical stress, and various behavioral and physiological processes have change in an attempt to restore homeostasis. Stress stimulates the effect of the main components of the stress system: brain elements, the corticotrophin - releasing hormone (CRH) system, the sympathetic nervous system with the peripheral specifies and pituitary-adrenal axis. Psychological stress is one of the most potent activator of the hypothalamic-pituitary-adrenal axis (HPA).

Peripheral adaptation has intended to induce the appropriate response, leading to the provision of essential energy sources to overcome the process that causes stress, which entails the movement of energy substrates from the storage areas to the bloodstream. The following stress cascade of metabolic, behavioral, and other neurobiological changes complemented by changes in some anabolic processes, such as digestion, growth, reproduction and immune function, which bring about their suppression. The both physical and emotional stress stimuluses drastically modify the function of various organs, including the liver - the main site of drug metabolism [173, 175].

Numerous clinical and experimental studies support the concept that the limitation of the response to stress is critical for the organism to avoid the negative effects of stress. Chronic activation of catabolic processes related to the stress response, may eventually become destructive and pathogenic. As such, prolonged exposure to physical or psychological stress connected to the pathophysiology of metabolic disruptions. Immunosuppression, followed by increased susceptibility to infections and cancer, as well as hypertension, slowing of growth and tissue regeneration, the formation of ulcers in the gastrointestinal tract and suppression of reproductive function are also included in the spectrum generated by the stress failure [178, 179].

Well documented that exposure to stress triggers a cascade of changes in various body functions to preserve the homeostasis, some of which the possibility can dramatically modify the metabolism of drugs in the liver [180-182].

The influence study of stress reactions on monooxygenase enzymes was for the first time undertaken in Tashkent city (Tashkent Medical Academy under the guidance of prof. Nadjimutdinov KN) in the 80-ies of the last century. During this period, only began revealing the multiplicity of cytochrome P-450 forms, but already in our research was conducted attempt a differentiated approach to the MOS under influence different factors. Thus, determining the activity of aminopyrine-N-demethylase (CYP 2C family), aniline hydroxylase (CYP 2E1, CYP 2C), NADPH cytochrome-c-reductase and the total content of P-450 cytochromes and b_5, in rats, depending on sex, age, properties of the nervous system, the treatment of various inducers and, the undertaking of castration, hormone replacement, stimulation and suppression of the nervous system different levels, it was possible to identify patterns of differential changes in the activity of various groups of cytochrome P-450 under the influence of various factors, in particular, stress factors. Studies with the differentiation of inducible, constitutive androgen and estrogen-

dependent forms, as well as alcohol-inducible CYP 2E1 isoform of cytochrome P-450 when animals of stressing led to the following results.

Immobilization stress (daily 3 or 6-hour immobilization animals for 3 or 6 days) contributed to the oppression of monooxygenase enzymes and reduce the total content of cytochrome P450 in the liver of male rats, the severity of which depended on the duration and frequency of impact stress-factor, and the degree of reduction of nonspecific resistance. It was found that the stress under the influence of sub-optimal temperature (cold and heat) of environment is characterized by a decrease in activity only aminopyrine-N-demethylase, which depends on the intensity of the stressor exposure. In female rats, changes in monooxygenase activity in response to stress exposure did not occur, but it is beginning to emerge after preliminary ovaryectomy, as in males. It is found that the mechanism of inhibition monooxygenase enzymes plays a role and increased levels of epinephrine in the blood of glucocorticoids, as well as the excitation of the sympathetic nervous system in response to stress factor [183].

More long unceasing immobilization by the content of the rats in the conditions of immobilization in close individual cells from 3 to 28 days led to a significant change. It is shown that hypokinesia leads to inhibition of the activity of a monooxygenase enzyme in the liver of male rats, which had a degree depending on the duration of exposure to the stress. Thus, these changes occurred according to the phase under stress with increased levels of epinephrine and glucocorticoids in the blood [184].

The degree of emotion of the body, determined by the severity of the reaction to the stress factor, it was playing a significant role in changing the MOS activity. For example, immobilization stress (discontinuous 3-hour 3-day immobilization) male's high emotional rats resulted in a more pronounced decrease in hepatic monooxygenase enzymes activity, compared to that of low emotional rats, but did not alter the activity of this system in the female, regardless of emotionality. Castration of rats with different emotional reactions led to a distortion of monooxygenase enzymes in response to immobilization stress. Character of monooxygenase enzyme reaction in ovaryectomized female to immobilization stress close to one in castrated low emotional male rats. It found that the observed changes during immobilization stress in rats with different emotionality due to their unequal sensitivity to catecholamine and steroid hormones. Inhibition of the activity of monooxygenase enzymes in the liver under the influence of stress mainly implemented in high emotional rats through modulation of the level of hormones, while low emotional - through activation of the sympathetic nervous system [185].

Our results show that the androgen-dependent constitutive isoforms of cytochrome P-450 are subject to considerable suppression effects under the influence of stress factors. These changes are consistent with the overall body's stress reaction and, apparently determined not only humoral and neurogenic factors, but also the degree of sensitivity of receptors.

In connection with the identified, to explore an interest aspects neuroregulation monooxygenase enzyme as previously focused on the humoral effects on them [186]. It found that the liver denervation leads to reduced activity of monooxygenase enzymes in male rats more pronounced in sympathectomy and its combination with parasympathetic nerves cutting (n. vagus). Pharmacological stimulation and blockade of various departments of the autonomic nervous system caused multidirectional changes in the activity of the MOS with more pronounced changes in the regulation of sympathetic

department directly dependent on the ratio of the activity of beta- and alpha-adrenergic receptors. In female rats, a similar exposure had no significant effect on the activity of the MOS. It was also established that the effect of implementing phenobarbital, methylcholantrene and glucocorticoid type of MOS inductors on the autonomic nervous system plays a significant role, and glucocorticoids realize their inductive effect through parasympathetic nerves, and the other inductors - through sympathetic.

The discovery and characterization of the different isoforms of CYP created now conditions for their separate study under the influence of various factors.

Thus, a number of studies have shown the effects of stress on the constitutive expression of CYP1A. It revealed that the repeated stress of mobility restrictions reduces CYP1A-catalyzed ethoxyrezorufin 7-dealkylase (EROD) activity in rat liver, whereas repeated exposure unpredictable mild stress increases it. Relatively CYP1A2, stress stimulates its constitutive expression in the liver of mice (~ 200% at mRNA and protein levels) [187, 188]. In addition, stress significantly stimulates CYP1A1 and CYP1A2 inducibility when exposed by PAH in rat liver (250% at mRNA and protein levels), whereas unpredictable mild stress has only little effect on it [173, 187, 189]. Psychological stress is seen as a critical factor in the regulation of constitutive and benzopyrene-induced CYP1A1/2 expression. Note that the effect of stress on CYP1A regulation depends on the variety and species belonging stress [173, 176, 190]. Differentiation CYP1A response to specific types of psychological stress may be due to differential neurobiological condition on these specific stress conditions. Species specificity in stress-induced regulatory modifications CYP1A may be associated with species neurochemical, neuroendocrine and behavioral and other physiological differences observed in response to stress, including species-specific differential sensitive to stressful stimuluses (Figure 3.6.) [191, 192]. Stress-mediated increase CYP1A inducibility upon exposure PAH toxicological paramount importance, since it indicates that exposure psychophysiological stress may further stimulate the production of PAH associated with carcinogenic metabolites and thus run carcinogenesis [193, 194].

There are some studies indicating a critical role of glucocorticoids main effectors stress response in regulating CYP microsomal enzymes (Figure 3.6.) [176]. Epinephrine, as well as an analogue of AMP, 8-BrcAMP inducible target genes in hepatocytes CAR, including Sult2A1 and UGT1A1, regulating the drug-metabolizing enzymes [195].

Several studies have clearly shown that stress is involved in the regulation of basic drug-metabolizing enzymes in the liver of rodents, including cytochromes CYP1A1, CYP1A2, Cyp2a5, CYP2B1/2, Cyp2j5, CYP3A4, CYP2C, CYP2D and CYP2E1 [172, 173, 176, 187, 191, 196]. According Zordoky and El-Kadi [197] in humans, several types of psychological stress lead to increased release of inflammatory mediators of oxidative stress and subsequently activate NF-kB, which in turn modifies the CYP regulation for post-transcriptional level or inducing oxygen saturation of heme or modifying CYP protein stability. Moreover, it revealed that the physiological changes that occur during surgical stress could lead to significant modifications in the regulation of various CYP [198].

Psychological stress - a significant regulator Cyp2a. In particular, it increases the stress limit Cyp2a5-dependent constitutive coumarin hydroxylation in the liver (~ 150%) and levels Cyp2a5 mRNA (~ 200%). It also enhances the 1,4-bis [2-(3,5-dichloropyridyloxy)] benzene (TCPOBOP) induced expression Cyp2a5 (~ 250% of the

activity and mRNA levels) [174, 199]. It is believed that psychological stress can trigger stimulate signaling pathways that play a critical role in the regulation Cyp2a exposure in individuals subjected TCPOBOP- drugs or other inducers CYP2A. This information should be taken into account, especially in cases where the use of coumarin products that have the ability to delay clotting.

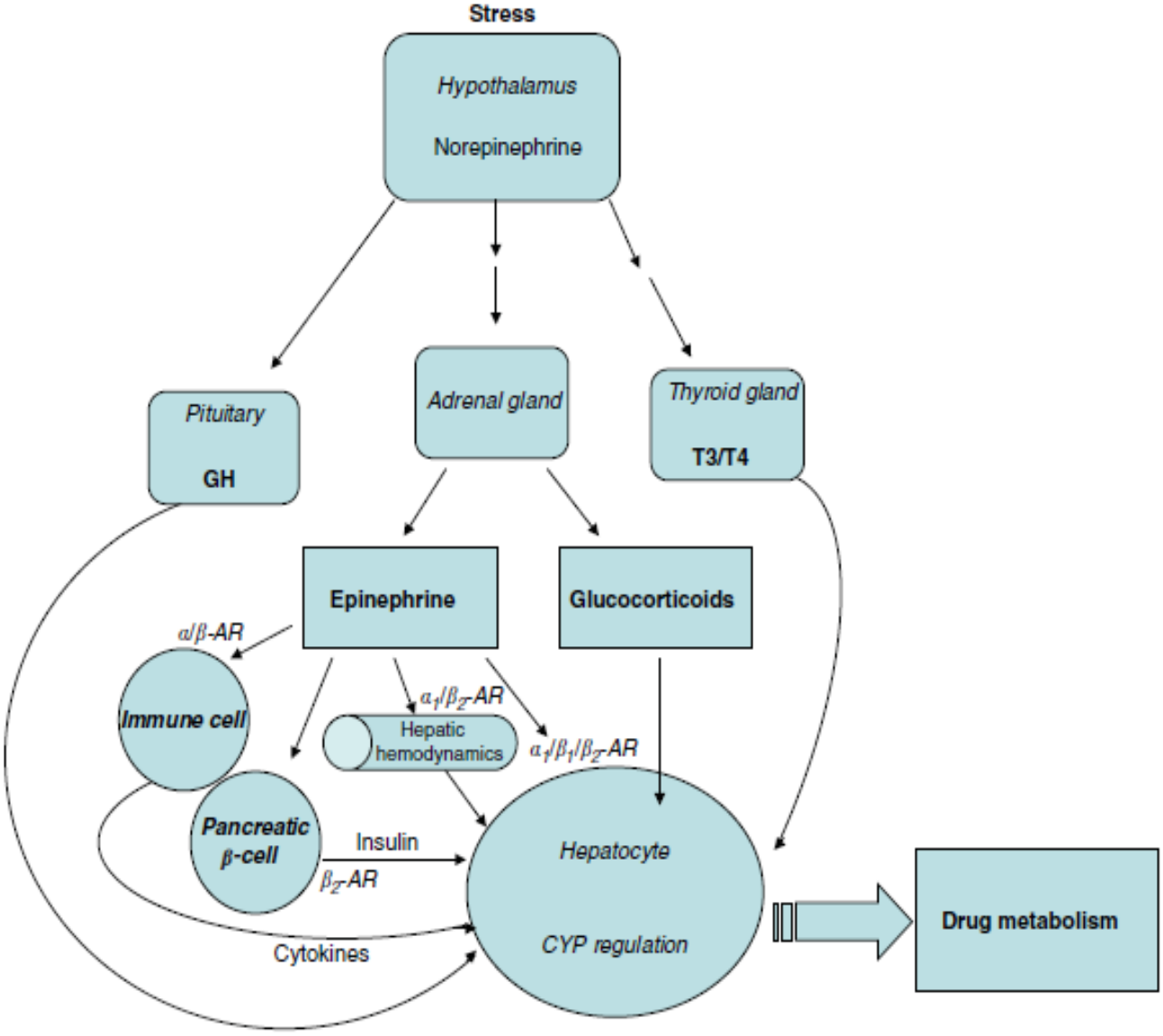


Figure 3.6. Schematic presentation of the major neuroendocrinological pathways involved in stress-mediated regulation of various CYP genes in the liver, the hypothalamic-pituitary-GH, the hypothalamic-pituitary-adrenal axis and thyroid hormones

Note: AR: adrenergic receptor; GH: growth hormone; PRL: prolactin; T3, T4: thyroid hormones. Reproduced respectively by [173].

Exposure to stress can significantly modify the expression CYP2B. In particular, the effects of repeated stress limit (animal model of psychological stress) significantly inhibits (50%) of the constitutive activity of CYP2B1/2- catalyzed pentoxyresorufin 7-dealkylase (the PROD) in the rat liver. At the same time, repeated exposure of rats occasional mild stress has no effect on the expression of CYP2B1/2. On the other hand, stress limitations led to increased CYP2B1/2 inducibility by benzopyrene (~ 200% at PROD activity level), whereas mild irregular stress had only a little effect [175]. These

data clearly show that the effect of stress on CYP2B regulation does stress the specific nature, in which the stress limits has a strong influence in this regulation, compared to mild irregular stress. Additionally, the mechanism underlying the stress limitations on CYP2B1/2 inducible effect is slightly different from that regulating constitutive expression of CYP2B1/2 [175]. In light of the variability CYP2B responses according type of stress, the data suggest that individuals under PAH exposure may experience greater induction of hepatic CYP2B expression, if they are simultaneously exposed to stress, which in turn lead to increased metabolism of CYP2B substrates with followed by an increased risk of drug therapy failure.

It found Cyp2C expression can also be modified by stress. Matamoros and Levine [175], using the three-day intraperitoneal injection of hypertonic (1.5 M) of saline, caused physical strain muscles, which ended significant decline in hepatic aminopyrine N-demethylation (the reaction of the enzyme is primarily carried out by CYP2C19 and CYP2B6 and then CYP2C8 and CYP2D6 [200]. It was reported also that the psychophysiological stress modifies the expression of CYP2C in the stress-specific manner. In particular, maternal stress deprivation early in life rats led to an increase in the expression of CYP2C11 and CYP3A1 in the liver of adult rats (~ 300% in the mRNA and protein level), whereas the impact on re-stress limit had no significant effect. For CYP3A2 in both kinds of stress observed increased expression. It has suggested that stress-induced effect in regulating CYP2C and CYP3A1 had can be mediated by epinephrine and glucocorticoid major peripheral effectors of the stress system [176]. Stress induced by epinephrine release from the adrenal medulla results in stimulation α_1- and $\beta_{1/2}$-ARs in the liver, the effect that initiates the activation of adenylyl cyclase and increased formation of cAMP that in turn, phosphorylates a protein kinase A (PKA).

On activation, of PKA phosphorylates CREB - nuclear transcription factor and thus starts the transcription of a CYP2C gene [176]. In addition, the hepatocyte processing with corticosterone leads to CYP2C11 stimulation (~ 300% at the mRNA level) [176]. Based in these particulars suggested that adrenergic substances with sympathomimetic properties and drugs that modify the status of the glucocorticoid could interfere with the regulation of CYP2C and therefore drastically increase the metabolism of CYP2C substrates, resulting in reduced efficacy of pharmacotherapy.

Despite intensive research, about any direct hormonal regulation has not been reported for CYP2D. The psychological stress has been shown to modify hepatic CYP2D expression in a stress-specific manner, but in the exact opposition that of CYP2C [176, 187].

Unlike the above described other CYP isoforms, CYP2E1-catalysed p-nitrophenol hydroxylation was suppressed in all stress models about half [172, 175].

Stress is able to change both the constitutive and induced expression of CYP. This property provides stress in the critical parameters determining the pharmacokinetic profile of drugs and, subsequently, the effects of drug therapy and toxicity results. Most studies that have investigated the role of stress in drug metabolism using experimental animal models. Of course, the conclusions derived from experimental studies cannot be directly extrapolated to humans, but they support the view that the stress profile of the patient should be taken into account when designing a therapeutic regimen. In particular, when it includes a life therapeutic agent values, drugs with little therapeutic window or with significant adversive effects.

REFERENCES

1. Yang J., Liao M., Shou M. et al. Cytochrome p450 turnover: Regulation of synthesis and degradation, methods for determining rates, and implications for the prediction of drug interactions. Curr Drug Metab. 2008;9:384–394.

2. Zhou ZW, Zhou SF Application of mechanism-based CYP inhibition for predicting drug-drug interactions. Expert Opin Drug Metab Toxicol. 2009;5:579–605.

3. Venkatakrishnan K., Obach RS In vitro-in vivo extrapolation of CYP2D6 inactivation by paroxetine: Prediction of nonstationary pharmacokinetics and drug interaction magnitude. Drug Metab Dispos. 2005;33:845–852.

4. Renwick AB, Watts PS, Edwards RJ. et al. Differential maintenance of cytochrome P450 enzymes in cultured precision-cut human liver slices. Drug Metab Dispos. 2000;28:1202–1209.

5. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138:103–141.

6. Zanger UM, Klein K., Thomas M. et al. Genetics, epigenetics, and regulation of drug-metabolizing cytochrome p450 enzymes. Clin Pharmacol Ther. 2014;95:258–261.

7. Wray GA, Hahn MW, Abouheif E et al. The evolution of transcriptional regulation in eukaryotes. Mol Biol Evol.2003;20:1377–1419.

8. Ingelman-Sundberg M., Zhong XB, Hankinson O. et al. Potential role of epigenetic mechanisms in the regulation of drug metabolism and transport. Drug Metab Dispos. 2013;41:1725–1731.

9. Kacevska M., Ivanov M., Ingelman-Sundberg M. Epigenetic dependent regulation of drug transport and metabolism: An update. Pharmacogenomics, 2012;13:1373–1385.

10. Kim IW, Han N., Burckart GJ, Oh JM Epigenetic changes in gene expression for drug-metabolizing enzymes and transporters. Pharmacotherapy, 2014;34:140–150.

11. Zhong XB, Leeder JS. Epigenetic regulation of ADME-related genes: Focus on drug metabolism and transport. Drug Metab Dispos. 2013;41:1721–1724.

12. Kim SJ, Kang HS, Jung SY et al. Methylation patterns of genes coding for drug-metabolizing enzymes in tamoxifen-resistant breast cancer tissues. J Mol Med (Berl), 2010;88:1123–1131.

13. Bonder MJ, Kasela S, Kals M et al. Genetic and epigenetic regulation of gene expression in fetal and adult human livers. BMC Genomics, 2014;15:860.

14. Park HJ, Choi YJ, Kim JW et al. Differences in the epigenetic regulation of cytochrome P450 genes between human embryonic stem cell-derived hepatocytes and primary hepatocytes. PLoS One, 2015;10:e0132992.

15. Ikemura K., Iwamoto T., Okuda M. MicroRNAs as regulators of drug transporters, drug-metabolizing enzymes, and tight junctions: Implication for intestinal barrier function. Pharmacol Ther. 2014;143:217–224.

16. Yu AM, Tian Y., Tu MJ et al MicroRNA Pharmacoepigenetics: Posttranscriptional Regulation Mechanisms behind Variable Drug Disposition and Strategy to Develop More Effective Therapy. Drug Metab Dispos. 2016;44(3):308-319.

17. Nakajima M., Yokoi T. MicroRNAs from biology to future pharmacotherapy: Regulation of cytochrome P450s and nuclear receptors. Pharmacol Ther. 2011;131:330–337.

18. Smutny T., Mani S., Pavek P. Post-translational and posttranscriptional modifications of pregnane X receptor (PXR) in regulation of the cytochrome P450 superfamily. Curr Drug Metab. 2013;14:1059–1069.

19. Tsuchiya Y., Nakajima M., Takagi S. et al. MicroRNA regulates the expression of human cytochrome P450 1B1. Cancer Res.2006;66:9090–9098.

20. Mohri T., Nakajima M., Fukami T. et al. Human CYP2E1 is regulated by miR-378. Biochem Pharmacol.2009;79:1045–1052.

21. Choi YM, An S., Lee EM et al. CYP1A1 is a target of miR-892amediatedpost-transcriptional repression. Int J Oncol. 2012;41:331–336.

22. Rieger JK, Reutter S., Hofmann U. et al. Inflammation-associated microRNA-130b down-regulates cytochrome P450 activities and directly targets CYP2C9. Drug Metab Dispos. 2015;43:884–888.

23. Kawakami H., Ohtsuki S., Kamiie J. et al. Simultaneous absolute quantification of 11 cytochrome P450 isoforms in human liver microsomes by liquid chromatography tandem mass spectrometry with in silico target peptide selection. J Pharm Sci. 2011;100:341–352.

24. Ohtsuki S., Schaefer O., Kawakami H. et al. Simultaneous absolute protein quantification of transporters, cytochromes P450, and UDP-glucuronosyl-transferases as a novel approach for the characterization of individual human liver: Comparison with mRNA levels and activities. Drug Metab Dispos. 2012;40:83–92.

25. Temesvari M., Kobori L., Paulik J. et al. Estimation of drug metabolizing capacity by cytochrome P450 genotyping and expression. J Pharmacol Exp Ther. 2012; 341:294–305.

26. Mendel DB, Crabtree GR. HNF-1, a member of a novel class of dimerizing homeodomain proteins. J Biol Chem. 1991;266:677–680.

27. Tirona RG, Lee W, Leake BF et al. The orphan nuclear receptorHNF4α determines PXR- and CAR-mediated xenobiotic induction of CYP3A4. Nat Med. 2003;9:220–224.

28. Martinez-Jimenez CP, Castell JV, Gomez-Lechon MJ, Jover R. Transcriptional activation of CYP2C9, CYP1A1, and CYP1A2 by hepatocyte nuclear factor 4a requires coactivators peroxisomal proliferator activated receptor-g coactivator 1a and steroid receptor coactivator 1. Mol Pharmacol. 2006;70:1681–1692.

29. Jover R., Bort R., Gomez-Lechon MJ, Castell JV Cytochrome P450 regulation by hepatocyte nuclear factor 4 in human hepatocytes: A study using adenovirus-mediated antisense targeting. Hepatology, 2001;33:668–675.

30. Kamiyama Y., Matsubara T., Yoshinari K. et al. Role of human hepatocyte nuclear factor 4a in the expression of drug-metabolizing enzymes and transporters in human hepatocytes assessed by use of small interfering RNA. Drug Metab Pharmacokinet. 2007;22:287–298.

31. Corchero J., Granvil CP, Akiyama TE et al. The CYP2D6 humanized mouse: Effect of the human CYP2D6 transgene and HNF4α on the disposition of debrisoquine in the mouse. Mol Pharmacol. 2001;60:1260–1267.

32. Hara H., Adachi T. Contribution of hepatocyte nuclear factor-4 to down-regulation of CYP2D6 gene expression by nitric oxide. Mol Pharmacol. 2002;61:194–200.

33. Morel Y., Barouki R. Repression of gene expression by oxidative stress. Biochem J. 1999;342:481-496.

34. Morel Y., Coumoul X., Nalpas A., Barouki R. Nuclear factor I/CCAAT box transcription factor trans-activating domain is a negative sensor of cellular stress. Mol. Pharmacol. 2000;58:1239-1246.

35. Hirsch-Ernst KI, Schlaefer K., Bauer D. et al. Repression of phenobarbital-dependent CYP2B1 mRNA induction by reactive oxygen species in primary rat hepatocyte cultures. Mol. Pharmacol. 2001;59:1402-1409.

36. Choi DW, Leininger-Muller B., Wellman M. et al. Cytochrome P-450-mediated differential oxidative modification of proteins: albumin, apolipoprotein E, and CYP2E1 as targets. J. Toxicol. Environ. Health A, 2004;67:2061-2071.

37. Goasduff T., Cederbaum AI NADPH-dependent microsomal electron transfer increases degradation of CYP2E1 by the proteasome complex: role of reactive oxygen species. Arch. Biochem. Biophys. 1999;370:258-270.

38. Roberts BJ, Song BJ, Soh Y. et al. Ethanol induces CYP2E1 by protein stabilization. Role of ubiquitin conjugation in the rapid degradation of CYP2E1. J. Biol. Chem. 1995;270:29632-29635.

39. Gharavi N., El-Kadi AO Down-regulation of aryl hydrocarbon receptor-regulated genes by tumor necrosis factor-αand lipopolysaccharide in murine hepatoma Hepa 1c1c7 cells. J. Pharm. Sci. 2005;94:493-506.

40. King-Jones K, Horner MA, Lam G, Thummel CS. The DHR96 nuclear receptor regulates xenobiotic responses in Drosophila. Cell Metab. 2006;4:37–48.

41. Ihunnah CA, Jiang M., Xie W. Nuclear receptor PXR, transcriptional circuits, and metabolic relevance. Biochim Biophys Acta, 2011;1812:956–963.

42. Kliewer SA, Willson TM Regulation of xenobiotic and bile acid metabolism by the nuclear pregnane X receptor. J Lipid Res. 2002;43:359–364.

43. Staudinger JL, Xu C., Biswas A., Mani S. Post-translational modification of pregnane X receptor. Pharmacol Res. 2011;64:4–10.

44. Lichti-Kaiser K., Brobst D., Xu C., Staudinger JL A systematic analysis of predicted phosphorylation sites within the human pregnane X receptor protein. J Pharmacol Exp Ther. 2009;331(1):65–76.

45. Gu X., Ke S., Liu D. et al. Role of nfkappab in regulation of PXR-mediated gene expression: A mechanism for the suppression of cytochrome p-450 3a4 by proinflammatory agents. J Biol Chem. 2006;281(26):17882–17889.

46. Zhou C., Tabb MM, Nelson EL et al. Mutual repression between steroid and xenobiotic receptor and nfkappab signaling pathways links xenobiotic metabolism and inflammation. J Clin Invest. 2006;116(8):2280–2289.

47. Shah YM, Ma X., Morimura K. et al. Pregnane X receptor activation ameliorates dss-induced inflammatory bowel disease via inhibition of nf-kappab target gene expression. Am J Physiol Gastrointest Liver Physiol. 2007;292(4):G1114–1122.

48. Kodama S., Koike C., Negishi M., Yamamoto Y. Nuclear receptors car and PXR cross talk with foxo1 to regulate genes that encode drug-metabolizing and gluconeogenic enzymes. Mol Cell Biol. 2004;24(18):7931–7940.

49. Bhalla S., Ozalp C., Fang S. et al. Ligand-activated pregnane x receptor interferes with hnf-4 signaling by targeting a common coactivator pgc-1alpha. Functional implications in hepatic cholesterol and glucose metabolism. J Biol Chem. 2004; 279(43):45139–45147.

50. Wada T., Gao J., Xie W. PXR and CAR in energy metabolism. Trends Endocrinol Metab. 2009;20(6):273–279.

51. Igarashi M., Yogiashi Y., Mihara M. et al. Vitamin K induces osteoblast differentiation through pregnane X receptor-mediated transcriptional control of the msx2 gene. Mol Cell Biol. 2007;27(22):7947–7954.

52. Zhai Y., Pai HV, Zhou J. et al. Activation of pregnane X receptor disrupts glucocorticoid and mineralo-corticoid homeostasis. Mol Endocrinol. 2007;21(1):138–147.

53. Zhou C., Verma S., Blumberg B. The steroid and xenobiotic receptor (SXR), beyond xenobiotic metabolism. Nucl Recept Signal. 2009;7:e001. [PubMed: 19240808]

54. di Masi A., De Marinis E., Ascenzi P., Marino M. Nuclear receptors car and PXR: Molecular, functional, and biomedical aspects. Mol. Aspects Med. 2009; 30(5):297–343.

55. Cheng J., Shah YM, Gonzalez FJ Pregnane X receptor as a target for treatment of inflammatory bowel disorders. Trends Pharmacol Sci. 2012;33:323–330.

56. Gao J., Xie W. Targeting xenobiotic receptors PXR and CAR for metabolic diseases. Trends Pharmacol Sci. 2012;33:552–558.

57. Lehmann JM, McKee DD, Watson MA et al. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. J Clin Invest.1998;102:1016–1023.

58. Goodwin B., Hodgson E., Liddle C. The orphan human pregnane X receptor mediates the transcriptional activation of CYP3A4 by rifampicin through a distal enhancer module. Mol Pharmacol.1999;56:1329–1339.

59. Matsumura K., Saito T., Takahashi Y. et al. Identification of a novel polymorphic enhancer of the human CYP3A4 gene. Mol Pharmacol. 2004;65:326–334.

60. Liu FJ, Song X., Yang D. et al. The far and distal enhancers in the CYP3A4 gene co-ordinate the proximal promoter in responding similarly to the pregnane X receptor but differentially to hepatocyte nuclear factor-4alpha. Biochem J. 2008;409:243–250.

61. Tang Q., Chen Y., Meyer C. et al. A comprehensive view of nuclear receptor cancer cistromes. Cancer Res. 2011;71:6940–6947.

62. Cui JY, Gunewardena SS, Rockwell CE, Klaassen CD ChIPing the cistrome of PXR in mouse liver. Nucleic Acids Res. 2010;38:7943–7963.

63. Backman JT, Filppula AM, Niemi M., Neuvonen PJ Role of Cytochrome P450 2C8 in Drug Metabolism and Interactions. Pharmacol Rev. 2016;68:168–241.

64. Ferguson SS, Chen Y., LeCluyse EL et al. Human CYP2C8 is transcriptionally regulated by the nuclear receptors constitutive androstane receptor, pregnane X receptor, glucocorticoid receptor, and hepatic nuclear factor 4alpha. Mol Pharmacol. 2005;68:747–757.

65. Kojima K., Nagata K., Matsubara T., Yamazoe Y. Broad but distinct role of pregnane X receptor on the expression of individual cytochrome p450s in human hepatocytes. Drug Metab Pharmacokinet. 2007;22:276–286.

66. Chen Y., Goldstein JA The transcriptional regulation of the human CYP2C genes. Curr Drug Metab. 2009;10:567–578.

67. Bernstein BE, Meissner A., Lander ES The mammalian epigenome. Cell, 2007;128:669–681.

68. Li Y., Cui Y., Hart SN et al. Dynamic patterns of histone methylation are associated with ontogenic expression of the Cyp3a genes during mouse liver maturation. Mol Pharmacol. 2009;75:1171–1179.

69. Dannenberg LO, Edenberg HJ Epigenetics of gene expression in human hepatoma cells: Expression profiling the response to inhibition of DNA methylation and histone deacetylation. BMC Genomics, 2006;7:181.

70. Hu G., Xu C., Staudinger JL Pregnane X receptor is SUMOylated to repress the inflammatory response. J Pharmacol Exp Ther. 2010;335:342–350.

71. Miki Y., Suzuki T., Tazawa C. et al. Steroid and xenobiotic receptor (SXR), cytochrome P450 3A4 and multidrug resistance gene 1 in human adult and fetal tissues. Mol Cell Endocrinol. 2005;231:75–85.

72. Habano W., Gamo T., Terashima J. et al. Involvement of promoter methylation in the regulation of pregnane X receptor in colon cancer cells. BMC Cancer, 2011;11:81.

73. Fiorucci S., Mencarelli A., Distrutti E., Zampella A. Farnesoid X receptor: From medicinal chemistry to clinical applications. Future Med Chem. 2012;4:877–891.

74. Kalaany NY, Mangelsdorf DJ LXRS and FXR: The yin and yang of cholesterol and fat metabolism. Annu Rev Physiol. 2006;68:159–191.

75. Teodoro JS, Rolo AP, Palmeira CM. Hepatic FXR: Key regulator of whole-body energy metabolism. Trends Endocrinol Metab. 2011;22:458–466.

76. Fiorucci S., Rizzo G., Donini A. et al. Targeting farnesoid X receptor for liver and metabolic disorders. Trends Mol Med. 2007;13:298–309.

77. Chen WD, Wang YD, Meng Z. et al. Nuclear bile acid receptor FXR in the hepatic regeneration. Biochim Biophys Acta, 2011;1812:888–892.

78. Hoeke MO, Heegsma J., Hoekstra M. et al. Human FXR regulates SHP expression through direct binding to an LRH-1 binding site, independent of an IR-1 and LRH-1. PLoS One, 2014;9:e88011.

79. Li T., Chiang JY Bile acid signaling in metabolic disease and drug therapy. Pharmacol Rev. 2014;66:948–983.

80. Mudaliar S., Henry RR, Sanyal AJ et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type2 diabetes and nonalcoholic fatty liver disease. Gastroenterology, 2013;145:574–582 e571.

81. Neuschwander-Tetri BA, Loomba R., Sanyal AJ et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): A multicentre, randomised, placebo-controlled trial. Lancet, 2015;385:956–965.

82. Chen Y., Goldstein JA The transcriptional regulation of the human CYP2C genes. Curr Drug Metab. 2009;10:567–578.

83. Tian Y. Epigenetic regulation of pregnane X receptor activity. Drug Metab Rev. 2013;45(2):166–172.

84. Venepally P., Chen D., Kemper B. Transcriptional regulatory elements for basal expression of cytochrome P450IIC genes. J Biol Chem. 1992;267:17333–17338.

85. Bort R., Gomez-Lechon MJ, Castell JV, Jover R. Role of hepatocyte nuclear factor 3 gamma in the expression of human CYP2C genes. Arch Biochem Biophys. 2004; 426:63–72.

86. Chen Y., Coulter S., Jetten AM, Goldstein JA Identification of human CYP2C8 as a retinoid-related orphan nuclear receptor target gene. J Pharmacol. Exp Ther. 2009;329:192–201.

87. Beltrao P., Albanese V., Kenner LR et al. Systematic functional prioritization of protein posttranslational modifications. Cell, 2012;150:413–425.

88. Jensen ON Modification-specific proteomics: Characterization of post-translational modifications by mass spectrometry. Curr Opin Chem Biol. 2004;8:33–41.

89. Zhao Y., Jensen ON Modification-specific proteomics: Strategies for characterization of post-translational modifications using enrichment techniques. Proteomics, 2009;9:4632–4641.

90. Chow CW, Davis RJ Proteins kinases: Chromatin-associated enzymes? Cell, 2006;127:887–890.

91. Knight JD, Pawson T., Gingras AC Profiling the kinome: Current capabilities and future challenges. J Proteomics, 2013;81:43–55.

92. Kurokawa M., Kornbluth S. Caspases and kinases in a death grip. Cell, 2009;38:838–854.

93. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosinekinases. Cell, 2010;141:1117–1134.

94. Sopko R., Andrews BJ Linking the kinome and phosphorylome A comprehensive review of approaches to find kinase targets. Mol Biosyst, 2008;4:920–933.

95. Jo Corbin C., Mapes SM, Lee YM, Conley AJ Structural and functional differences among purified recombinant mammalian aromatases: Glycosylation, N-terminal sequence and kinetic analysis of human, bovine and the porcine placental and gonadal isozymes. Mol Cell Endocrinol. 2003;206:147–157.

96. Zhang LH, Rodriguez H., Ohno S., Miller WL Serine phosphorylation of human P450c17 increases 17,20-lyase activity: Implications for adrenarche and the polycystic ovary syndrome. Proc Natl Acad Sci USA, 1995;92:10619–10623.

97. Redlich G., Zanger UM, Riedmaier S. et al. Distinction between human cytochrome P450 (CYP) isoforms and identification of new phosphorylation sites by mass spectrometry. J Proteome Res. 2008;7:4678–4688.

98. Gandhi M., Aweeka F., Greenblatt RM, Blaschke TF Sex differences in pharmacokinetics and pharmacodynamics. Annu Rev Pharmacol Toxicol. 2004;44**:**499–523.

99. Dhir RN, Shapiro BH Interpulse growth hormone secretion in the episodic plasma profile causes the sex reversal of cytochrome P450s in senescent male rats. Proc Natl Acad Sci USA, 2003;100:15224–15228.

100. Waxman DJ, Holloway MG Sex differences in the expression of hepatic drug metabolizing enzymes. Mol. Pharmacol. 2009;76:215–228.

101. Schwartz JB The current state of knowledge on age, sex, and their interactions on clinical pharmacology. Clin Pharmacol Ther. 2007;82:87–96.

102. Cotreau MM, von Moltke LL, Greenblatt DJ The influence of age and sex on the clearance of cytochrome P450 3A substrates. Clin Pharmacokinet. 2005;44:33-60.

103. Wolbold R., Klein K., Burk O. et al. Sex is a major determinant of CYP3A4 expression in human liver. Hepatology, 2003;38:978–988.

104. Lamba V., Panetta JC, Strom S., Schuetz EG Genetic predictors of inter individual variability in hepatic CYP3A4 expression. J Pharmacol Exp Ther. 2010; 332:1088–1099.

105. Yang X., Zhang B., Molony C. et al. Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver. Genome Res. 2010;1020–1036.

106. Shapiro BH, Agrawal AK, Pampori NA Gender differences in drug metabolism regulated by growth hormone. Int J Biochem Cell Biol. 1995;27:9–20.

107. Thangavel C., Garcia MC, Shapiro BH Intrinsic sex differences determine expression of growth hormone-regulated female cytochrome P450s. Mol Cell Endocrinol. 2004;220:31–39.

108. van den Berg G., Veldhuis JD, Frölich M., Roelfsema F. An amplitude-specific divergence in the pulsatile mode of growth hormone (GH) secretion underlies the gender difference in mean GH concentrations in men and premenopausal women. J Clin Endocrinol Metab. 1996;81:2460–2467.

109. Engström BE, Karlsson FA, Wide L. Marked gender differences in ambulatory morning growth hormone values in young adults. Clin Chem. 1998;44:1289–1295.

110. Jansson JO, Edén S., Isaksson O. Sexual dimorphism in the control of growth hormone secretion. Endocrin Rev. 1985;6:128–150.

111. Agrawal AK, Shapiro BH Differential expression of gender-dependent hepatic isoforms of cytochrome P-450 by pulse signals in the circulating masculine episodic growth hormone profile of the rat. J Pharmacol Exp Ther. 2000;292:228–237.

112. Cheung NW, Liddle C., Coverdale S. et al. Growth hormone treatment increases cytochrome P450-mediated antipyrine clearance in man. J Clin Endocrinol Metab. 1996; 81:1999–2001.

113. Sinués B., Mayayo E., Fanlo A. et al. Effects of growth hormone deficiency and rhGH replacement therapy on the 6β-hydroxycortisol/free cortisol ratio, a marker of CYP3A activity, in growth hormone-deficient children. Eur J Clin Pharmacol. 2004;60:559–564.

114. Jaffe CA, Turgeon DK, Lown K. et al. Growth hormone secretion pattern is an independent regulator of growth hormone actions in humans. Am J Physiol. 2002; 283:E1008–E1015

115. Liddle C., Goodwin BJ, George J. et al. Separate and interactive regulation of cytochrome P450 3A4 by triiodothyronine, dexamethasone and growth hormone in cultured hepatocytes. J Clin Endocrinol Metab. 1998;83:2411–2416

116. Dhir RN, Dworakowski W., Thangavel C., Shapiro BH. Sexually dimorphic regulation of hepatic isoforms of human cytochrome P450 by growth hormone. J Pharmacol Exp Ther. 2006;316:87–94.

117. Span JP, Pieters GF, Sweep FG. et al. Gender differences in rhGH-induced changes in body composition in GH-deficient adults. J Clin Endocrinol Metab. 2001;86:4161–4165.

118. Soares DV, Conceição FL, Brasil RR et al. Insulin-like growth factor I levels during growth hormone (GH) replacement in GH-deficient adults: a gender difference. Growth Horm IGF Res. 2004;14:436–441.

119. Biggs JS, Wan J., Cutler NS et al. Transcription factor binding to a putative double E-box motif represses *CYP3A4* expression in human lung cells. Mol Pharmacol. 2007;72:514–525.

120. Martínez-Jiménez CP, Jover R., Donato MT et al. Transcriptional regulation and expression of CYP3A4 in hepatocytes. Curr Drug Metab. 2007;8:185–194.

121. Simpson ER, Mahendroo MS, Means GD et al. Aromatase cytochrome p450, the enzyme responsible for estrogen biosynthesis. Endocr Rev. 1994;15:342–355.

122. Griffing GT, Melby JC, Holbrook M., Johnston ON Antihypertensive effects of an aromatase inhibitor in inbred salt-sensitive rats. Hypertension. 1991;17:771–775.

123. Melby JC, Azar ST, Delaney M. et al. 19-nor-corticosteroids in genetic hypertension. Effects of inhibitors of 11 beta, 18, 19-hydroxylase activity. J Steroid Biochem Mol Biol. 1993;45:13–18.

124. Tworoger SS, Chubak J., Aiello EJ et al. Association of cyp17, cyp19, cyp1b1, and comt polymorphisms with serum and urinary sex hormone concentrations in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2004;13:94 –101.

125. Dunning AM, Dowsett M., Healey CS et al. Polymorphisms associated with circulating sex hormone levels in postmenopausal women. J Natl Cancer Inst. 2004;96:936 –945.

126. De Castro F., Moron FJ, Montoro L. et al. Re: Polymorphisms associated with circulating sex hormone levels in postmenopausal women. J Natl Cancer Inst. 2005;97:152–153, author reply 153–154.

127. Baghaei F., Rosmond R., Westberg L. et al. The cyp19 gene and associations with androgens and abdominal obesity in premenopausal women. Obes Res. 2003;11:578–585.

128. Baghaei F., Rosmond R., Westberg L. et al. The lean woman. Obes Res. 2002;10:115–121.

129. Simpson ER, Zhao Y., Agarwal VR. et al. Aromatase expression in health and disease. Recent Prog Horm Res.1997;52:185–213; discussion 213–184.

130. Ramirez-Lorca R., Grilo A., Martinez-Larrad MT et al. Sex and body mass index specific regulation of blood pressure by CYP19A1 gene variants. Hypertension, 2007;50:884-890.

131. Peter I., Shearman AM, Zucker DR et al. Variation in estrogen-related genes and crosssectional and longitudinal blood pressure in the Framingham Heart Study. J Hypertens. 2005;23:2193–2200.

132. Skowronek R., Czekaj P., Suszka-Świtek A. et al. Expression of cytochrome P450 2C and 3A in female rat liver after long-term administration of gonadoliberin analogs. Int J Occup Med Environ Health, 2016;29(2):293–314.

133. Wang JY, Tsai CH, Lee YL et al. Gender-dimorphic impact of PXR genotype and haplotype on hepatotoxicity during antituberculosis treatment. Medicine (Baltimore), 2015;94(24):e982.

134. Konstandi M. Psychophysiological stress: a significant parameter in drug pharmacokinetics. Expert Opin. Drug Metab. Toxicol. 2013;9(10):1317-1334.

135. Anderson GD Pregnancy-induced changes in pharmacokinetics: A mechanistic-based approach. Clin Pharmacokinet. 2005;44:989–1008.

136. Pavek P., Smutny T. Nuclear receptors in regulation of biotransformation enzymes and drug transporters in the placental barrier. Drug Metab Rev. 2014;46:19–32.

137. Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. Clin Pharmacokinet. 2004;43:487–514.

138. Tracy TS, Venkataramanan R., Glover DD et al. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A activity) during pregnancy. Am J Obstet Gynecol. 2005;192:633–639.

139. Dickmann LJ, Tay S., Senn TD et al. Changes in maternal liver Cyp2c and Cyp2d expression and activity during rat pregnancy. Biochem Pharmacol. 2008;75:1677–1687.

140. Topletz AR, Le HN, Lee N. et al. Hepatic Cyp2d and Cyp26a1 mRNAs and activities are increased during mouse pregnancy. Drug Metab Dispos. 2013;41:312–319.

141. Koh KH, Pan X., Shen HW et al. Altered expression of small heterodimer partner governs cytochrome P450 (CYP) 2D6 induction during pregnancy in CYP2D6-humanized mice. J Biol Chem. 2014;289:3105–3113.

142. Ning M., Koh KH, Pan X., Jeong H. Hepatocyte nuclear factor (HNF) 4a transactivation of cytochrome P450 (Cyp) 2d40 promoter is enhanced during pregnancy in mice. Biochem Pharmacol. 2015;94:46–52.

143. Koh KH, Pan X., Zhang W. et al. Kruppel-like factor 9 promotes hepatic cytochrome P450 2D6 expression during pregnancy in CYP2D6-humanized mice. Mol Pharmacol. 2014;86:727–735.

144. Kaczynski JA, Conley AA, Fernandez Zapico M. et al. Functional analysis of basic transcription element (BTE)-binding protein (BTEB) 3 and BTEB4, a novel Sp1-like protein, reveals a subfamily of transcriptional repressors for the BTE site of the cytochrome P4501A1 gene promoter. Biochem J. 2002;366:873–882.

145. Pabona JM, Simmen FA, Nikiforov MA et al. Kruppel-like factor 9 and progesterone receptor coregulation of decidualizing endometrial stromal cells: Implications for the pathogenesis of endometriosis. J Clin Endocrinol Metab. 2012; 97:E376–E392.

146. Simmen RC, Heard ME, Simmen AM et al. The Kruppel-like factors in female reproductive system pathologies. J Mol Endocrinol. 2015;54:R89–R101.

147. Zhang XL, Zhang D., Michel FJ et al. Selective interactions of Kruppel-like factor 9/basic transcription element-binding protein with progesterone receptor isoforms A and B determine transcriptional activity of progesterone-responsive genes in endometrial epithelial cells. J Biol Chem. 2003;278:21474–21482.

148. Rizzo G., Renga B., Mencarelli A. et al. Role of FXR in regulating bile acid homeostasis and relevance for human diseases. Curr Drug Targets Immune Endocr Metabol Disord. 2005;5:289–303.

149. Hoyert DL, Mathews TJ, Menacker F. et al. Annual summary of vital statistics: 2004. Pediatrics, 2006;117:168–183.

150. Yoon PW, Olney RS, Khoury MJ et al. Contribution of birth defects and genetic diseases to pediatric hospitalizations. A population-based study. Arch Pediatr Adolesc Med. 1997;151:1096–1103.

151. Leeder JS, Mitchell AA Application of pharmacogenomic strategies to the study of drug-induced birth defects. Clin Pharmacol Ther. 2007;81:595–599.

152. Boyle CA, Decoufle P., Yeargin-Allsopp M. Prevalence and health impact of developmental disabilities in US children. Pediatrics, 1994;93:399–403.

153. Kinirons MT, O'Mahony MS Drug metabolism and ageing. Br J Clin Pharmacol. 2004;57:540–544.

154. Stevens JC New perspectives on the impact of cytochrome P450 3A expression for pediatric pharmacology. Drug Discov Today, 2006;11:440–445.

155. Stevens JC, Marsh SA, Zaya MJ et al. Developmental changes in human liver CYP2D6 expression. Drug Metab Dispos. 2008;36:1587–1593.

156. Treluyer JM, Jacqz-Aigrain E., Alvarez F., Cresteil T. Expression of CYP2D6 in developing human liver. Eur J Biochem. 1991;202:583–589.

157. Blake MJ, Gaedigk A., Pearce RE et al. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. Clin Pharmacol Ther. 2007;81:510–516.

158. Croom EL, Stevens JC, Hines RN et al. Human hepatic CYP2B6 developmental expression: the impact of age and genotype. Biochem Pharmacol. 2009;78:184–190.

159. Bieche I., Narjoz C., Asselah T. et al. Reverse transcriptase-PCR quantification of mRNA levels from cytochrome (CYP)1, CYP2 and CYP3 families in 22 different human tissues. Pharmacogenet Genomics, 2007;17:731–742.

160. Gaedigk A., Baker DW, Totah RA et al. Variability of CYP2J2 expression in human fetal tissues. J Pharmacol Exp Ther. 2006;319:523–532.

161. Mavlyanov IR Clinic-experimental motivation of antenatal preventive maintenances of infants respiratory distress syndrome by monooxygenase system inducers. Abstract of dissertation on doctor of medical science– Tashkent, 1994.

162. Lopatco OV The transplacental influence of the inducer phenobarbital to the surfactant system of fetal lungs. Abstract of dissertation on candidate of medical science– Tashkent, 1994.

163. Abdullaeva GH The inducer benzonal impact to the surfactant system of fetal lungs in pregnant with late toxicoses. Abstract of dissertation on candidate of medical science–Tashkent, 1990.

164. Sharapov BU Efficacy of the phenobarbital therapeutic usage in lungs atelectasis of born prematurelies. Abstract of dissertation on candidate of medical science–Tashkent, 1994.

165. Inagamova MG The alteration of lungs surfactant system in infants with respiratory distress syndrome and its correction. Abstract of dissertation on candidate of medical science–Tashkent, 1995.

166. Muzafarova LE The correction of pharmacodynamics and pharmacokinetics alterations of drugs metabolized in liver in the postnatal period hypotrophy by benzonal, phytin and their composition. Abstract of dissertation on candidate of medical science– Tashkent, 1993.

167. Rahmanov AH The pharmacodynamic particularities of drugs metabolized by liver in rat with malnutrition in early ontogenesis. Abstract of dissertation on candidate of medical science–Tashkent, 1987.

168. Kaufman DW, Kelly JP, Rosenberg L. et al. Recent patterns of medication use in the ambulatory adult population of the United States: the slone survey. JAMA, 2002; 287:337-344.

169. Verstappen S., Jacobs J., Kruize A. et al. Trends in economic consequences of rheumatoid arthritis over two subsequent years. Rheumatology, 2007;46(6): 968-974.

170. Mori K., Blackshear PE, Lobenhofer EK et al. Hepatic transcript levels for genes coding for enzymes associated with xenobiotic metabolism are altered with age. Toxicol Pathol. 2007;35:242–251.

171. Amador-Noguez D., Dean A., Huang W. et al. Alterations in xenobiotic metabolism in the long-lived Little mice. Aging Cell, 2007;6:453–470.

172. Matamoros RA, Levine BS Stress response and drug metabolism in mice. Fund Appl Toxicol. 1996;30(2):255-263.

173. Konstandi M., Johnson EO, Marselos M. et al. Stress-mediated modulation of B (alpha)P-induced hepatic CYP1A1: role of catecholamines. Chem Biol Interact. 2004;147:65-77.

174. Konstandi M., Marselos M., Radon-Camus AM et al. The role of stress in the regulation of drug metabolizing enzymes in mice. Eur J Drug Metab Pharmacokinet. 1998;23:483-490.

175. Konstandi M., Johnson E., Lang MA et al. Stress modulates the enzymatic inducibility by benzo[alpha]pyrene in the rat liver. Pharmacol Res. 2000;42:205-211.

176. Daskalopoulos EP, Malliou F., Rentesi G. et al. Stress is a critical player in CYP3A, CYP2C, and CYP2D regulation: role of adrenergic receptor signaling pathways. Am J Physiol Endocrinol Metab. 2012;303(1):E40-54.

177. Chrousos GP Stress and disorders of the stress system. Nat Rev Endocrinol. 2009;5:374-381.

178. Chrousos GP, Kino T. Glucocorticoid signaling in the cell. Expanding clinical implications to complex human behavioral and somatic disorders. Ann NY Acad Sci. 2009;1179:153-166.

179. Tsigos C., Chrousos GP Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53:865-871.

180. Gonzalez FJ, Gelboin HV Role of human cytochromes P450 in the metabolic activation of chemical carcinogens and toxins. Drug Metab Rev. 1994;26:165-183.

181. Guengerich FP Cytochrome p450 and chemical toxicology. Chem Res Toxicol. 2008;21(1):70-83.

182. Nebert DW, Roe AL, Dieter MZ et al. Role of the aromatic hydrocarbon receptor and [Ah] gene battery in the oxidative stress response, cell cycle control, and apoptosis. Biochem Pharmacol. 2000;59(1):65-85.

183. Inogamova RS The chance of hepatic monooxygenase enzymes activity under some type of stress. Abstract of dissertation on candidate of biological science–Alma-Ata, 1990.

184. Komarin AS Effect and toxicity peculiarities of drug that metabolized in the liver in experimental hypokynesia. Abstract of dissertation on candidate of medical science–Tashkent, 1982.

185. Kasimova ZM The monooxygenase enzymes activity of animals with different individual peculiarities of nervous system in immobilization stress. Abstract of dissertation on candidate of biological science– Tashkent, 1991.

186. Ashirmetov AKh Vegetative regulation of hepatic monooxygenase system. Abstract of dissertation on doctor of medical science–Moscow, 1991.

187. Flint MS, Hood BL, Sun M. et al. Proteomic analysis of the murine liver in response to a combined exposure to psychological stress and 7,12-dimethylbenz (a) anthracene. J Proteome Res. 2010;9(1):509-520.

188. Mikhailova ON, Gulyaeva LF, Filipenko ML Gene expression of drug metabolizing enzymes in adult and aged mouse liver: a modulation by immobilization stress. Toxicology, 2005;210(2-3):189-196.

189. Konstandi M., Kostakis D., Harkitis P. et al. Role of adrenoceptor-linked signaling pathways in the regulation ofCYP1A1 gene expression. Biochem Pharmacol. 2005;69:277-287.

190. Jorgensen EH, Celander M., Goksoyr A., Iwata M. The effect of stress on toxicant-dependent cytochrome p450 enzyme responses in the Arctic charr (Salvelinus alpinus).Environ Toxicol Chem. 2001;20(11):2523-2529.

191. Konstandi M., Johnson E., Lang MA et al. Noradrenaline, dopamine, serotonin: different effects of psychological stress on brain biogenic amines in mice and rats. Pharmacol Res. 2000;41(3):341-346.

192. Prasad BM, Sorg BA, Ulibarri C., Kalivas PW. Sensitization to stress and psychostimulants. Involvement of dopamine transmission versus the HPA axis. Ann NY Acad Sci. 1995;771:617-625.

193. Shimada T., Fujii-Kuriyama Y. Metabolic activation of polycyclic aromatic hydrocarbons to carcinogens by cytochromes P450 1A1 and 1B1. Cancer Sci. 2004; 95(1):1-6.

194. Flint M., McCarty K., Jenkins F. et al. Psychological stress accelerates the onset of tumour formation and alters the type and location of tumours in a DMBA mouse carcinogenesis model. Stress Health, 2010;27(3):129-138.

195. Ding X., Lichti K., Kim I. et al. Regulation of constitutive androstane receptor and its target genes by fasting, cAMP, hepatocyte nuclear factor alpha, and the coactivator peroxisome proliferator-activated receptor gamma coactivator-1alpha. J Biol Chem. 2006;281(36):26540-26551.

196. Konstandi M., Kostakis D., Harkitis P. et al. Benzo(alpha)pyrene-induced up-regulation of CYP1A2 gene expression: role of adrenoceptor-linked signaling pathways. Life Sci. 2006;79:331-341.

197. Zordoky BN, El-Kadi AO Role of NF-kappa B in the regulation of cytochrome P450 enzymes. Curr Drug Metab. 2009;10(2):164-178.

198. Kennedy JM, Riji AM Effects of surgery on the pharmacokinetic parameters of drugs. Clin Pharmacokinet. 1998;35(4):293-312.

199. Konstandi M., Kostakis D., Johnson E. et al. Evidence of alpha2-adrenoceptor involvement in B[alpha]P induction processes of drug-metabolizing enzymes: the effect of stress. Eur J Drug Metab Pharmacokinet. 1998;23:491-495.

200. Niwa T., Tsutsui M., Kishimoto K. et al. Inhibition of drug-metabolizing enzyme activity in human hepatic cytochrome P450s by bisphenol A. Biol Pharm Bull. 2000;23(4):498-501.

HEAD IV. CYTOCHROME P-450 AND ITS ISOFORMS AS THE BASIS FOR THE DEVELOPMENT OF PERSONALIZED PHARMACOTHERAPY

IV.1. INFLUENCE OF PATHOLOGICAL FACTORS ON MONOOXYGENASE ENZYMES ACTIVITY

IV.1.1. Changes in CYP expression and activity in liver disease

It is known that the liver plays a major role in the metabolism of drugs, chemicals and endogenous substrates and hepatic disease can have a suppressive effect on the activity of CYPs [1, 2]. This pattern is most pronounced in toxic hepatitis and hepatic cirrhosis. In the experimental conditions of change of hepatic MOS activity is fairly well understood in our studies on models heliotrinous and CCl_4-hepatitis back in 70-80 last century. The suppression of the activity of aminopyrine-demethylase, aniline-hydroxylase and a decrease in the total content of cytochrome P-450 in the liver of the animals were detected also in partial hepatectomy, diacetamide and alcoholic liver disease [3, 4]. At study of different MOS inductors influence on these hepatic enzymes in condition some pathologies such experimental models of toxic hepatitis and liver cirrhosis were considered classical. They have been tested and proved inductive and therapeutic effect benzonal to his research and implementation in clinical practice [4]. Using antipyrine test in further studies were conducted MOS of liver in patients with hepatitis and cirrhosis of the liver, and measured the effectiveness of the developed way of drug correction [5].

Later it was revealed that the level and activity of CYP1A2, 2C19 and 3A4/5 were particularly vulnerable to development of hepatic diseases, whereas CYP2D6, 2C9 and 2E1 was less damaged [2]. Patterns of changes in CYP expression and activity also varied according to the etiology of hepatic diseases. Therefore, there are significant relationships between the activity of CYPs and the severity of hepatic cirrhosis [2].

In the analysis of patients with different etiologies and severity of liver disease using the cocktail approach, showed a significant inhibition of debrisoquine, caffeine and chlorzoxazone metabolism relative to healthy subjects, whereas, mephenytoin metabolism was significantly reduced in patients with mild liver disease and patients with moderate and severe degree in the assessment of severity according to the criteria of Child-Pugh [6].

Hepatitis C annually become infected at least 170 million people in all countries, and this infection is a leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma [7, 8].

Now the combination therapy of pegylated IFN plus ribavirin is the only approved treatment for hepatitis C [9, 10, and 11]. Nevertheless, this mode of treatment is effective in only about 50% of all patients infected with hepatitis C. Immune-mediated hepatic injury, viral product-mediated cytotoxicity and oxidative stress plays an important role in the pathogenicity of hepatitis C.

Renal and hepatic microsomal type 1 antibodies (LKM-1) directed against CYP2D6 in hepatocytes were found in the plasma of patients with chronic hepatitis C [12, 13, 14]. Autoimmune hepatitis type 2 turned out to be related with drug-metabolizing enzymes as auto antigens, for example, anti-LKM-1 against of CYP2D6, anti-LKM-2 against CYP2C9-tienilic acid, anti LKM-3 against the -UGT1A and anti-LC1 (liver cytosol antigen)-1 and anti-APS (autoimmune polyglandular syndrome type 1) against CYP1A2,

CYP2A6 and others [15]. The main antigenic epitopes on CYP2D6 are residues 193-212, 257-269, 316-327, 321-351, 373-389 and 410-429, as well as Asp263 is essential [13]. Aberrant degradation of CYP2D6 may result in auto antigenic peptides that can stimulate B-cells, helper T- cells and CD8+ T-cells, but whether CYP2D6 is still unknown as the auto antigen through molecular mimicry or antigenic changes. Some drugs, such as phenobarbital, phenytoin, carbamazepine and halothane may produce autoimmune hepatitis with anti-CYP3A and anti-CYP2E1 [46]. Autoantibodies against CYP11A1, CYP17 and/or CYP21 involved in the synthesis of steroid hormones also found in patients with adrenal insufficiency, gonadal failure, and/or Addison disease [15].

Patients with chronic hepatitis C show a significant reduction in the activity of CYP3A4 and 2D6 as compared to healthy volunteers. Certain fraction of patients with chronic hepatitis C (from 1% up to 79%) has produced LKM-1 antibodies. Sera from LKM-1 positive patients with autoimmune hepatitis type 2 were able to precipitate CYP2D6 in vitro, leading to a decreased activity for debrisoquine hydroxylation [16, 17]. In chronic hepatitis C patients with LKM-1 antibodies average CYP2D6 metabolic activity decreases by 80%.

It is unknown how the LKM-1 antibodies inhibit CYP2D6 in vivo. It is possible that the antibodies will cause targeted functional inhibition via ligand-like interaction at the level of CYP2D6 cavity, corresponding to the immune-dominant epitope. At the same time, there are reports that subjects with hepatitis C initially expressed almost 2.6-fold less than the low activity of CYP2D6 relative to hepatitis C negative patients [18]. It was revealed that the 2060A/A and -2053G/G variations in the CYP2D6 promoter were associated with significantly lower levels of CYP2D6 mRNA in the liver. Two novel genetic variants, -1822A>G and -1740C>T, have also been found only in two patients with hepatitis C. In addition, the mRNA levels of CYP1A2, 2E1, 3A4 and transporters of drugs, including Na^+-taurocholate-cotransporting polypeptide (NTCP/SCL10A1), OATP1B1/OATP-C/SLC21A6 and OCT1/SLC22A1 decreased in patients with chronic hepatitis C with progression of liver fibrosis [19]. It is possible that the inflammation and cytokines induced by hepatitis C viral infection will play a role in the inhibition of CYP2D6 activity, other CYPs, and drug transporters.

CYP-mediated activation drugs such as acetaminophen, carbamazepine, clozapine and halothane to toxic metabolites lead to the development of hepatotoxicity [20, 21]. In some instances, the covalent bond with CYP toxic metabolite leads to the formation of anti-antibody immune development and CYP-mediated hepatotoxicity (e.g., hydralazine and tienilic acid) [1, 21]. Antibodies against CYP2D6 found in the blood of patients with autoimmune hepatitis type II [12, 15, 22], but the mechanisms of their formation and pathogenesis significance is still unclear.

In the study of liver biopsy specimens from patients with chronic hepatitis C, stimulation of IL-6 and TNF-α and inhibition of CYP2E1 detected as compared with the control [23, 24]. It is also shown that the levels of IL-6 and TNF-α in patients with hepatic fibrosis stages 2-4 are significantly higher than those in patients with the first stage of fibrosis only [23].

CYP2E1 plays a critical role in the generation of ROS, which is a key component in the pathogenesis of alcoholic and non-alcoholic fatty liver diseases [25]. In many studies CYP2E1 regarded as causative factor in the development of alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) is

likely through enhancement of hepatic lipid peroxidation [26, 27]. In addition, chronic alcohol consumption is recognized as a major indicator of risk for esophageal cancer, probably because carcinogenic and genotoxic effects of acetaldehyde and oxidative stress [28, 29].

Due CYP2E1 particular relevance for toxicology caused its role in the metabolic activation of procarcinogens and chemical carcinogenesis, pharmacogenetic studies, mostly focused in association with different types of tumors. For example, genetic polymorphism in CYP2E1 associated with altered susceptibility to hepatic cirrhosis caused by ethanol, and with increased risk of development of esophageal cancer and other malignant tumors. It seems that long-term consumption of CYP2E1 inducers also recognized as a risk factor for the development of malignant tumors, especially for carriers of certain variant CYP2E1alleles.

IV.1.2. Effect of kidney failure on the activity of monooxygenase enzymes

Since the kidney is a major organ for excretion of water-soluble toxic components, xenobiotic, including drugs, a violation of its functions can cause major changes in the homeostasis, particularly in the functioning of the MOS.

Our studies have shown that acute renal failure caused in the experiment by ligation of the ureters and the removal of both kidneys, leading to a sharp reduction in the activity of enzymes in the liver of rats MOS, the cause of which was carried by the inhibitory effect of increased amounts of urea and creatinine in the blood [30, 31].

Hereinafter appeared proof that uremic mediators directly inhibit the CYP enzyme. In one in vitro studies have shown that the combination of free or protein-associated small-molecular uremic toxins: benzyl alcohol, p-cresol, indoxyl sulfate, hippuric acid is more than 50% reduced activity of CYP1A2, CYP2C9, CYP2E1, CYP3A4 in a similar concentration those detected in patients with renal insufficiency [32]. Velenosi et al. [33] failed to demonstrate a decrease in CYP2C11 and CYP3A2 in the liver of rats with renal failure caused by subtotal nephrectomy (5/6 part), by reducing the connection of nuclear transcription factors: the pregnane X receptor (PXR)/retinoid X receptor heterodimers, hepatocyte nuclear factor-4 and RNA polymerase II to the promoter regions of CYP2C11 and CYP3A2.

Chronic kidney disease is a health problem that affects 420 million people in the United States. To date, nearly 500,000 patients require chronic hemodialysis. Pharmacokinetic studies performed in patients with chronic renal failure (ChRF), show that the extra renal clearance of many drugs that are substrates of CYP different, reduced [34-36]. More than 75 of commonly used drugs show a modified extra renal clearance in patients with chronic renal failure and most of them eliminated through CYP mediated metabolism. For example, the identification of 7-fold increase in AUC of nimodipine, this is a good substrate for CYP3A4/5. Enhanced per-orally bioavailability and reduced systemic clearance were found for other substrates of CYP3A4/5, such as reboxitin, nicardipine and nitrendipine [34].

Although the mechanisms for this are unclear, several studies have shown that ChRF affects drug metabolism, inhibiting the key enzyme systems in the liver, intestines and kidneys. Uremic toxins form disturbances through transcriptional activation, causing inhibition of gene expression mediated by pro-inflammatory cytokines, and direct

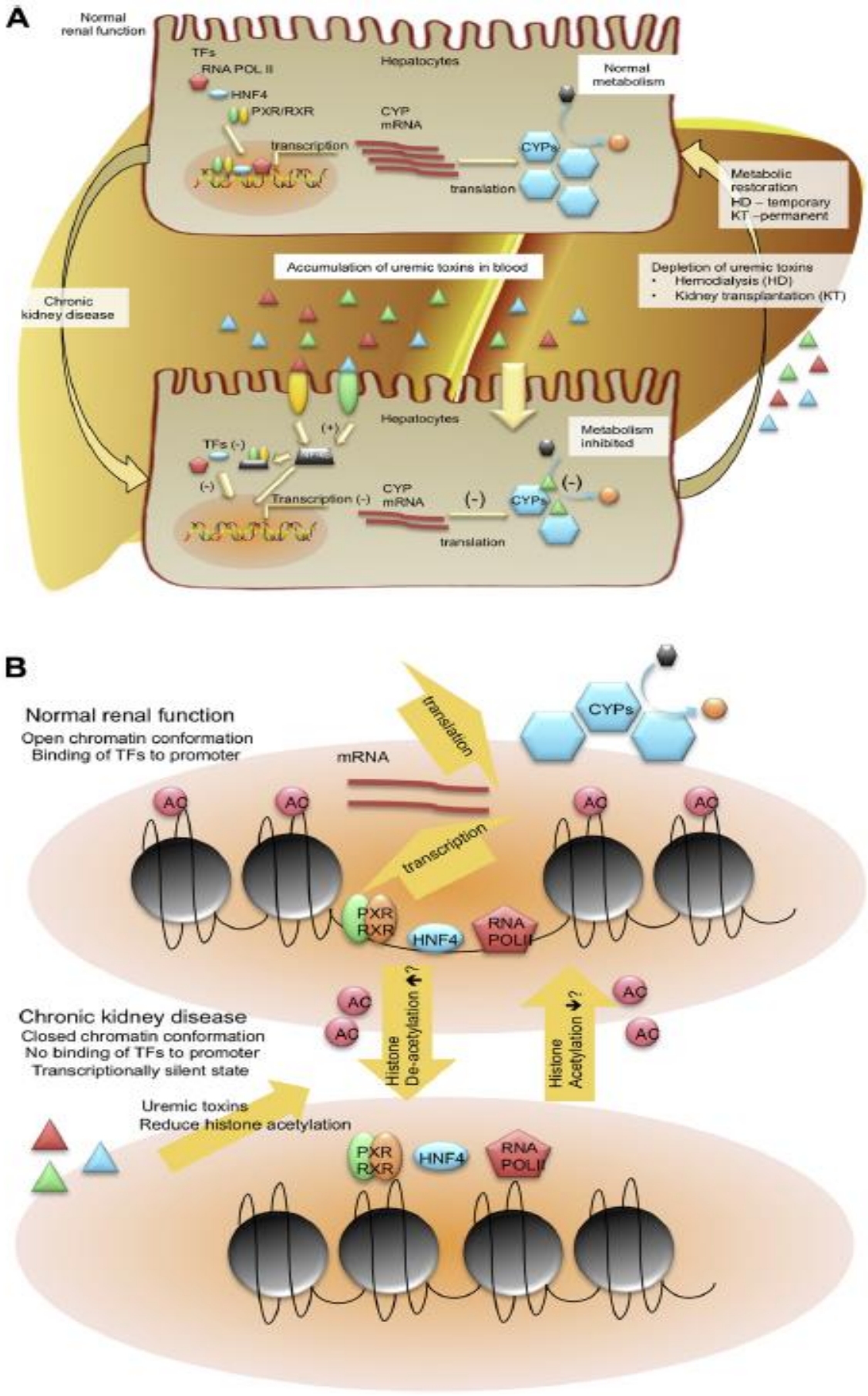


Figure 4.1 Representative regulatory mechanisms of CYP P-450 in chronic renal failure

Note: The circuit shown in Figure 4.1 shows the following representative mechanisms for regulating CYP P-450 in patients with chronic renal failure and in accordance by Ladda Goralski [37].

(A) In patients with normal renal function are synthesized, activated and binds to the promoter regions of CYP genes various factors of the nuclear transcription (TFs), promoting transcription of CYP messenger-RNA (mRNA), which is then translated into the functional CYP enzymes and normal metabolism of drugs. In chronic renal failure progress, the accumulation of uremic toxins in the blood occurs. These includes macromolecules such as: parathyroid hormone and inflammatory cytokines that bind to cell surface receptors to activate intracellular signaling pathways, which results in suppression of CYP gene transcription leading to reduction CYP mRNA and eventually functional CYP enzymes. The second mechanism may include direct inhibition of CYP metabolism by uremic toxins (colored triangles), that enters into the cell. By removing uremic toxins, dialysis temporarily restores normal metabolism, because the kidney transplantation has a permanent effect.

(B) The mechanisms of epigenetic CYP regulation in chronic renal failure. In normal renal function, chromatin associated-histone proteins are acetylated (AC) at specific residues that cause the appearance of open chromatin conformation, allowing the binding of TFs to the CYP promoter regions on DNA, leading to the normal transcription and translation into functional CYP enzymes. In chronic renal failure, histone acetylation reduced and could occur at elevated histone deacetylase activity and/or reduced activity of histone acetylases. This causes decision-closed confirmation of chromatin, which is a transcriptional silent state, which reduces the production of functional CYP enzymes. Black hexagons and orange circles represent respectively the parent drug and metabolites.

The symbol (-) indicates inhibition, HNF_4 - hepatic nuclear factor 4, PXR/RXR - pregnane X receptor /retinoid X receptor heterodimer, RNA POL II - RNA polymerase II.

inhibition of CYP activity and drug transporters such as: P-gp/MDR1, organic anion transporters (OAT) and organic cation transporters (OCT) [34, 36], which leads to a reduction in CYP-related drug metabolism.

Systemic clearance of orally administered propranolol and bufuralol decrease in patients with ChRF [38], but these changes not observed for metoprolol and propafenone [34]. Low-molecular fraction of the UF (510 kDa) uremic plasma obtained from patients ChRF was able to brake CYP2D6- and 1A2-mediated oxidative metabolism of S-propranolol in human liver microsomes. Liver enzymes of phase II and many drug transporters also inhibited when ChRF; where in the observed increased bioavailability of some medicines, reflected in a reduction of intestinal first-pass metabolism of drugs or extruding associated with P-gp and other transporters [35].

In our studies found that, the hepatic monooxygenase system in patients with chronic renal failure inhibited in depending on the disease stage, and the use of antiplatelet agents (aspirin, trental) restores it by changing the microcirculation [39]. In addition, in patients with urolithiasis, chronic pyelonephritis complicated, installed hidden phenomenon of liver function, including the activity of monooxygenase, which could subjected to pharmacological correction [40].

IV.1.3. Monooxygenase enzymes activity at some surgical disorders

Surgical diseases most often accompanied by the development of toxic effects and required not only the surgery, but also the introduction of large amounts of highly potent drugs. Of course, in this case, underestimation by clinicians MOS functions disorders can lead to tragic consequences, so we primarily carried out intensive research in this area.

Because of our investigations revealed that, the activity of a monooxygenase enzyme in the liver of rats suppressed largely by thermal injury, the degrees of which depend on the area of deep burn [41]. A similar reduction observed in acute diffuse peritonitis in rats at different times after the intraperitoneal administration of standardized doses autoexcrements [42]. This effect was also dependent on age it proven that not only under experimental conditions, but also in the clinic [43]. In acute obstructive intestinal obstruction and strangulation the activity of the monooxygenase enzymes in rat liver was suppressed, the cause of which would be in addition to CNS depression, exposure to toxic components, to suck the blood from the intestines of dead areas [44]. A similar decrease in hepatic monooxygenase enzymes activity observed in acute pancreatitis. At the same time, one of the factors contributing to the oppression MOS enzymes was hyperinsulinemia rather than an increase in the level of proteases in the blood. Furthermore, it revealed that this process implemented mainly by the sympathetic nervous system - namely, through the alpha-adrenergic receptors, whereas beta-adrenergic receptors have an opposite effect [45].

It has also revealed that in experimental traumatic brain injury reduces the activity of monooxygenase enzymes in the liver and the lungs, which is able to restore the use of MOS inductor - benzonal [46]. At the same time, it appears that the very conduct of surgery for the treatment of surgical diseases and depressing effect on the activity of the MOS, and the role of these factors were a general anesthetic (ether anesthesia), operative trauma, limitation of physical activity and diet [47]. Accepting this in attention offered using the inductor benzonal when undertaking preoperating preparation, especially in patients with chronical nonspecific lungs disease [48].

As you can see, inhibition of monooxygenase enzyme observed in all the studied surgical pathologies. Moreover, in rats, it developed only in male but not in female animals. Moreover, it turned out that the castration decreases, but the ovariectomy does not change the activity of MOS [31]. Then, on this background reproducing the burn, injury leads to similar changes in MOS in both males and females. Changing sexual orientation through treatment by synestrole of ovariectomized females and testosterone of castrated males leads to a diametrically opposite changes MOS in burn injury. It was further found that the basis MOS suppression (especially "male P-450 forms) for all of these pathologies are the accumulation of endotoxins, catecholamines and biogenic amines in blood as well as stress response [31].

IV.1.4. Expression of CYP isoforms and oncologic diseases

It known that individuals with the phenotype of high inducibility by CYP1A1 might be at greater risk than individuals with low inducible, for incidence of bronchogenic carcinoma of lung, caused by cigarette smoking [49].

About 10% of the Caucasian population has a very inducible form of the enzyme of CYP1A1, which is associated with an increased risk of lung cancer among smokers.

Although studies were not all positive in the Japanese and Caucasian populations of certain parts, an increased risk of lung cancer was correlated with one or two polymorphisms in CYP1A1: the so called MspI polymorphism and closely associated with it 2455A> G (I462V) [50-53]. It turns out those lung tumors in Japanese smokers with significantly more likely to exhibit p53 mutations when they had just such a genotype of CYP1A1 [53].

In the Chinese population of variant CYP1A1 Ile462Val it was associated with a lower risk of non-small cell lung cancer [54] while the polymorphism in exon 7 of CYP1A1, on the contrary, it promoted greater risk of its developments [55].

Besides lung cancer, CYP1A1 genotype associated with several types of cancers that may be relevant to CYP1A1-mediated activation of estrogen, such as breast cancer [56, 57], prostate cancer [58, 59], and ovarian cancer [60-62]. There was an increased risk of breast cancer was associated with the presence of the allele CYP1A1*2 at the high exposure of the body polychlorinated biphenyls, known as a potent inducer of CYP1A1 [63].

CYP1A2 may also bioactivate the procarcinogens. Therefore, Chinese smokers homozygous for CYP1A2 haplotype -3860G/-3113G/5347C have at high risk for hepatocellular carcinoma [64]. In addition, 2-fold increased risk for squamous lung cancer has observed in patients who have -2467del mutation [65]. Increased risk of lung cancer has also found in non-smokers Japanese with -163A/A genotype [66]. Similarly, an increased risk of stomach cancer was diagnosed in non-smokers -3860 mutation carriers [67], whereas alleles -163C and -2467delT been associated with pancreatic cancer in heavy smokers [68]. On the other hand, the lower the risk of breast cancer observed in carriers CYP1A2 -163C/C [69], but this allele still was associated with endometrial and ovarian cancer [70].

It also contemplated that the CYP2A6 genotype may modulate the risk of lung cancer [71]. Theoretically, the absence of CYP2A6 enzyme could reduce the risk of lung cancer because the procarcinogens activation founded in tobacco smoke, such as, NNK and NNN, must reduce. This was confirmed in studies carried out in Japan, where the identification of CYP2A6*4 was associated with a reduction in lung cancer risk [72]. However, France did not reveal any significant difference in the distribution of CYP2A6 * 2 or *4 allele in healthy and lung cancer patients [73]. Although studies in Caucasian populations is limited by presence of the low frequencies of inactive alleles, these data indicate that the relationship between CYP2A6 polymorphism and lung cancer is quite complex, and more research is needed to determine CYP2A6 participate in individual susceptibility to lung cancer.

Few clinical studies have found an association between CYP2D6 genotype and susceptibility to cancer of the head and neck, thoracic and lung [74-76]. It believed that CYP2D6 could affect the growth and spread of cancer cells through modulation bioactivation, procarcinogens and estrogen detoxification [77]. The same found in respect of 1A1, 1B1, 2E1 [78].

RsaI/PstI polymorphism of CYP2E1 is also closely associated with the risk of developing certain types of tumors. Background meta-analysis showed that RsaI/ PstI polymorphism CYP2E1 was related to esophageal cancer susceptibility [79], lung cancer [80, 81], liver cancer [82], head and neck cancer [83], colorectal cancer [84], and bladder cancer [85] however, two other meta-analyzes have failed to identify the significance of

the association RsaI/PstI polymorphism CYP2E1s risk of developing gastric cancer or oral cavity [86, 87]. Some Epidemiological studies have investigated the association between RsaI/PstI polymorphism of CYP2E1 and the risk of urological tumors; these studies seem to have ended controversial results. Solid meta-analysis recently conducted only for bladder cancer [85], while the sentence for prostate cancer, urothelial and renal cancer are still inconclusive.

A recent meta-analysis involving a total of 2712 cases and 2977 controls from 12 studies of case-control [88-92] in Caucasian and Asian populations, unable to find an association between the RsaI/PstI polymorphism in the gene CYP2E1 and the risk of urological cancer. This significant association indicated that the c2 allele or c2c2 homozygous carriers have a lower risk of urological cancer.

IV.1.5. Monooxygenase enzymes activity in some diseases of the cardiovascular and respiratory systems

Since the highest death rate in our country is the result of diseases of the cardiovascular and respiratory systems, the disease also caught our attention. Attack of a myocardium and related diseases first evaluated for detection of violations by monooxygenase enzymes.

In an experimental myocardial infarction develops endogenous intoxication, the degree of which depends on the functional state of hepatic monooxygenase enzymes in process of heart attack. Induction MOS by benzonal leads to a change in the ratio of differentiated cytochrome P-450 isoforms (inducible and constitutive (especially cholesterol metabolizing forms) [93]. It has also revealed that in experimental myocardial infarction preliminary induction of monooxygenase enzymes with benzonal contributed to a significant reduction in the size of necrosis in the myocardium, whereas preliminary MOS inhibition led to the expansion of necrotic center to account of the growth of deceased cardiomyocytes of perinecrotic zone [94]. In the clinical setting was found that the treatment patient by actovegin and essentiale have favorable effect on the free radical oxidation system and hepatic monooxygenase enzymes in acute period myocardial infarction [95].

In patients with angina have revealed significant inhibition of enzymes in the liver MOS respectively severity of the clinical course of the disease, defined based on studies pharmacokinetic parameters of antipyrine and cardio green. Including diphenine in the complex treatment of coronary artery disease (CAD) had a positive effect on MOS enzymes activity and hepatic blood flow without reducing the effect of antianginal therapy [96].

In hypertensive disease was also studied the drug metabolizing ability depending on its extent, type of nervous system and hemodynamics then was performed individualized treatment of patients [97].

In diseases of the respiratory system also revealed changes in activity and monooxygenase enzymes. In particular, our conducted studies have shown that in patients with chronic bronchitis were altered the pharmacokinetics of antipyrine, theophylline, amidopyrine, sulfadimezine and ethazol and in animals with experimental bronchitis oppressed MOS in the liver and lungs. Conventional therapy is not restored MOS activity [98]. The dynamics of theophylline pharmacokinetics parameters in patients with chronic

obstructive bronchitis is largely dependent on the severity of the disease and the individual properties of the body, which could to some extent, to control and regulate by verapamil introduction [99]. Adding to the treatment regimen of bronchitis the MOS inhibitor chloramphenicol has led to an even greater decrease in the MOS activity, and inductor zycsorine - to increase it in all organs. At the same time, benzonal showed a greater degree of induction, which has mainly manifested on hepatic monooxygenase enzymes [98].

Similar effects of benzonal on MOS been identified when enabling it in complex therapy of bronchial asthma [100].

IV.1.6. Changes in monooxygenase enzymes activity in some endocrinological diseases

Diabetes can also change the distribution and metabolism of clinically used drugs depending on the type and time of disease diagnostics, as well investigated substrates [101]. Diabetes can alter the pharmacokinetics of a variety of mechanisms, including a change in intestinal absorption, distribution and elimination of using drugs [101].

It has found that type 2 diabetes and gestational diabetes inhibit of CYP3A4/5 and/or CYP1A2, with the identification UGT1A induction and CYP2B7 in women with gestational diabetes [102, 103]. In the study of patients with diabetes type, one and two is not detected changes in the CYP2D6 mediated metabolism of dextromethorphan [104]. In diabetes melitus type 1 detected the certain alterations in metabolism, whereas diabetes melitus type 2 no alters the metabolism of any of the test drugs. The apparent oral clearance of antipyrine in patients with diabetes melitus type 1 appeared increased by 72%, and formation of hydroxy-antipyrine and 3-hydroxymethyl-antipyrine - respectively by 74% and 137%, relative to control, whereas metabolic index of caffeine (a measure of CYP1A2 activity) was increased only by 34% [104]. Diabetes did not show significant effects in CYP2D6 activity. The majority of children with type 1 diabetes belonged to PMs, relative to control [105]. At the same time, patients with gestational diabetes CYP2D6- and 3A4-mediated metabolism and transplacental distribution of metoprolol and its metabolites have not changed [106].

Given these results, our study assessed the effectiveness of the treatment of diabetic patients with benzonal including in complex therapy [107]. The obtained positive results were the basis for the introduction of such a scheme of treatment in clinical practice.

Hyperthyroidism in patients and experimental animals has resulted in decreased hepatic monooxygenase enzymes activity depending on the severity of the process. Herewith benzonal as phenobarbital had a positive impact on the MOS, and current disease [108].

IV.1.7. Monooxygenase enzymes activity in some diseases of the nervous system

Alzheimer's disease (AD) is the most common disease of dementia. Pathogenesis it is unclear, but probably based on the interaction between environment and genetic characteristics. The results for the effect of CYP2D6 genotype/phenotype on AD risk are contrary. A recent meta-analysis indicates that the CYP2D6*4 polymorphism, but not the phenotype of CYP2D6, is associated with increased risk of AD, particularly in European populations [109]. Nevertheless, no association between the phenotype, CYP2D6 or CYP2D6*4, and the risk of AD found in other studies [110, 111, 112], and in addition,

CYP2D6*4 polymorphism may be associated not only with an increased risk of AD. Polymorphism of CYP2D6*4 and GSTP1 may interact with b-HCH, dieldrine and copper, promoting the appearance of AD risk [111]. Possible efficiency genotype has proposed for use in the prediction and monitoring of response to treatment in patients who have a high risk of the AD, coronary artery disease and possibly other diseases. To study the role of CYP2D6 in AD pathogenesis regardless of CYP2D6 polymorphisms requires further study, since the results of pharmacogenomics studies on cholinesterase inhibitors, became aware of the impact of polymorphism of CYP2D6*4, rs6720975A (in intron PRKCE region) and rs17798800A (cis-regulator NBEA) on the pharmacokinetics of drugs and/or response to treatment.

Parkinson's disease (PD) is a progressive neurodegenerative condition. Its etiology remains unknown, but a complex interaction between genetic factors and the influence of environmental factors considered involved in the development of PD.

Several studies observed an association between CYP2D6 polymorphisms and PD in the European population [110, 113], but other studies have found no such association [114-116]. Studies have found that the frequency of mutations in the CYP2D6 *4 almost 2 times higher for patients with PD compared to healthy controls. In contrast, other studies did not find significant differences in the frequency of the genotype CYP2D6 [113]. Several studies in Asian populations are also not identified any significant effect of CYP2D6 genotype on the risk of PD [117, 118]. A recent meta-analysis suggests that CYP2D6 PM phenotype has a significant susceptibility to PD in the European population, particularly in the white British subjects [119]. Similarly, another meta-analysis shows that the CYP2D6*4 polymorphism has an increased genetic susceptibility to PD in Europeans but not in Asians [120]. It turns out that the same CYP2D6 polymorphism has different effects in PD susceptibility among different ethnic populations. Many factors influence the environment, such as diet, living conditions in rural areas, exposure to sunlight and pesticides, could interact with the genotype CYP2D6 and thus modulate the risk of developing PD in other ethnic groups.

IV.1.8. Monooxygenase enzyme activity in some diseases, accompanied by changes in the immune system

Changes in the immune system, moreover different-directional nature, accompany many diseases. Hyperimmune states occur in allergic reactions at the initial stages of autoimmune diseases and several other disorders. Rheumatoid arthritis accompanied by such a state, according to the results of our research led to the MOC reduction. His manifestation in patients occurred against the background of reduction of Tc and intracellular imbalance of the immune system. This MOS enzyme activity correlated with seropositivity, activity and course of the disease [121]. Appointment inductor phenobarbital these patients had not only inductive but also therapeutic effect [121, 122].

CYP2D6 metabolic genotypes and phenotypes were determined for 53 patients with rheumatoid arthritis and 73 healthy control persons [123]. There were no significant differences in genotype distribution between the two groups have not found. When the frequency of individual alleles, significant differences in allele frequency for CYP2D6D ($p>0.005$) was investigated occurred in fewer patients with rheumatoid arthritis who have this mutation. Moreover, metabolic phenotypes between patients and controls were

similar to [123]. However, for some patients with rheumatoid arthritis found higher expected metabolic rates for their specific genotype due to the interference of the analgesic drug dextropropoxyphene in phenotyping procedure.

Inflammatory conditions manifested in a number of diseases depressed of MOS activity. For example, MOS depression found in the liver and kidneys of rats with post-delivery endometritis, the severity of which corresponds to the degree of violation of indicators characterizing reactivity [124].

Infectious diseases, mostly accompanied by a different orientation of the immune system changes in disease dynamics. According to our data, in the initial stages of a number of infections observed decline in activity MOS. For example, in rats with salmonellosis infection MOS activity decreases similar to that with the introduction of endotoxins E.Coli and S.typhimuriumi incubation of microsomes in vitro. At the same time, the severity of acute intestinal disease and salmonellosis correlates with a decrease in the clearance of antipyrine [125].

Accordingly, the results of our research in allergic reactions are also observed MOS depression [126], which some correspond to the well-known concept of reciprocity monooxygenase and immune systems. In connection with this study were undertaken relations of these two systems in experimental conditions.

It found that MOS activity depression was more expressing in mice with strong respond to immunization. Benzonal eliminated the inhibitory effect of immunization on MOS and then immuno-depressor - immuran stimulated MOS. Benzonal reduced transplantation immunity, cellular immunity and rendered lymphotropic effect. The results confirm the well-known concept of contingency monooxygenase and immune systems [127].

It established that a variety of cytokines and inflammation could change the expression and activity of CYP [128-130]. Cytokines, acting through their respective receptors - a large group of low-molecular proteins, which are produced by macrophages, lymphocytes, neutrophils, fibroblasts, endothelial and mast cells [131-133]. A number of cytokines such as chemokines, interleukins (ILs), tumor necrosis factor (TNF-α) and interferons (IFNs), emitted in response to infection, and other inflammatory diseases [131-133]. In cultured human hepatocytes, IL-1 and TNF inhibit the expression of mRNA CYP2C8 and 3A4, respectively 75% and 95%, but have no effect on CYP2B6, 2C9 and 2C19 [134]. In contrast, IL-6 causes a decrease in the expression levels of mRNA for CYP2B6, 2C8, 2C9, 2C19 and 3A4. CYP2C18, normally expressed in the liver is very low; it does not change when exposed to cytokines. Another study demonstrated in vitro that IL-1 and IL-6 inhibit CYP3A4, whereas IL-12 and IL-23 have no effect on the expression or activity of CYP [135]. IL-1b reduces the expression of CAR and reduces phenobarbital- or bilirubin- mediated induction of CYP2B6, 2C9, 3A4 in human hepatocytes [136]. In human lung cells isolated from adult subjects, found the CYP2A13 suppression of transcriptional expression by lipopolysaccharides [137]. IL-6 treatment induces significantly CYP1B1 and 2E1, but not 1A1, in colorectal cancer [138]. Regulation of the CYP2E1 expression by IL-6 occurs through a transcriptional mechanism, involving signal transducer and activator of transcription 3 (STAT3), whereas IL6 inhibit CYP1B1-miR27b through modulation of DNA methylation [138].

A study in healthy volunteers showed that the inflammatory response even at a very low dose of the liposaccharide reduces the activity of CYP1A2 and 2C19. Infection and inflammation of the liver usually cause a decrease in the ability of drug metabolism and distribution [130]. In particular, NAT2, CYP 2C19 and 2D6 are subject to changes in the conditions of inflammation associated with increased levels of cytokines, such as human immunodeficiency virus infection, cholestasis, liver disease and cancer [130]. MRNA expression and protein Cyp2d suppresses pro-inflammatory cytokines in rat and mice liver. Introduction IL-10 in healthy volunteers not changes CYP1A2, CYP2C9 or CYP 2D6 activity, but decreases CYP3A activity [139, 140]. Thus, in the process of infection, inflammation and tumors, circulating pro-inflammatory cytokines such as interleukin (IL) -1β, TNF-α and IL-6 that act as signaling molecules to produce significant changes in hepatic gene expression profile, lead to serious oppression of many drugs metabolizing enzymes. The mechanism of these effects is at least partial transcriptional suppression [134].

IV.1.9. Monooxygenase enzymes activity at some other diseases

A number of skin diseases also caused inhibition of monooxygenase system. Therefore, in vitiligo according antipyrine test it is revealed set correction process of disease treatment using MOS inductors [141]. Reduced clearance of antipyrine found also in children with atopic dermatitis in adult patients with true eczema, the extent of which depended on the strength of expression of the processes of excitation in the central nervous system, leading to the conclusion about the negative impact of stress factors on the monooxygenase system in these diseases [142, 143].

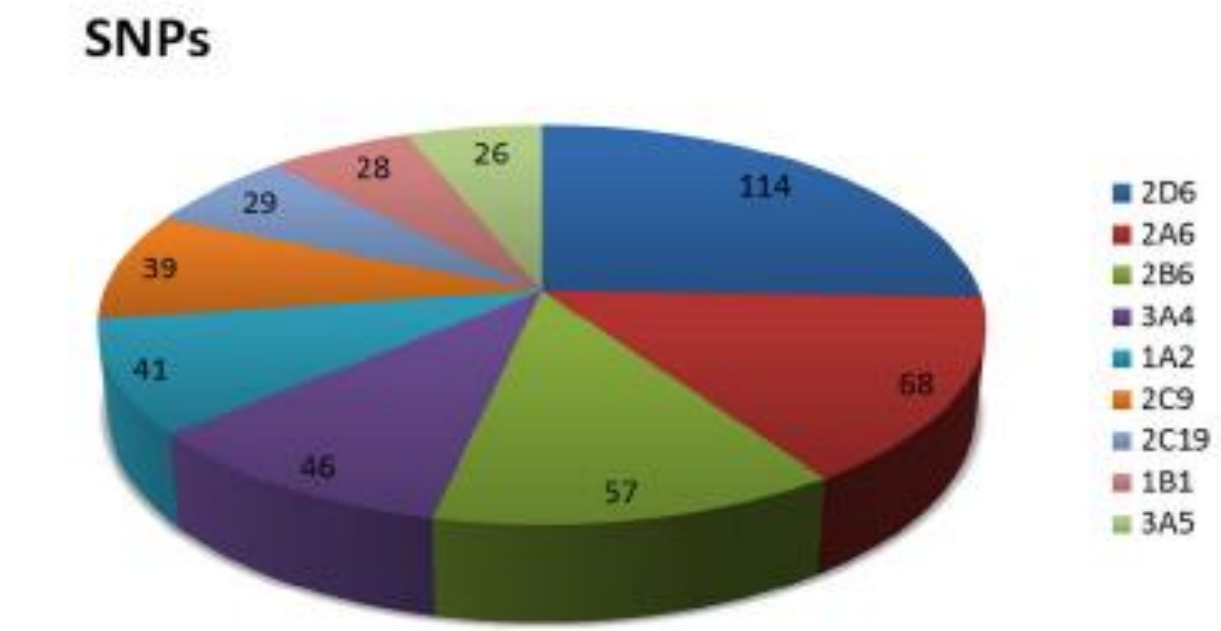
A significant reduction in the activity of the hepatic MOS was found also at a 12 finger gut ulcer, where was carried out the study of cytoprotetive action mechanisms of MOS inductors and the possibility of their use in the treatment of peptic ulcer [144, 145]. A similar pattern observed also in patients with iron deficiency anemia, which also considered asking her to pharmacological correction [146].

IV.2. POPULATION VARIATIONS OF CYP GENE EXPRESSION

The scarcity of available spectrum and efficient testing methods and continuous identification of clinically important genetic variants have delayed the transfer of genetic information into human clinical practice. Population studies have proved invaluable in filling this gap. Individuals from each subject populations have genetic similarities that might potentially distinguish it from other populations.

The number of the identified SNP for different isoforms of CYP is increasing day-by-day (Figure 4.2.)

Accordingly, data from the PubMed search engine, found many articles on the prevalence of 34 different alleles of CYP, defined by more than one percent of cases in the Caucasian population, and which may indicate a change in the metabolism of substrates. CYP 2D6 and 2B6 had the largest number of alleles with known effects on metabolism in the Caucasian population (11 and 6, respectively).



.

Figure 4.2. The number of the identified SNPs for different isoforms of CYP. According by [147].

The maximum frequency of alleles of CYP 2D6 ranged from 20.7% to 32.4%. In the analysis of 34 alleles, the most common alleles were CYP 3A5 * 3C - in 81.3% (lower enzyme activity) and then CYP 1A2*1F - 33.3% (increased activity of the enzyme) [147]. In addition, the major alleles, leading to increased metabolism, were CYP 2A6*1B (30, 0%), 3A4*1B (17.0%), 1A1*2A (19.0%) and 2C19*17 (18.0 %). In contrast, decreased metabolism was observed in 2D6*2A (32, 4%), 2D6*4 (20.7%) and 2C9*2 (16.0%). Carriage 2A6*4 allele (1.0%) resulted in undetectable inactivation of the enzyme substrate metabolism.

Comparative studies among the various ethnic groups have revealed significant differences in the frequency and heterogeneous distribution of alleles of CYP. For example, for the CYP2A6*2 in Asian and African populations detected frequency respectively 28.0% and 62.0%, whereas it was observed Caucasians at a frequency of only 8.0%. For more information on CYP SNP information in Caucasians and other ethnic groups presented in Table 1 (see attachment).

African populations show the cultural, linguistic, phenotypic, genetic and ethnic differences [148]. Within Africa, the existing border between the two countries - often are not the best for distinguishing between different populations, as marking the most part of the African continent by colonial powers took place relatively recently, and did not take into account the significant inter-ethnic diversity within regions [149]. There known genetic differences between Northern and Sub-Saharan African groups that are separated by Sahara desert, acting as a barrier to gene flow through the region [150]. A detailed genetic analysis of the population of East Africa [151], and the Kalahari Desert [152], also shows considerable inter-ethnic diversity within geographical regions across the continent.

IV.2.1. Cluster of CYP3A genes

Of all the enzymes CYP450, CYP3A sub-family (CYP3A4, CYP3A5, CYP3A7 and CYP3A43), plays a central role in drug metabolism. CYP3A4 and CYP3A5 are involved in the metabolism of more than 50% of all substrates known CYP450 [153], including many drugs used in the treatment of disease endemic areas in Africa and Asia. Carrying identification of important variants within a population, rather than individuals, allowed us to determine the differences in the CYP450 loci (Figure 4.3). One example is the allele CYP3A5*3, which reduces the expression of CYP3A5 to undetectable levels [154].

Previous studies have identified differences between individuals with recent African origin and European Caucasians in frequency allele CYP3A5*3 [155, 156]. A recent study of intra-African variation in the CYP3A5 gene found significant differences between the populations of the continent [157]. Figure 4.3 shows the frequency of CYP3A5*3 allele for 91 global populations that were genotyped [157, 158]. Here, individuals grouped within populations based on the similarity of language or ethnicity. The frequencies of allele CYP3A5*3 were lower in Africa than in other global regions. The population of the Western, Central-West and South-Eastern parts of Africa, belonging to the Niger-Congo language family, is very similar allelic frequencies.

The population of East Africa is more diverse. In Ethiopia, the frequency of CYP3A5*3 in Africa-Asian speaking population in the northeast of the country are comparable to those obtained for the Yemen people. Whereas, CYP3A5*3 frequency Nilo-Saharan speaking population from the south-west Ethiopia closer to groups of Southern Sudan. North Africans are also different from the sub-Saharan African populations [157]. The data shown in Figure 4.3 show the intra-African variations and intercontinental diversity in CYP450 genes, giving a significant population structuring within continent. There is significant substrate-specific overlap between the CYP3A enzymes [159]. Many previous studies have shown that CYP3A4 have the most significant role in the therapeutic drug metabolism among all CYP3A enzymes [160]. However, CYP3A5 is one of the most pharmacologically active drug metabolizing enzymes in Africa [157].

CYP3A5 is at least 50% of the baked-intestinal content of CYP3A in individuals [159]. This led to the conclusion that a change in the DNA sequence of CYP3A5 may be the most important genetic region for inter-ethnic and inter-population differences in CYP3A population dependent clearance of drugs.

IV.2.1.1.*CYP3A5*

Polymorphic expression of CYP3A5 exhibits intra-ethnic differences sufficiently. For example, the concentration of protein molecules of the enzyme in the liver and intestine-issue varies from level to 202 pmol/mg. [154]. Approximately, 10-25% of Europeans, 30-50% of the population in Asia and South America, 55-95% of African-Americans can be found the personnel detector protein levels CYP3A5 [154, 155]. Four CYP3A5 alleles are the most common determinants of interethnic variability in their protein expression. The first allele - CYP3A5*1, is considered the main, which defines the expression of the phenotype. Each of the CYP3A5*3, CYP3A5*6 and CYP3A5*7

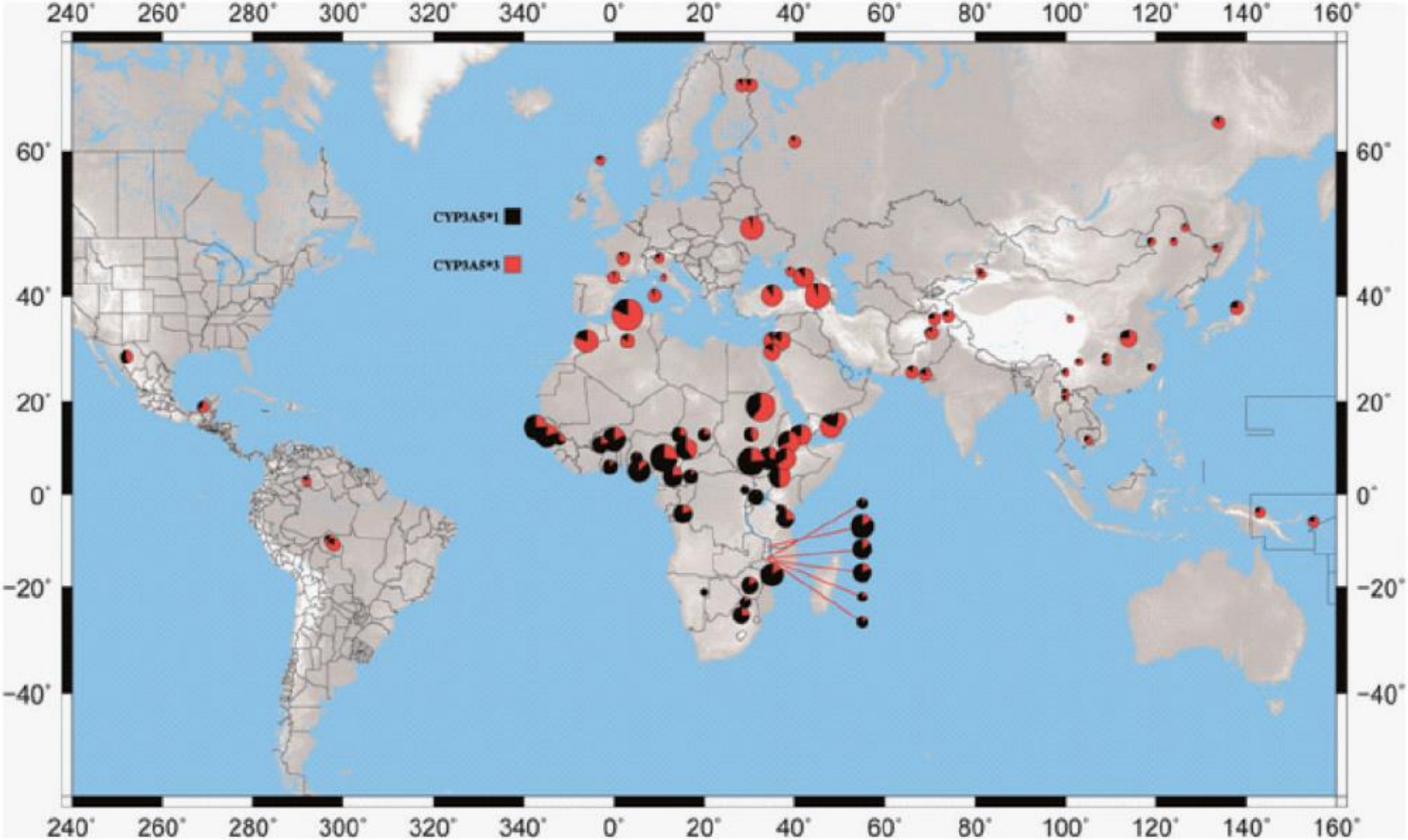


Figure 4.3. The geographical distribution of global frequencies of CYP3A5 * 3 allele.
Note: It were used the published data on more than 90 global populations classified by ethnic or linguistic groups. Scheme represented respectively by Bains [157].

allele is defined as the derivative exhibiting phenotypes of low activity or complete absence [154,161-163].

In one of works, which studied global population differentiation in frequency distribution of functionally important variants in genes encoding enzymes responsible for the absorption, distribution, metabolism and excretion of drugs, found the most significant inter-population differences in allele frequencies of CYP3A5*3 [164]. The frequencies of CYP3A5*3 were significantly different between ethnic groups and the mutation was clearly detected in the European population [154-156, 161, 162]. For example, a CYP3A5*3 variant, resulted by the defective enzyme activity is common in some ethnic groups, including the Caucasian [154], Afro-American [154], Japanese [165] populations. Its frequency varies from 50% in African-American and 70% in China before 90% in Caucasian populations.

Genotyping data show that Asian populations polymorphic diverse compared with other ethnic groups. The frequency of allelic variants of CYP3A5*1 and *3 in the Chinese population are similar to those in the Caucasus [154] and Japan [168] populations, but different from the African-American [154]. Allele frequencies of CYP3A5*1 in the populations of Malaysia and India, however, is similar to African-American, whereas the frequency of CYP3A5*3 allele in Malaysia and India, higher compared to the Afro-American population. The higher the frequency of CYP3A5*1 in Malaysia and India suggests that these populations of Asia are more likely to have a higher expression of CYP3A5, than the Chinese, the Japanese and Caucasian populations.

Allele frequencies of CYP3A5*6 was absent in Asian [168] and Caucasian populations [154]. However, this allele is dominant in Africa, with the registered rate of ~7.5% [154].

The lowest rate found in sub-Saharan Africa. However, even within this sub-continent have been found significant differences between the ethnic distribution of the frequencies of CYP3A5*3. Similarly expressed allocation of frequency differences have been identified there, and in respect of CYP3A5 *6 *7 and CYP3A5.

Combinations of frequencies of these alleles and the phenotypic effects of low enzyme activity or its complete absence suggested that the level of expression of CYP3A5 in the population of sub-Saharan Africa is likely to be significantly lower than that reported previously, though still higher than in other global areas [157]. According to Bains et al. [157], people living in this region, have an increased risk of EM phenotypes compared to the population of other areas. In this respect, it is important to note that Africans are likely to be at risk for numerous clinical phenotypes (slow, intermediate and rapid metabolism) in case of treatment of patients with drugs that are substrates of CYP3A.

IV.2.1.2.*CYP3A4*

Unlike CYP3A5, the CYP3A4 polymorphisms weakly was expressed. The variability in the protein expression detected mainly as a response to environmental stimuli that affect gene transcription and regulation (Figure 4.4) [169]. CYP3A4 gene was characterized by an excess of rare variants, relatively neutral manifestation [170], and currently only one rare mutation was able to inactivate CYP3A4 expression [171]. One of the most common mutations in this gene is considered CYP3A4*1B, which occurs in the area of the proximal promoter of CYP3A4 [172, 173]. Effects of mutations in expression

of the enzyme are mixed. Functional studies in his attitude led to contradictory results, some have determined that the mutation increases the expression of the enzyme [173], but most studies have failed to replicate this information [174].

A

Haplotype	Nucleotide position in reference sequence																												Frequency		
	73018	73084	73172	73216	73333	73346	73368	83269	83448	83566	83643	88726	93937	96611	96643	104033	105031	105074	105168	105191	105490	105576	105648	105674	105924	105938	106358	106490	Chinese	Caucasians	Africans
Hap 1	A	G	A	C	G	A	C	G	A	C	T	T	C	T	A	A	G	C	C	A	T	G	G	T	A	C	T	G	0.862	0.792	0.354
Hap 2	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		0.021	0.083
Hap 3	.	C	.	.	.	.	.	C	G	T	C	C	.	Del	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0.017	0.063	0.021
Hap 4	.	C	.	.	.	.	.	C	G	T	C	C	.	.	.	.	A	.	.	.	.	T	.	.	.	.	.	.			0.083
Hap 5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	0.052		
Hap 6	.	.	.	.	.	.	.	C	G	T	C	C	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.			0.063
Hap 7	.	C	.	.	.	.	.	C	G	T	C	C	.	Del	.	.	.	.	.	.	.	.	.	.	.	T	.	.		0.021	0.042
Hap 8	G	.	.	.	.	.	.	C	G	T	C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			0.063
Hap 9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	C	.	.	.	.	.	.	.	0.017	0.021	
Hap10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	0.034		
Hap11	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.			0.042
Hap12	.	.	.	.	.	G	T	C	G	T	C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T			0.042
Hap13	.	.	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		0.042	
Hap14	.	C	.	.	.	.	.	C	G	T	C	C	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.			0.042
Hap15	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	0.017		
Hap16	.	.	.	.	.	.	.	.	.	.	.	.	.	Del	.	.	.	.	.	.	.	.	.	.	.	.	.	.			0.021
Hap17	.	.	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		0.021	
Hap18	.	.	.	.	.	.	.	C	G	T	C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			0.021
Hap19	.	.	.	.	.	.	.	C	G	T	C	C	.	Del	.	.	.	.	.	.	.	.	.	.	.	.	.	.			0.021
Hap20	.	.	.	.	.	G	T	C	G	T	C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			0.021
Hap21	.	.	.	.	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			0.021
Hap22	.	.	.	G	.	.	.	C	G	T	C	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		0.021	
Hap23	.	C	.	.	.	.	.	C	G	T	C	C	.	Del	.	.	.	.	.	C	.	.	.	.	.	T	.	.			0.021
Hap24	.	C	.	.	.	.	.	C	G	T	C	C	.	Del	.	.	.	.	A	A	.	.	T	C	.	T	.	.			0.021
Hap25	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			0.021
Chimp	.	.	.	.	.	.	G	.	G	.	C	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			

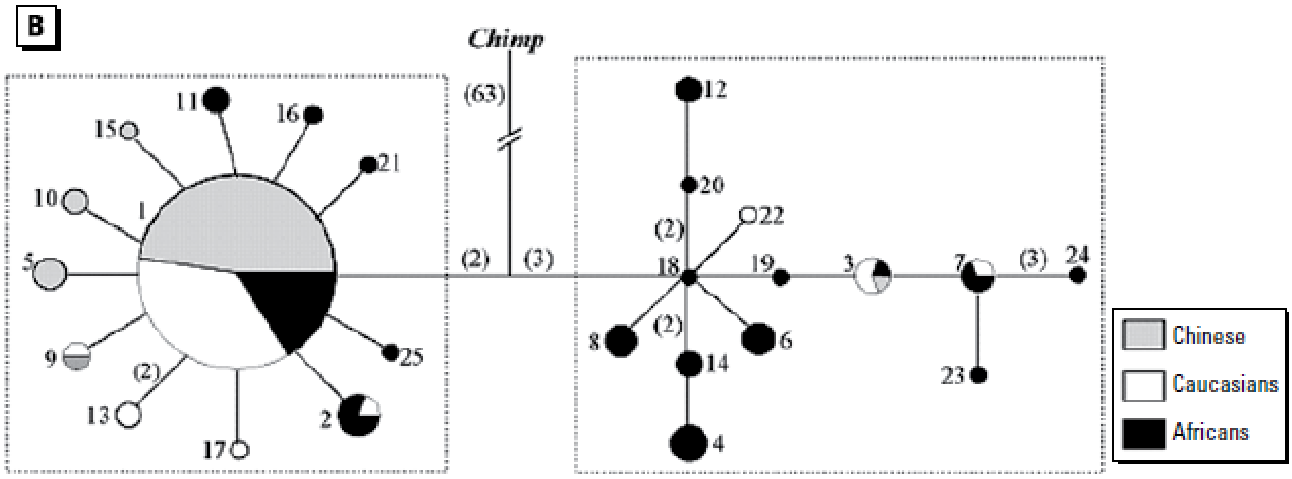


Figure 4.4. Haplotype in the region between A73018G and G106490T SNPs in CYP3A43 and MST of the haplotypes.

Note: (A) haplotypes and their estimated frequencies in each population, including chimpanzee's ancestral haplotype (Chimp).

(B) MST of the haplotypes in this region: one main cluster with only one common haplotype (left) and one minor cluster containing haplotypes of low or intermediate frequency (right). The size of each node is proportional to haplotype frequency in all three populations, while the frequency of each haplotype within each subpopulation contains different shades within each node. The branches represent one nucleotide substitution, unless otherwise noted in parentheses. Data presented respectively by [177].

Consequently, the exact effect of mutation CYP3A4*1B in CYP3A4 expression and hence clinical phenotypes while still not set. CYP3A4*1B is often found in high non-equilibrium due to the CYP3A5*1 allele. Due to the significant overlap in substrate, specificity with CYP3A5 is difficult to determine the independent influence of CYP3A4 variability on the safety and efficacy of CYP3A-mediated drug metabolism.

It was found that for certain medicinal substrates, the association between the variable expression of CYP3A4 and sub-optimal clinical outcomes the results are not as significant as for CYP3A5 [175]. It is possible that the association between variants and clinical phenotypes CYP3A is the result variable CYP3A5 expression largely than the expression of CYP3A4, due to non-equilibrium relationship between CYP3A4* 1B and CYP3A5*1. This probably is the reason for the greater CYP3A5 expression in populations with recent African origin than in non-African populations [157].

It is possible that CYP3A4 genetic polymorphism more distributed in Caucasian populations than in Asian. The frequency of CYP3A4*1B, carrying the -392A> G, was high in Spaniards and other Europeans (3.6-11.0%), but significantly higher in Negroes (53.0-69.0%). Like other ethnic Asian groups, CYP3A4*1B is absent in Japaneses [176]. It is possible that ethnic differences in the polymorphism of CYP3A4, especially in the Asian population is very low and does not allow fully explain the large individual variation in CYP3A4 activity.

Allelic frequency CYP3A4*3 mutations 1334T> C and, respectively, with a change in M445T, was equal to 1.1% in the Caucasian population [178]. Allele CYP3A4*2 was found with a frequency of 2.7% in the Caucasian population and absent in Negroes and Chinese [179]. The sharp decrease in CYP3A4 activity, due to the presence *4, *5 and *6 alleles found in China [180], and Caucasian populations [181].

Further studies will highlight the level of non-equilibrium relationship between these two mutations in a large cohort of African and to determine the extent to which it will contribute to the security of therapeutic use of drugs in Africa.

IV.2.2. CYP2D6

CYP2D6 is involved in the metabolism of 25-30% of all CYP450 substrates. Expression CYP2D6 is highly polymorphic, and the concentration of the enzyme is 0-25% of the general content of hepatic CYP450 [182]. This gene identified numerous single nucleotide polymorphisms (the SNPs), insertion (insert) and deletions (absence), genetic conversion and duplication. In addition, numerous studies in this locus also found CNV.

Consequently, on research more often pay attention to identify the effect on the expression of haplotype compositions CYP2D6, than individual polymorphisms that are frequently cannot predict expression phenotypes.

Individual haplotypes may either increase or decrease the expression of CYP2D6 (see Table 1 in the attachment). Variability in CYP2D6 expression contributes to the development of sets of clinical phenotypes, including ultra-fast, slow and accelerated metabolism of drugs used in the clinic [182]. A significant number of CNV, which identified in this locus are only of limited interest to clinicians. The most clinically significant of these are - CYP2D6*1xN and CYP2D6*2xN, where N refers to the number of copies of specific haplotypes. As CYP2D6*1 and CYP2D6*2 determine the normal phenotype of CYP2D6 expression. However, CNV may cause these haplotypes UM phenotype and lead to adverse clinical outcomes [183]. Effects of ultra-fast metabolism are serious also as slow metabolic capabilities. The number of copies of both functional and non-functional CYP2D6 gene may influence the clinical phenotypes [184].

Considerable variability in CYP2D6 phenotypes of expression exists both within and between populations [184, 185]. Based on Human Genome Diversity Panel data (HGDP) in respect of CYP2D6 expression phenotype in 52 populations, it concluded that the non-African groups were the most stable, despite the fact that EM phenotypes were not yet drawn conclusions for East Asian population [186]. It turns out that Africans from the Northern and Eastern parts of the continent have a higher rate of detection of individuals with an increased activity of the enzyme. Across Africa, the regional differences were apparent; the nonexpressors percentage was higher in West Africa than in other African regions, as the expression of the enzyme phenotypes in South Africa were in normal range [185, 186].

According to one study, the population of Zimbabwe found a significant frequency (34%) alleles of CYP2D6*17, which is associated with a significant decrease in the activity of the enzyme [187, 188]. When these results considered in the context of the HGDP posts for the African Group, it suggested that the South Africans are likely to have a greater variability in the level of expression of CYP2D6 than previously reported. These findings also remind us that regional differences were probably high in sub-Saharan Africa.

IV.2.3. Clusters of CYP1A2 and CYP2C genes

CYP2C sub-family (CYP2C8, CYP2C9, CYP2C18 and CYP2C19) is responsible for the metabolism of 20% of all the CYP450 substrates [189]. Despite considerable sequence homology (82% amino acid identity), CYP2C family members have not only a clear substrate specificity, but also have some substrate overlaps. They represent about 20% of hepatic CYP450 and one metabolized about 25% of drugs used in clinic.

CYP2C8, CYP2C9 and CYP2C19 are the most pharmacologically active enzymes of this sub-family. Each of these three enzymes exist polymorphically expressed and ethnic differences in the expressions of the protein molecules phenotypes [185, 190, 191].

The most common alleles are CYP2C9 - CYP2C9*2 (possibly impaired function) and CYP2C9*3 (impaired function) (Table 1 in the Attachment). CYP2C9*2 allele was not found in the Asian population, dominates about 15% of Caucasians, and varies from African descent (1-3.6% in African Americans, 4.3% in Ethiopia and 0% in Benize). CYP2C9*3 allele has a low incidence in Africans (0.5-2.3%) and in individuals with East Asia (1.1-6.8%), but a higher value from the Indians (8%) and Caucasians (3.3-17%) [190]. Considerable interest is the effect of the polymorphism on the activity of CYP2C9

and warfarin dosing. Limdi et al. found an association between allele carriers of CYP2C9 and a lower dosing of warfarin in American Caucasians, but not in Afro-Americans. They also found a much higher spread of variant genotypes in Caucasians, against Afro-Americans (29.82 vs. 9.73%), despite the presence of *5, *6, and *11 variants identified only in Afro-Americans [192]. In the Scott et al. [193] it found that the allele of CYP2C9, designated as *8, with the lowest possible functional capacity, may have spread close to 9% in Afro-Americans. The authors noted that in addition to the alleles for screening in the panels is necessary to make more accurate forecast warfarin dosing in Afro-Americans.

CYP2C8 is about 7% of the total CYP450 liver metabolizes and about 5% of clinical medicine. The carriage of CYP2C8*2 allele is quite common, clinically results in an impaired metabolic activity [190].

The geographical distribution of CYP2C8 allelic frequencies presented in Figure 4.5. At the same time the highest frequency of CYP2C8*3 alleles was found in individuals of European descent. In the European population, the allele frequency of CYP2C8*3 ranges from 0.069 to 0.198 to the Faroe Islands in the Portuguese population, with a clear north-south direction from a lower to a higher frequency [189, 194-196]. Allele is also quite common in populations of European Americans and North American Spanishes, with frequencies of 0.09 and 0.08, respectively [197]. In a mixed Brazilian and Ecuadorian populations, the frequency of this allele was 0.08 and 0.07, and in the metis population of Chile - 0.06 [196, 198, 199].

CYP2C8*4 (c.792C.G, p.Ile264Met) allele has the highest rate in the European population, with a frequency oscillating from 0.04 to 0.07 in the Spanish populations in the Irish [189, 194]. The population of European Americans and mixed Brazilian population, its frequency found to be 0.03 [197]. The populations of Peru, Colombia, Puerto Rico and North American Spanishes, the frequency of this allele ranges from 0.01 to 0.02 [195, 197]. CYP2C8*4 allele found in Indian individuals with a frequency of about 0.03-0.04 and in Pakistan individuals with a frequency of 0.01 [195, 201]. In East Asia population, CYP2C8* frequency 4 is usually 0.01 or less, and the frequency of 0.02 was found in the Chinese population Uighur [189, 195, 202, 203]. Allele CYP2C8*4 is quite rare in individuals originating from sub-Saharan Africa, with a frequency of less than 0.01 in all populations studied sub-Saharan Africa and 0.01 in the African-American population [195, 197, 204].

CYP2C8*2 allele is relatively common in the mixed Brazilian population with a frequency of 0.06 in the Spanish population of New York City area with a frequency of 0.02, as well as the populations of the north and south of India, respectively, with frequencies of 0.03 and 0.01 [196, 197, 201, 205]. Allele CYP2C8*2 - rare or absent in East Asia and the European populations, with the exception of allelic frequency 0.01 in samples of Portuguese Europeans [194, 197, 202, 206].

In general, allele CYP2C8*2 is very common in people of African descent. Conversely, CYP2C8*3 allele (which encodes hypo functional - enzyme) and CYP2C9*2 is highly prevalent in persons of South European origin [190]. CYP2C8*3 and 2C9*2 - are also in strong no equilibrium coupling [189]. Through haplotype analysis, Speed et al. [189] found that 90% of individuals with CYP2C8*3 allele also worn CYP2C9*2 in the same chromosome. Suarez-Kurtz et al. [196] revealed a significant association between

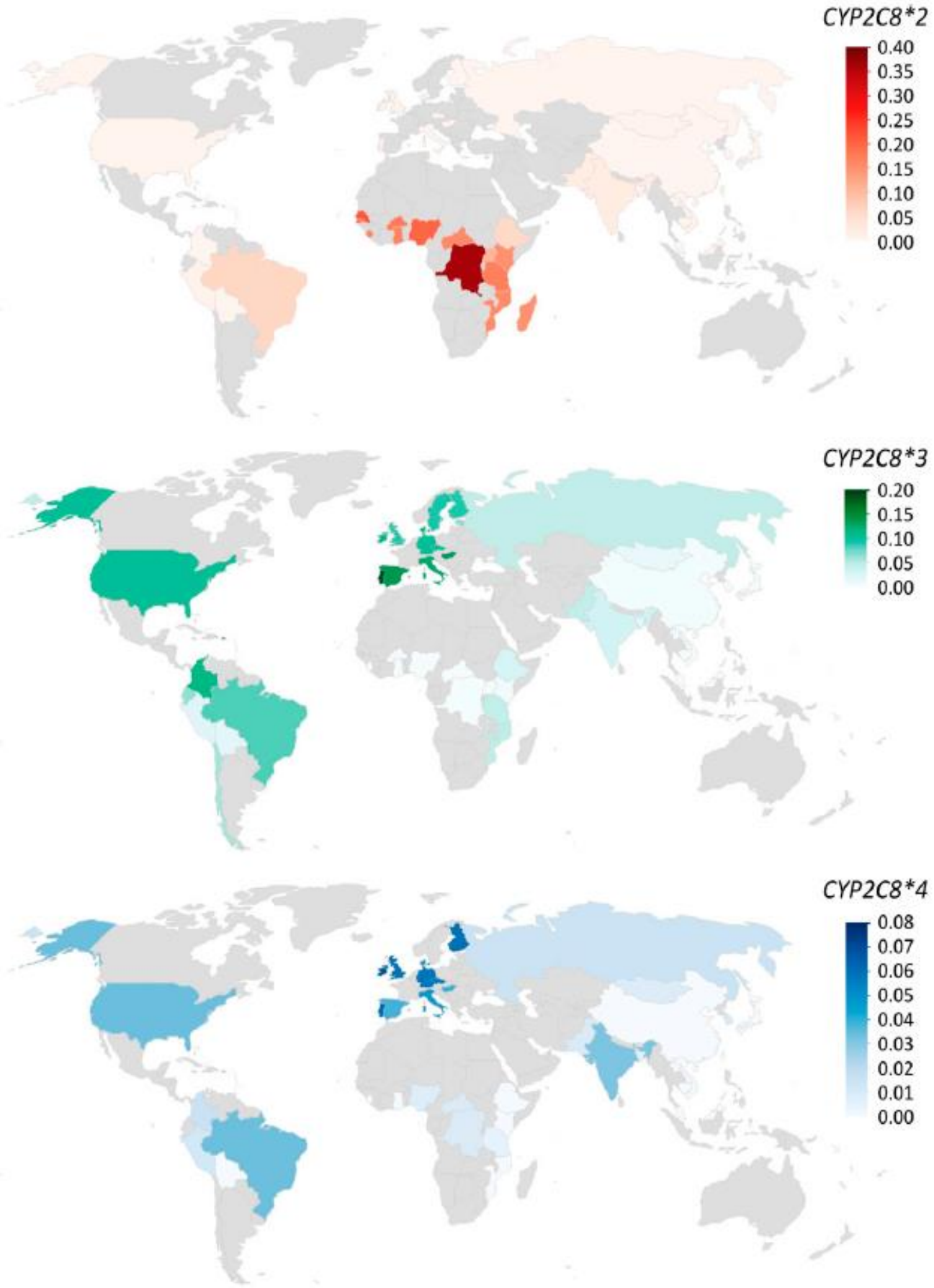


Figure 4.5. The global distribution of CYP2C8*2, CYP2C8*3 and CYP2C8*4 alleles.

Note: The color intensity indicates allele frequency. Scheme represented respectively by [200].

high ethnically diverse Brazilian population of Africans, Native American and Caucasian individuals who themselves categorized as black, brown and white. They found significantly reduced the frequency trend for the CYP2C8*3, 2C9*2 and 2C9*3 when compared group by categories from white to brown and black. This trend was reversed for the CYP2C8*2. No association was found between CYP2C19 genotype and race start.

The frequencies of CYP2C19 alleles exhibit the most substantial ethnic variation and different geographical distribution patterns, relative to other CYP [207]. CYP2C19 highly polymorphic with at least 24 different alleles, many of which have no enzymatic activity. Options *2 - *8 are inactive [208]. They also have different alleles in a different distribution of racial/ethnic groups. Unlike other forms of the CYP450, in Caucasians and black Africans revealed similar overall frequency of the PM phenotype (1-8%), whereas a higher distribution of PM (13-23%) observed among Asians [209, 210]. The phenotypes were defined as ultra (two C19*17 alleles), intense (two functional alleles), intermediate (one functional/dysfunctional one) and PM (two different alleles).

CYP2C19*17 variant CYP450 have an interesting distribution in different populations. It is highly common in Caucasians (~ 20%), it has a similar frequency in Africans (18% Ethiopians, 17% Ugandians), but lower frequency in the Asian population (0.3% Koreans, Japanese and Chinese 1% 4%) [211-213]. CYP2C19*17 exhibits an increased functional capacity and demonstrates the highest spread among northern populations. It is believed that CYP2C19*17 is in communication with others no equilibrium functional alleles CYP - CYP2C8 and 2C9. This hypothesis is supported by information Pedersen et al. [211], who showed that the most common haplotypes in Scandinavia were wild type (CYP2C8*1, 2C9*1 and 2C19*1 - 49%), combined with the advanced haplotype CYP2C19*17 (CYP2C8*1, 2C9*1 and 2C19*17-19%).

In general it can be argued that the alleles of CYP2C19*2 and CYP2C19*3 are more frequent in individuals East Asia and the indigenous inhabitants of Oceania than in populations of the rest of the world as CYP2C19*17 was more frequent in Mediterranean Sea-South and Mid-Eastern Europeans ($P<0.001$, for all cases). Regarding the metabolic phenotype distribution of PM was the most common among Asians, while the ultra-fast metabolism "forecasted" of genotype was frequent in African, Europe, America and the Middle East populations.

Accordingly, the size of the studied populations of each geographical region [214] who have knowledge of CYP2C19 by world populations apparently based on over Europe and Oceania subjects of presentation. In reports for Africa and Asia, the percentage of represented subjects surveyed on CYP2C19, were below the world average values for Africa (6.68% vs. 14.72%) and Asian populations (31.71% vs. 55.67%). To date, some of the well-known alleles of CYP2C19 have been widely studied in all countries; nevertheless, there is a gap with respect to many other allelic variants turned out be poorly understood, but it is of considerable interest. Many of the described CYP2C19 alleles have no synonymous polymorphisms and might affect the protein product.

Therefore, analyzing a higher number of alleles not only increases the knowledge of the CYP2C19 variants, but also gives an idea of their potential value to predict response to pharmacotherapy in the appointment of CYP2C19 substrates, particularly in those

geographic regions where found high prevalence of PM or UM. With regard to ethnicity analysis CYP2C19 allele frequencies showed interethnic variability for all global populations that may have occurred under the influence of tribal migrations and history of human populations [215]. In this sense, an unusually high frequency of CYP2C19*2 and CYP2C19*3 alleles in Oceania may be the result of several factors: first, <99% of studied populations in Oceania were indigenous to the Pacific from Papua New Guinea, Vanuatu and Melanesia, which include geographically isolated and ethnically diverse population; and, secondly, it is believed that the colonization of the Pacific Islands began with the South-East Asia, where the alleles CYP2C19*2 and CYP2C19*3 were very common, and thus, the process of genetic drift may be involved [216]. For other geographical regions, CYP2C19*2 and CYP2C19*3, are associated with reduced activity, often found in Asian populations, whereas in the European, American and African populations was detected only CYP2C19*2. Allele CYP2C19*17 was common in Africa, America, Asia and Central Europe, while in Asia it is found rarely. The variability in the distribution of CYP2C19 alleles worldwide may have clinical significance for drug development processes, and clinical trials. Consequently, ethnic differences, and the phenomenon of migration should serve as a warning to physicians about the value based on genetic determinants in the response to the drug when the drug used in a variety of populations, or in subjects with a diverse genetic basis [217].

Genetic polymorphisms in CYP450 genes may lead to adverse clinical outcome due to their effect on the expression and/or activity of the enzyme. The variability in the expression and function of CYP450 shown in four clinical phenotypes: poor (PM), intermediate (IM), extensive (EM) and the ultra-rapid metabolizers (UM).

1) PM has two copies of the allele that reduce or knock out expression of specific CYP450. In PM lacks certain part enzyme activity and they metabolize drugs less effective compared to EM, IM and UM.

2) PM has two copies of the allele that reduce or knock out expression of specific CYP450. In PM lacks certain part enzyme activity and they metabolize drugs less effective compared to EM, IM and UM.

3) UM are carriers of more than two active copies of the gene. Ultra-fast metabolism is the result of gene duplication [i.e., copy number variation (CNV) of the gene coding and regulatory regions]. Gene copy number correlated with an increase of protein expression levels and rapid metabolism of substrates.

4) IM is heterozygous for null and functional copies of certain alleles of CYP. This results in an easy reduction of the enzyme activity, but there is usually no need to change the dosage of medicines for IM.

The distribution of these phenotypes among populations can be quite different, but in general, their relationship might look like this, as shown in Figure 4.6. For example sparteine oxidation phenotype in the population of Germany.

Typically phenotype enzyme activity is determined based on the clearance rate or biotransformation of certain test drugs that are metabolized mainly how any particular CYP, but allows genotyping "predict" phenotype from genotype detected depending on the combination of alleles. In most cases, they are the same, but sometimes exceptions identified and, as it happened in the Ocean populations.

CYP2C19 discrepancy between the "predicted" phenotype from genotype and "measured" metabolic phenotype of CYP2C19 (58.15% vs. 7.01%, respectively) observed

for Oceania, may be due to various reasons. Studies were carried out in different populations within Oceania, and while genotype analysis was developed in the population of Papua New Guinea, Vanuatu, Australia and Melanesia [216, 218-220]. Metabolic same phenotype studies performed only in New Zealand [221, 222]. In addition, ethnic diversity and geographic isolation of these populations impedes correlation studies, and even more so, none of these studies included both genotypic and phenotypic measurements within the same population. However, in the rest of the geographical regions and ethnic groups, GPMS frequency strongly correlated with the frequency of MPM, which indicates that the genotype CYP2C19 may reasonably predict poor metabolic phenotype.

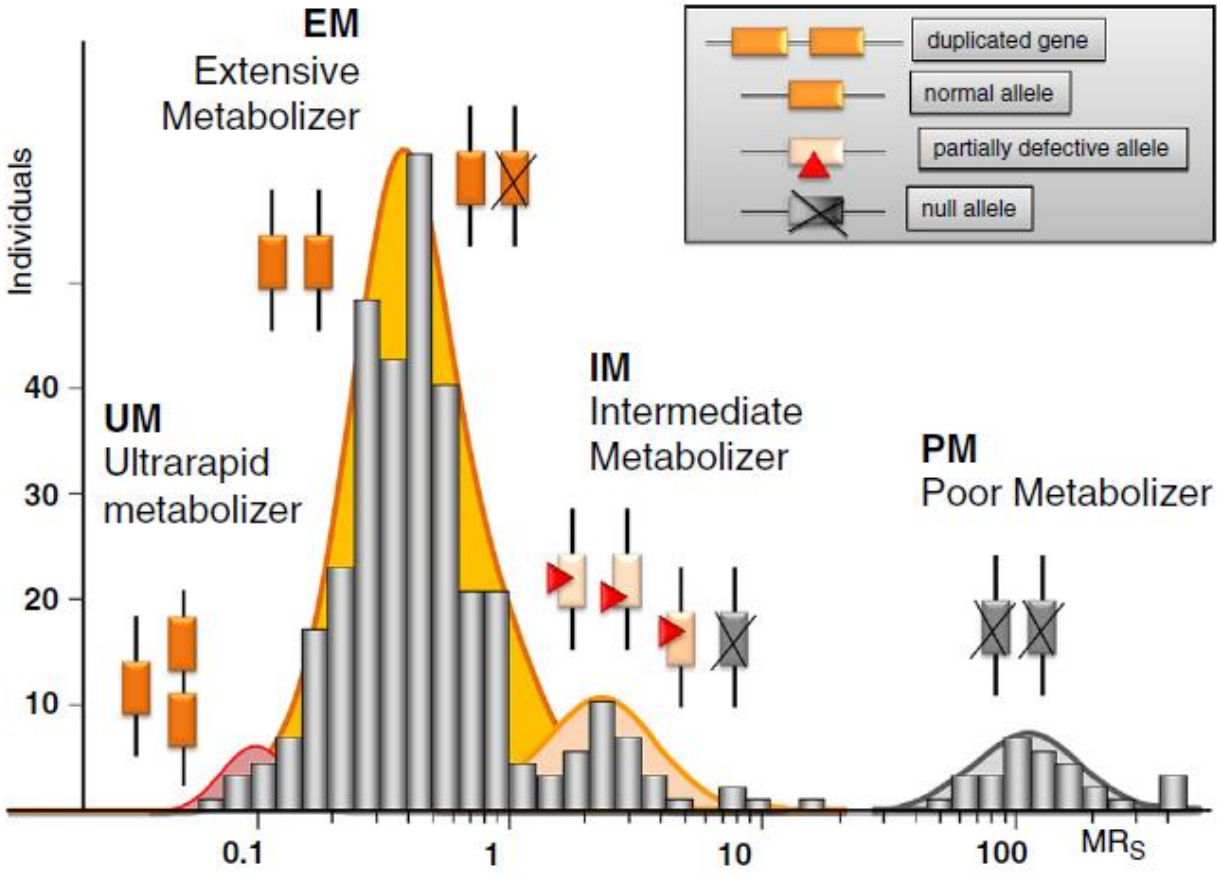


Figure 4.6. Sparteine oxidation phenotype and genotype distribution in a German population

Note: MR_S- urinary metabolic ratio for sparteine. Reproduced respectively by [223].

As GPMs, and PM CYP2C19 more commonly found in Asian than in Caucasian populations, which is the opposite phenomenon to that observed in the geographical distribution of CYP2D6, for which GPMs was more common in Europe and other Caucasian populations than in Asian populations [207]. In the so-called ultra-fast metabolism UM individuals considered as whether they were heterozygous or homozygous for the alleles CYP2C19*17 [224-226].

However, some other reports considered individuals with wt/*17 genotype extensive metabolizers [227, 228]. Consequently, UM frequency calculated to be more cautious, and more research is required to confirm the extensive activity of this option for all populations. Inter-ethnic differences in frequencies and PM may have important clinical significance, and genotype association studies clinical outcome assessment to guarantee the clinical meaning of these differences. For example, the Pacific Islands, there is a wide spread of malaria and in this situation was very necessary proguanil, therefore, can be expected in a dose-dependent adverse effects, even if it has not yet been fully confirmed [229]. Concerning clopidogrel pro-drugs, in clinical consequences PMs CYP2C19 can be more serious, as they would represent the lack of efficiency in antiplatelet therapy. It was recently reported fatal case in Hawaii in the appointment of clopidogrel, the patient in this case was posthumously genotyped both of CYP2C19*2/*3. In this connection, it created the need to allocate special attention to the value of CYP2C19 genotyping to prescription antiplatelet therapy for the inhabitants of the Pacific Islands and in populations with a high incidence of invalid CYP2C19 alleles [230].

In addition, there is sufficient information on the correlation between CYP2C19 genotype and phenotype in African populations. However, due to significant genetic heterogeneity in this region it is likely that this ratio was less robust.

The CYP2C genes [191] and the resultant expression levels [185], the frequency of clinically important alleles were essentially constant over the entire sub-Africa. At the same time, there are some differences in the haplotype structures between the populations of the regions [189]. The most significant ethnic differences were between the populations of sub-Saharan Africa and Africans [189, 190].

To summarize the findings, it is necessary to conduct research as "predicted" phenotypes from genotypes and metabolic "measured" phenotypes simultaneously. While the available data [231], only 20.5% of individuals who measured using a metabolic phenotype of the test drug were also determined CYP2C19 genotype. Furthermore, when the correlation analysis performed between the frequencies phenotypes were not included those individuals who are limit for this assay.

Consequently, for additional research, including as "predicted" phenotypes from genotypes and "measured" metabolic phenotypes is still necessary to confirm whether it is possible for the genotype CYP2C19 accurately predict the actual metabolic phenotype for all individuals.

Large individual differences found in the contents of protein and hepatic level mRNA CYP2B6, a staggering range of 20-278 times [232-235]. CYP2B6 activity varies by 25 times when using S-mephenytoin as a test substrate [233], up to 80 times when using bupropion as a model substrate [236]. Such a large variation occurs, probably due to the effects of exposure to genetic polymorphism or drugs, which are inducers or inhibitors of CYP2B6.

Lang et al. [237] identified nine SNP CYP2B6 genes in the Caucasian population, five of which caused by an amino acid substitution in exons 1, 4, 5 and 9. In the Caucasian population, the SNP found at different frequencies up to 30%. They found six different alleles identified as CYP2B6 *2, *3, *4, *5, *6 and *7 (*1 = wild type). Hiratsuka et al. [238] found a lower frequency of allelic variants of CYP2B6 in the Japanese population, compared to Caucasian. 516G>T SNP was only five no synonymous SNP CYP2B6, identified only in combination with other amino acid mutations in both populations. Xu

et al. [239] found that allele 516G>T CYP2B6 in the Chinese population has been associated with a defective metabolism of efavirenz that, therefore, can predispose to drug toxicity. This allele exhibits more widespread (34.5%) in an ethnic Chinese population, compared to other Asian and Caucasian populations. The frequency of 516T/T genotype was higher among the group of the Han ethnic majority (23.1%) than the other three ethnic minority (that is, respectively, 7.4, 9.1 and 15.8%) Va, Bulang and Lahu of Yunnan in southern China [239].

CYP1A2 activity varies very widely (40-130 times) [240]. Induction has a major influence in the variability of CYP1A2 activity, especially when exposed to certain drugs and xenobiotic. Using the test substrates allowed establishing the prevalence of the phenotype of poor metabolizers (PM) of this enzyme in a number of major populations of the world, which was equal to the Japanese - 14% of Australians - 5%, and the Chinese - 5%. However, Asian and African populations had lower activity of CYP1A2, as compared to the Caucasian [241]. Table 1 (see. Annex) shows the presence of high common allele CYP1A2*1F studied among racial/ethnic groups. This allele increases the inductive function, as evidenced by higher CYP1A2 activity among smokers [242-244].

However, a variety of designations allele CYP1A2*1F in the literature, prevent the truth of laws, as have led to confusion and constant debate sponsors. Therefore, Ingelman-Sundberg et al. identified variant CYP1A2*1F allele as the 163A (-163C> A), indicating a 163C allele CYP1A2*1A, while others took the opposite range [245, 246]. One study on migrants, who used triptan, showed they have a higher frequency of allele 163A. The authors describe the 163C allele as an allele having a lower metabolic activity and identified it as CYP1A2*1F [247].

Much more work has done to identify common variants of CYP450 and determine their global distribution of the population by HGDP. However, many African populations not be represented in the panel of the 52 groups. The revealed considerable diversity observed within sub-Saharan Africa, but many of the available data and SNP microarrays may not adequately capture the diversity in certain loci within the continent. To understand the association between the genetic variant and CYP450 enzyme expression level required extensive research using re-sequencing. One such example is an extended examination of the diversity of CYP1A2 variants in the population of Ethiopia, which revealed many new options, not identified in the other global groups, including West Africa [248]. Focused studies using re-sequencing must take into account the stratification of the population within Africa and is likely to become very important in the development of drug treatment regimens throughout the continent.

IV.2.4. Another types of CYPs

CYP2A6 activates several known procarcinogens, aflatoxin B1, for example, as well as a big CYP isoform responsible for the metabolism of nicotine [249]. The most common alleles for CYP2A6 are considered to be CYP2A6* 1A and *1B alleles. The prevalence of these alleles is 40% each in the Asian population, whereas in the Caucasian population - 66% for the CYP2A6*1A and 30% for the CYP2A6*1B [67, 68]. Four new dysfunctional alleles (*4G, *4H, *1B4 and *1L), were found later in black Africans combined with the spread of 7.3% [250, 251]. The authors noted that some options remain undetected when using previously developed systems introductions substrates.

It found that Latin Americans have the highest activity of CYP2A6, while European Americans, African Americans, Hawaiians and Japanese-Americans had the lowest levels [252]. After adjustment for age, sex, race/ethnicity, and body mass index, revealed that by CYP2A6 diplotipes can predict total nicotine equivalent (TNE) levels, especially among African-Americans and Japanese-Americans (at $P<0.0001$). However, only in a population of Japanese-Americans lower activity coefficient supports lower levels of smoking intensity TNE, carcinogen exposure, and thereby lower the risk of lung cancer. Although the association between nicotine metabolism (activity phenotype CYP2A6 and diplotypes) and smoking intensity (TNE), CYP2A6 levels were not consistent either with higher levels of TNE detected in African Americans, or with lower levels of TNE, identified at the Latin Americans, which suggests the presence of other factors could affect the dose of smoking in these populations [252].

New polymorphisms (2A6R3 and 2A6R4) - specifically African origin were important because they can help to explain the lower nicotine clearance observed in individuals of African populations, relatively Caucasian [253-255]. These differences of metabolism are also important for African-Americans, highly suffering from diseases related to smoking [250]. A similar characteristic in respect of polychlorinated biphenyls (PCB), metabolized by CYP2A6, which are very common in the environment, but quickly metabolized by the majority of people [258]. PCB found in higher concentrations in women of African-Americans with exceptional African origin, with respect to enforcement, women of African-Americans of mixed race/ethnicity [257].

CYP2B6 is very polymorphic and highly inducible enzyme (20-250-fold change) from 53 allelic variants described so far [208, 258]. Multiple SNPs of CYP2B6 may be present in one allele. The most common SNP, present in numerous alleles is c.516G> T. This SNP is responsible for defective phenotype and is often found in combination with c.785A> G [259].

There are many heterogeneities frequency c.516G>T allele in various Asian populations. 516G>T in different Asian groups as follows: Han Chinese (21%), Chinese Hong Kong (43%), Indians (39%), Japanese (14-20%), Koreans (15%), the southern Chinese (35%), Taiwanese (14%), Thais (32%), the Uighurs of China (28%) and Vietnamese (27%) [259-265]. Phenotype CYP2B6 activity for many embodiments and is not described several embodiments, it turns to behave very differently with respect to other substrates. Two of the most common options are the CYP2B6*5 and CYP2B6*6. CYP2B6*6 significantly reduces the activity in cases correlate with aberrant splicing in vivo [266]. Hitherto, alleles with reduced activity in vivo include CYP2B *2, *6, *7, *11, *15, *16, *18, *26, *27 and *28. Another allele, CYP2B*4A shows increased activity, but it is canceled if it is the association with the defective allele. It shown dysfunctional alleles that are present in more than 45% of individuals, but this figure varies widely depending on the population. Another option dysfunctional SNP - c.983T>C is present in the alleles CYP2B6 *16 and *18. Allele CYP2B*18 found in the West African population (4.7%), African Americans (7.5%) and Spanish (1.1%), but not in those of the Caucasian population and Asian Americans.

Up to now, have been identified, at least 9, and variants CYP2J2 indicated as *2 to *10 (http://www.cypalleles.ki.se/). Although CYP2J2 *2, *3, *4 and *6 show a lower CYP2J2 related epoxygenase activity in an in vitro conditions, these options have been extremely rare and are only found in some ethnic groups.

CYP2J2*7 has a substitution G4T in the regulatory region in the 76th position (-50) from the start of transcription, CYP nomenclature Committee recommends the use of G-76T instead of G-50T. Accordingly, this leads to a reduction in the amount of protein and the level CYP2J2 circulating metabolites in vivo [267]. CYP2J2*7 have been identified in all examined ethnic groups and the frequency of this variant alleles varies in specific populations with 1.1-1.2% in Russia [268, 269] to 11-17% in Africa [267, 270-272], indicating the presence of a specific genetic heterogeneity distribution -76G4T polymorphism CYP2J2*7 worldwide.

In 2005, it was reported about identification of two new CYP2J2 variants in Korea, named CYP2J2 *8 and *9, with frequencies respectively 0.8% and 0.18% [273]. Allele CYP2J2 *8 has a point mutation in exon 6 (G9344A), leading to G3124R change [273]. This allele is almost complete disappearance CYP2J2 mediated astemizole O-demethylation and ebastine hydroxylation activities.

The Russian population, demonstrated a significant association between CYP2J2*7, and essential hypertension. After adjustment by multivariate logistic regression for age, gender and family history of hypertension, the association of G-76T genotype with hypertension remained significant [269]. Similarly, a significant higher frequency carriers of mutant alleles CYP2J276 T (TT genotypes, and GT) in hypertensive cases observed, compared with control in Arabia. In contrast, there was no association found between CYP2J2*7 and hypertension [270] in the African-American population. In accordance with this analysis, King et al. [271] also found that the genotype distribution of alleles CYP2J2*7 had no significant differences between African-Americans with and without hypertension. However, a significant protective effect of this SNP found in men of Caucasian population and in Caucasians without a family history of hypertension [271]. In the other case-control studies, no relationship between CYP2J2*7 and hypertension has not been observed in China [274] and Sweden [275].

The association between other genetic variations CYP2J2, such as: CYP2J2 *2, *3, *4, *5, *6, CYP2J2 R49S, L50L, V113M and N124S, and blood pressure were studied in 215 African. However, no association detected between any of these alleles and hypertension [270]. In a subsequent study [274] were found significant differences rs1155002 genotype distribution between hyper- and normotensive Han Chinese women ($p = 0.014$).

Marciante et al. [276] compared 856 patients who suffered myocardial infarction, 368 stroke patients and 2688 healthy US control of persons and found a higher prevalence of coronary events in carriers of two intrinsic CYP2J2 SNP, rs10889160 and rs11572325, however, revealed no differences between CYP2J2 option and distribution of strokes. The Chinese case-control study [277] found that the risk of myocardial infarction increased in subjects with a C allele CYP2J2 SNP rs2271800.

With respect to the study of the frequency of polymorphic alleles and genotypes of CYP system in the countries of the former Soviet Union are well-known studies in Russia almost all isoforms [278, 279].

For example, the study of polymorphism of CYP-450 indigenous peoples of Siberia has shown differences in the frequencies of allelic variants of CYP2C9 [280]. So if CYP2C9*2 Russian Siberia was detected at a frequency of 12%, then the Tuvins (1.1%) and Yakuts (1.1%) was almost 12 times, from the Buryats (2.3%) 6 times and Altai (5.7%) is almost 2 times less. Compared with other representatives of the Caucasian population,

Russian in this parameter is intermediate between the Belgians (10%) and Croats (17%). Similarly, CYP2C9*3 frequency was in Russian 7%, which is comparable with most of the results obtained from the Europeans. While the frequency of this allele was the highest in the Altai group, where it was, 9% compared to 1.7% for the Buryats and 0.6% in Yakuts.

When comparing the CYP2C9*2 alleles frequencies of Armenians and Russian from Stavropol to Russian from Siberia revealed no significant differences. However, it cannot said of the Karachais, where it was (2.9%) almost 5 times less than that of the Slavs, but was comparable to that in the tundra Nenets (2.56%), Nganasans (3.49%) and the Evenkes (3.0%) [281].

In a study of the genetic characteristics of the polymorphic genotypes CYP2D6 in groups of indigenous people in Western Siberia (Caucasians) and a small group of tundra Nenets, belonging to the northern Mongoloid, it was revealed intermediate frequency CYP2D6*4 allele in tundra Nenets, was 7%, compared with Europeans (20%) and Asians (0.3%) [282].

At the same time, it is significantly more common in Karachai ethnic group (20.0%) compared with groups of Armenians (11.4%) and the Slavs (11.4%).

Based on these data, and the lack of CYP2C9*2 alleles in Japanese, Vietnamese and Koreans, a number of authors [283] suggested that the CYP2C9*2 mutant allele has Europeoid origin, and CYP2D6*4 - intermediate position between Asians and Europeans.

In Azerbaijan, according to the work Hasanova NA [284], a clinically significant allele CYP2C9*2 detected at 8%, 7% and 7% in groups Kurds Lezghins and Azerbaijanis, respectively, and even more significant allele CYP2C9*3 - with a frequency of 14%, 9% and 11% in Kurdish groups Lezgins and Azeris respectively.

However, you must note with regret that the population-based studies of CYP-450 polymorphism (except for the measurement C-344T-polymorphic marker of CYP2B1 in 58 healthy and 184 patients with essential hypertension of Uzbeks [285] and CYP2C9 polymorphism in atrial fibrillation [286], which doubtful can be called population-based) and in our neighboring countries of Central Asia have not yet carried out, but the results would be very relevant and in demand for personalized pharmacotherapy.

Thus, ethnic differences in genetic polymorphism of CYP installed in many regions of the world. Mutations that are typical for the population of one region or ethnic group are significantly different from those in other geographical areas or for other ethnic groups. Apparently, this is due to the accumulation of certain genes in populations limited geographically and socially, where gene exchange occurs primarily within a population. A major population factors and mechanisms that determine natural fluctuations in the number of mutations in different regions and populations may be differences in food, serious infections (including AIDS), environmental adaptation, selective advantage of heterozygotes (heterosis effect), genetic drift (random fluctuations in the population of alleles) and several others, may be yet unidentified, phenomena.

In any case, conducting pharmacogenetic monitoring in different ethnic groups has prospects for development and implementation of pharmacogenetic tests, as well as to evaluate the effectiveness and economic feasibility of their application, which should subsequently lead to more reliable results and valid conclusions on the impact of the application and tactics individualized approach pharmacotherapy.

IV.3. APPLIED ASPECTS OF PERSONALIZED PHARMACOTHERAPY

The explosive nature of the growth rate of the global drug market, the rapid development of pharmacology in the last decade and the emergence of a large number of new drugs, of course, increased the possibility of treatment. However, this abundance of drugs causes considerable difficulty taking optimal solutions by specialists when selecting medicines in each case. Thus, according to WHO (2002) in the world at 50% of cases, medications are written and issued incorrectly, to the same 50% of the patients taking them are not properly [279]. At the same time, we know that 95% of doctor's appointments it are drugs [287, 288].

Today, no one doubts that the main cause of mortality and side effects associated with the use of drugs is irrational use of medications [289]. Despite the achievement of modern medical science and practice, this problem remains a serious problem in almost all countries of the world, including in Uzbekistan. According Zurdinova AZ [290], more than half of all medicines complications arise due to mismanagement and illiterate selection and application of even the most effective drugs. In most cases not taken into account the interaction between a drug, food and other factors not taken into account the patient's age and comorbidities.

Another obvious reason considered lack of training. Since the rational use of drugs require a doctor literacy skills, adequate selection and appointment of effective and safe drugs to determine the optimal dosing regimen for each patient depending on the purpose of treatment, taking into account the weight, severe, variants and stage of disease. It is obvious that this complex, multi-step process requires appropriate training of doctors in the field of drug treatment, based on the principles of systematic and continuous training in order to develop relevant skills.

By assigning a medical treatment practitioner goes through several stages: it should select a group of drugs, which is optimal for a given patient within the group to choose a particular drug, finally, select the dosage form of the drug [291].

Choosing the most effective and at the same time safe medication and its proper destination for a particular patient is one of the most difficult processes in the doctor's activities. The complexity of drugs choice - it is primarily the complexity of study (motivation) of choice, which is a multifaceted and deep analytical process.

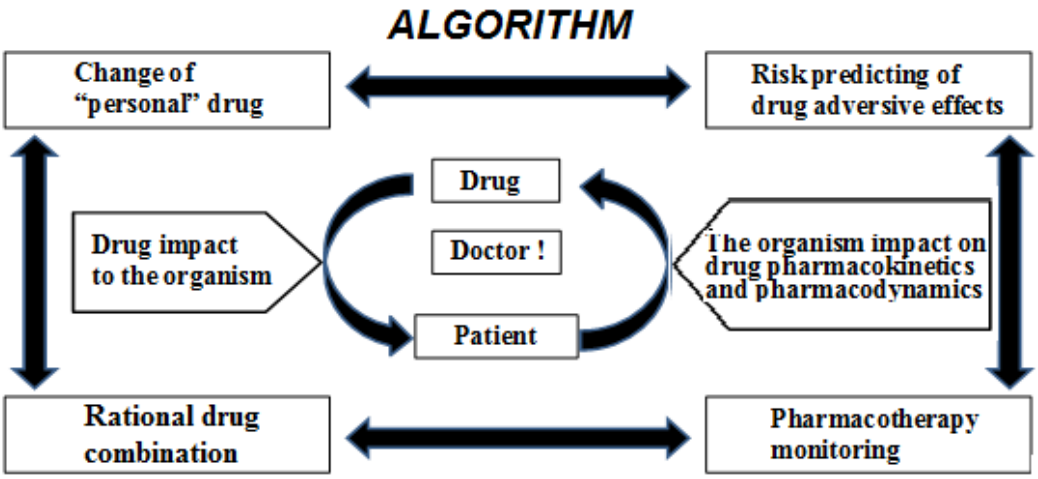


Figure 4.7. The scheme of rational drugs using algorithm

This circumstance dictates the need to develop an algorithm rational and safe use of medicines. In this work, we proposed drug selection algorithm for a particular patient.

As seen from the scheme (Figure 4.7) algorithm is a multi-step and logically coherent system [292].

The first step of the algorithm is to choose the "P" of drugs. Personal drugs (P-drug) are medication that a doctor based on sound scientific information chose to assign their patients as priority drugs.

Most doctors use in their activities, as a rule, no more than 50-60 of drugs, so the choice of drugs to be included in the list of personal carried out very carefully and only after studying all the scientific information on the medicine. To select the "P" medicine physician should make a list of P-drugs.

Making a list of P-drugs - is a creative, dynamic process, in which the doctor constantly improves and updates the list in accordance with the development of science, the development of new drugs, the identification of new, previously unknown, or known properties of drugs with the creation of new dosage forms. Essentially, the entire doctor's knowledge about drugs accumulated in the process of studying the relevant scientific information and a private medical practice, reflected in the list of P-drugs in the form of drug name, its dosage forms, dosing regimen and duration of use. Consequently, the P-drug list is not the likeness of the inventory, having the pharmaceutical drug market. That is why the preparation of P-drugs list is very complex creative process that must performed in a doctor throughout his medical practice, because medical science is in constant development.

To select P-drugs of the P-drug list requires a certain purpose of treating a particular patient. As a rule, after the diagnosis of the disease it is necessary to determine the therapeutic objectives, namely - what is to be achieved in the course of treatment (cure of disease, elimination of violations; elimination of symptoms of the disease, prevention of illness, and their combination).

In this regard, P-selection process involves medication, firstly, deep knowledge of the etiology and pathogenesis, pathophysiology, and clinical disease and, secondly, deep knowledge of the mechanisms of drugs only, this knowledge can be the basis for choosing the most efficient way of treatment.

After the establishment of specific treatment, goals start to the choice of the pharmaceutical group, which carried out in accordance with three essential criteria: efficacy, safety, acceptability.

From the above it becomes clear that the clinician must first determine the target drug combinations within pharmacotherapy particular patient. Then form list of desirable and undesirable drug interactions of P-drugs with other drugs with provision for pharmaceutical, pharmacodynamics and pharmacokinetic interactions. After determining the range of medicinal products for combination drug therapy within a particular patient decide on their dosage regimen.

The doctor, having carried out the choice of P-drugs for a particular patient, determines the probability of the risk of developing PD, forming a circle of drugs for combination embarking on pharmacotherapy. However, this path is traversed consuming intellectual process depends on the degree of professional training of specialists - an

empirical way. Therefore, it requires an assessment as defined in the course of pharmacotherapy.

The basic principle of this algorithm is to implement drug therapy not only in view of the pharmacological action of drugs on the human organism, but also taking into account the organism actions (or factors) of a particular patient on the clinical and pharmacological characteristics of drugs. This approach is the one hand contributes to deep analysis of drug therapy and other scrutiny from the perspective of patient body modification of drugs pharmacokinetic parameters.

Individual variability in drug response and clearance of drugs is a complex and common problem in clinical practice. Overlapping of the substrate specificity of the enzyme, many single-nucleotide polymorphisms (SNPs) and variations among ethnic groups make it difficult to forecast the phenotypic response to the medication. To avoid failures of pharmacotherapy and the appearance of toxicity, for each patient will be essential adaptation of dosage regimen and the use of drug cocktails.

The differences in response to drugs can relate to the variability in the DNA sequences of specific genes whose products considered critical for drug metabolism.

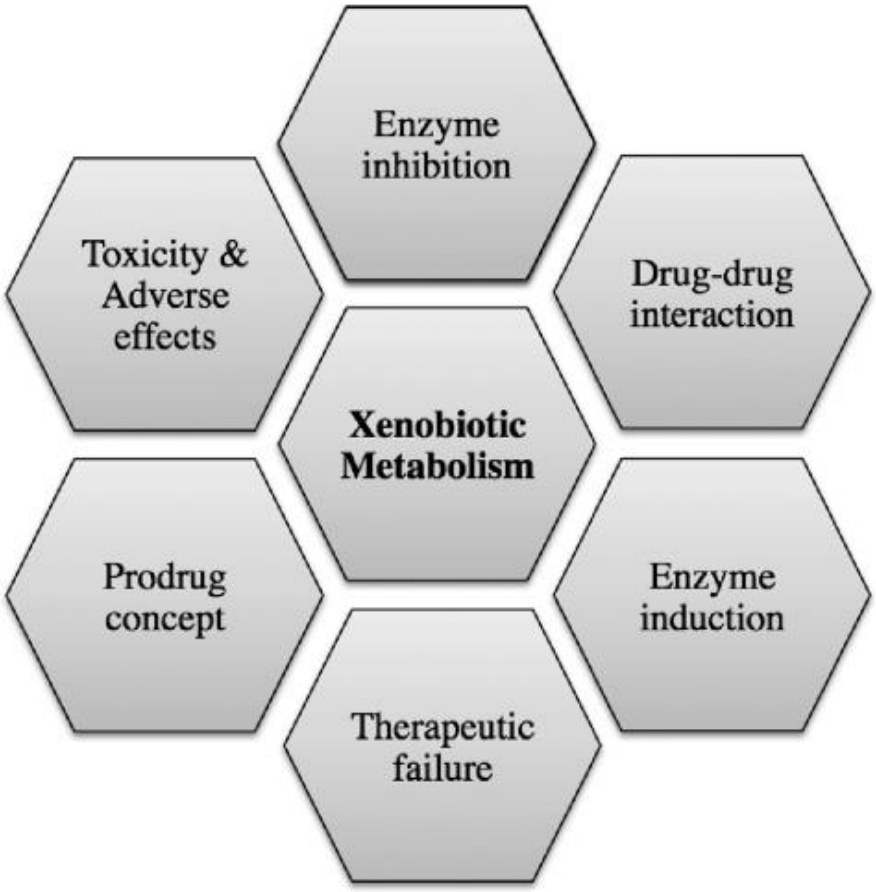


Figure 4.8. Xenobiotic metabolism and its broad spectrum of pharmacodynamics and pharmacokinetic effects.

Note: Potential issues of metabolic liability *and biological activity of xenobiotics on metabolizing enzymes include DDIs (especially enzyme inhibition and induction), which in turn can cause the therapeutic* failure, *toxicity and adverse effects. Metabolic reactions can use also for the rational design of prodrugs. Scheme represented respectively by [293].*

Existing large interindividual variability in the expression of CYP activity in turn, can be cause: the changes in the clearance of drugs and therapeutic efficacy increase the risk of adverse side effects and drug-drug interactions. In adults, the differences in relatedness CYP expression and metabolism mainly genetically determined variability enzyme induction due pharmacotherapy, xenobiotic exposure or dietary factors (Figure 4.8).

This has important implications for the implementation of precision medicine when needed individualized pharmacotherapy for drugs that mainly metabolized by CYP.

Many CYP enzymes display considerable individual variability in their expression and function, which is determined by a combination of genetic, epigenetic and non-genetic parameters (e.g., gender, age, pathophysiological conditions) and environmental factors (e.g., diet, tobacco smoke, medications) [223]. Therefore, each person has his or her own metabolic profile of CYP. As revealed major CYP enzymes involved in 70-80% phase 1 reactions of metabolism of drugs widely used clinically [294], the variability in the activity of the enzyme which may result variability in drug levels in the bioavailability and hence change the response to drug therapy.

Most drugs used in clinic patients prescribed, not knowing the differences in patterns of SNP or genomic variations associated with differential responses to drugs. Since most of the drugs have a low therapeutic index, genetic differences usually result in no or less effective responses to drugs that were unsafe and usually associated with severe and fatal side effects.

The metabolism of most drugs in many cases has to do more than one enzyme CYP. For example, antidepressant fluvoxamine metabolized CYP2D6, CYP2C9, and CYP2C19, therefore only one type genotype CYP insufficient for clinical analysis as genetic confirmation. Effective therapy for most difficult diseases usually requires a combination therapy rather than a mono-drug approach, including more than one type of response pathways for drugs. Furthermore, as shown in Figure 4.9, the drugs response can often conditioned by another, more complex relationships of genes. Therefore, for an accurate assessment of response to the drug becomes extremely important systematic functional analysis of combinations. For example, two functional combination with the upper frequencies (10.94% and 4.69%), include not-EM CYP2D6 and of CYP2C19, and these data could be useful to assess the response to the drug for many antidepressants metabolized by these two genes.

Data profiles combined alleles and functional combinations of the four major CYP genes could be the basis for a systematic evaluation of the effectiveness of pharmacogenomics medications in the context of individualized therapy. The potential consequences range from P-450 polymorphism serious toxicity to drug treatment ineffective. Genetically determined to reduce P-450 activity of the enzyme may have important implications for drugs with a narrow therapeutic index, such as warfarin plasma concentrations, which increase leads to drug toxicity.

When the parent drug is pharmacologically active, the damaged enzyme function may increase the risk of adverse drug reactions (ADRs). For example, Phillips et al. [296] found that 59% of the drugs described in ADR studies, at least partially metabolized by enzymes with reduced function.

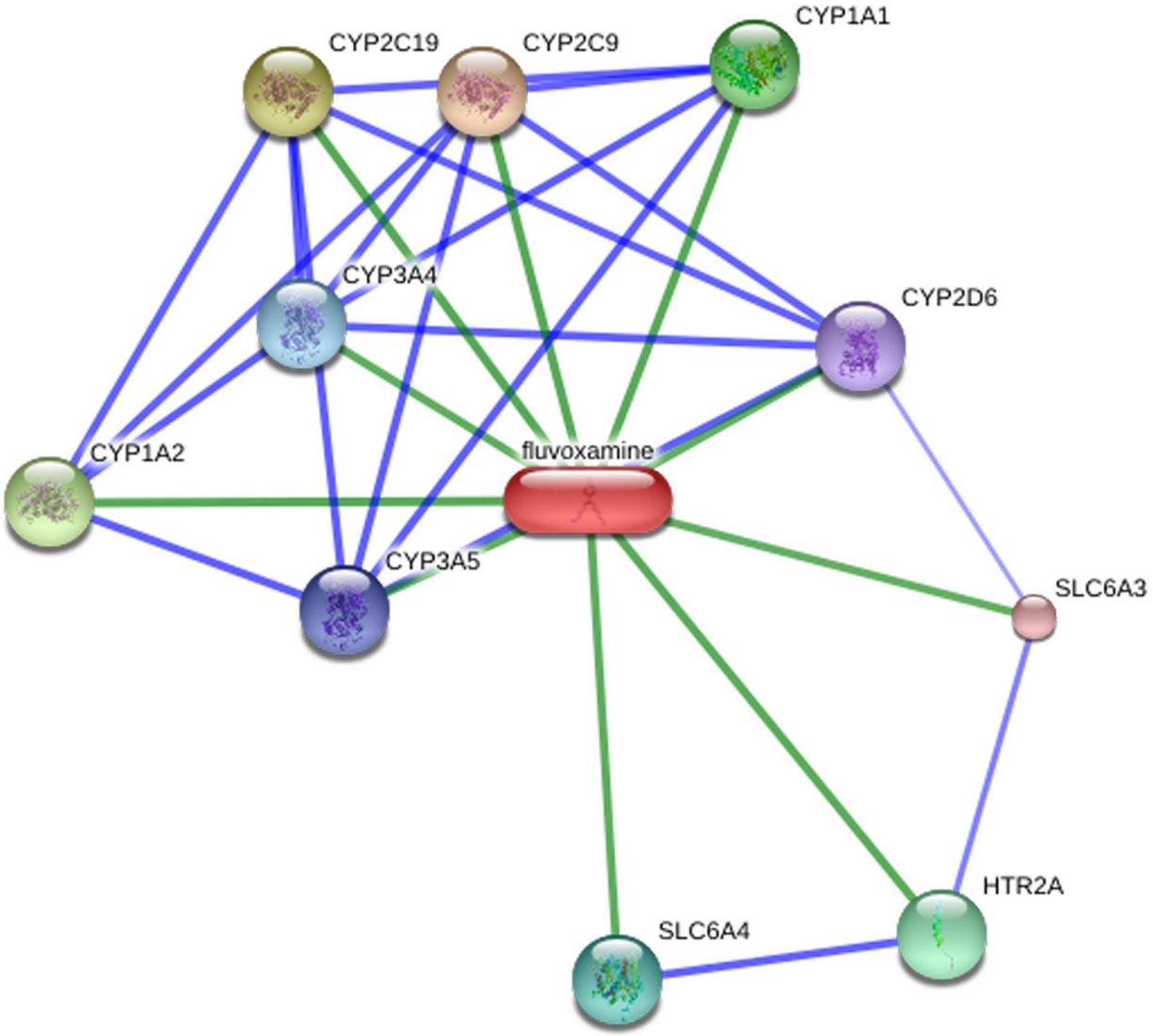


Figure 4.9. Drug-gene relationship network centered on fluvoxamine. Presented respectively by [295].

For pro-drugs, such as codeine and clopidogrel, insufficient activity of the enzyme may prevent achieving a therapeutic plasma concentration of the drug and lead to failure of therapy. Nevertheless, the CYP2D6 gene duplication can lead to toxic reactions to codeine due to the accumulation of the active metabolite of morphine. For drugs with a wide therapeutic index, e.g., SSRIs and beta-blockers, the clinical significance of gene variations P-450 is less important. In cases, if the resultant metabolic inactivation of the parent drug may lead to the failure of drug therapy in greater degree than normal its enzyme activity, increasing the dose of medication is required to achieve effective therapy [223, 297].

Therefore, the evaluation of the metabolic status of the individual for a given path can be a useful tool for explaining the unexpected plasma concentrations of drugs in the identification of the causes of the ADR, the development of targeted therapy, or even predict a suitable dose of medication prior to initiating therapy. Some of CYP enzymes, in particular, CYP2D6, CYP2C19 and of CYP2C9, encoded by the genes are very polymorphic, and may be distinct subpopulation is identified Wane-based genetic recipe

[294, 298, 299]. For many drugs metabolized by these enzymes, clinical outcome can agreed certain genotype and the patient would have been a reliable genotyping strategy to assess the metabolic phenotype [223, 297, and 299]. This approach has the advantage that it can execute only once for each individual and the administration of test drugs are required.

Additionally, the genotypes for enzymes CYP2C9, CYP2C19, and CYP2D6 have a minimum value for susceptibility to disease, as compared with the response to the medication. After all, the hereditary deficiency in CYP2C9 can go completely undetected during the whole of human life, yet it does not appoint a drug with a narrow therapeutic index, such as warfarin, which metabolized through CYP2C9. Similarly, a person with an inactive CYP2D6 cannot suffer any adverse effects, while not taking a medication, such as thioridazine, which may cause cardiac complications in PM by CYP2D6.

For other enzymes important CYP450, such as, CYP1A2 and CYP3A4, it is also described the wide individual variability in enzyme activity. Although multiple polymorphisms identified the relevant genes, different alleles that cause variation in enzyme functions are very rare and only genetic indicators cannot fully explain the variation in enzyme functions [300]. These enzymes significantly influenced by environmental factors, such as inhibitors or inducers of drug, diet components and tobacco-smoking [223].

For obvious ethical reasons, the possible toxicity of drug candidates being developed cannot normally experimentally tested in humans in vivo conditions. Consequently, this requires replacement of the system, such as for in vivo animal studies or human or animal cells in culture. In these replacement systems, biotransformation of drugs are very often largely deviates from the scenario that occurs in humans in vivo, and the consequences can be dramatic.

Identification of CYP activity can be performed reconstructed systems using isolated hepatocytes, liver tissue slices or isolation of microsomal liver tissue biopsy. These techniques are very invasive and treat other problems in interpretation. The cultured hepatocytes are beginning to lose its ability to CYP expression shortly after their release. Microsomes maintain their metabolic activity for an extended period, but require a significant amount of tissue to achieve an adequate level for testing. None of these methods can take account of other physiological parameters, which affect the metabolism, for example, of hepatic bloodstream. To overcome these limitations, the substrate samples identified through metabolism of many isoforms CYP. The test substrates are drugs that undergo CYP mediated metabolism in the liver selectively through one CYP isoform. The test-drug into the body may be monitored elimination of specific metabolites to characterize the activity of CYP isoforms. The list of recommended CYP substrates test was created after watching Zhou literature and the recommendations of the Committee for Proprietary Medicinal Products (CPMP), FDA US, online drug interaction Flockhart tables, European Federation for Pharmaceutical Sciences (EUFEPS) and the American Association Pharmaceutical Sciences (AAPS).

Therefore, the introduction of selective substrates is considered the preferred method to assess the in vivo activity of these enzymes, because then taken into accounts both genetic and non-genetic factors and environmental influences. Moreover, even for those enzymes whose function is primarily genetically controlled, individuals are genotyped as extended metabolizer may express (transiently) poor phenotype due to consumption

inhibiting enzymes drugs or having certain concomitant diseases affecting enzyme activity, such as HIV disease and liver cancer. This phenomenon, called pheno-conversion generally observed for CYP2D6 and CYP2C19. It can be combining the genotyping with phenotyping to obtain an integrated image of enzyme function.

In general, the phenotyping of drug-metabolizing enzymes performed by introducing a selective substrate of the enzyme, the resulting determination of a specific phenotypic indicator. The latter may include various pharmacokinetic parameters such as systemic drug clearance test, the only point concentration or concentration ratios metabolite\parent drug (or coefficient of parent drug/metabolite) usually obtained from plasma or urine samples. Numerous drug test protocols described for a variety of enzymes CYP, some of which have significant confirmation of the ability to provide a reliable estimate of the actual activity of the enzyme.

Thus, CYP genotyping may deliver less ethical difficulties than genotyping for disease-related variants. As such, of CYP genotyping, it is likely to lead to the introduction of clinical pharmacogenomics, as evidenced by the current events at the University of Vanderbilt Children's Hospital and St Jude. Genotyped devices that detect wide variations in numerous genes CYP are commercially available. The use of such devices, providing a list of drugs that metabolized by P-450, could trigger a broad implementation of CYP genotype - guided drug therapy.

Until now, clinicians slowly mastered pharmacokinetics, despite the addition of pharmacogenetic information in the labeling of many drugs. Two notable exceptions are clopidogrel and opioid analgesics. Vanderbilt University Medical Center in Nashville, TN, recently announced by CYP2C19 genotyping variants measures in all patients with a high probability of needing major antiplatelet therapy in the future [301]. Genotyping results described in the electronic medical record for use in selecting the appropriate antiplatelet therapy, in case of acute coronary syndrome or percutaneous coronary, need for intervention. Similarly, children's academic clinicians of StJude Memphis clinics were tested on knowledge of patients CYP2D6 genotype to individualize pain therapy (Figure 4.10.) [302].

In the last decade, pharmacogenomics has become a promising area in the field of personalized medicine. An increasing amount of information that emphasizes the influence of genetic variations on the figure of adverse drug effects or inefficacy of drugs [304-306].

However, the clinical use of pharmacogenetic knowledge is still underdeveloped and mainly concentrated in specialized centers and in clinical trials [307-310]. One reason for this may be the lack of education of doctors in the field of pharmacogenetics, and therefore confidence in these data when working with such information [311].

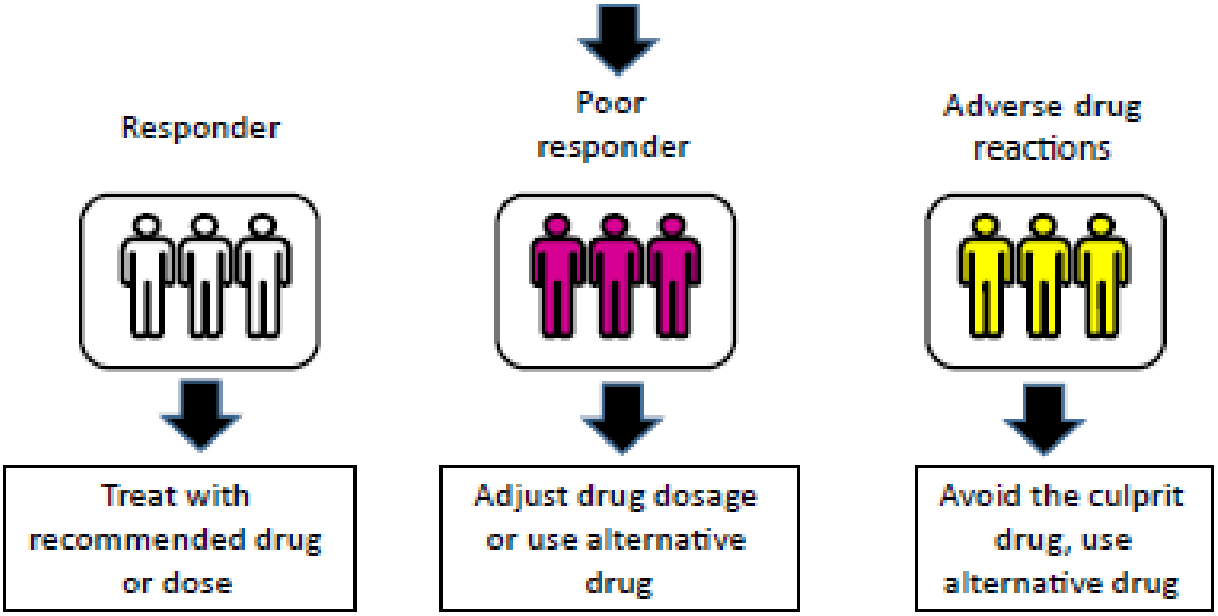


Figure 4.10. Pharmacogenetic testing for pain management.

Note: Pharmacogenetic tests provide information about likelihood of the patient's adverse drug reaction (ADR) and/or therapeutic response to a medication before prescribing pain medication. Accordingly, by Tai-Ming Ko et al. [303].

Support System pharmacogenomics clinical solutions (CDS), if well designed, could help overcome these problems. CDS systems are machine systems that designed to assist and improve medical decision-making, providing at this stage of the finely filtered knowledge of health providers, such as specific recommendations for patient treatment. CDS system may be integrate also into the existing health IT infrastructure, such as, Electronic Health Record (EHR) and Computerized Provider Order Entry (CPOE), or they may be designed as separate programs, web services or mobile applications. In addition, the CDS system may differ in the way of presenting the user to important information: When active the CDS, an automatic alarm triggered in response to an event or action, such as certain medication prescribed to the patient, which is subject to the risk factors, which makes it more vulnerable to the development of adverse drug reactions. Conversely, passive CDS requires the user that he is actively looking for a recommendation, for example, by clicking a button or opening a table.

Studies have shown that physicians have a positive attitude to the CDS system, assessing them as tools to manage and make the best use of a large amount of complex information in which they are often limited [312, 313]. In addition, there is evidence that the implementation of CDS systems can have a positive impact on the health care processes [314, 315]. Finally, the increase amount of knowledge available in pharmacogenetics structural formats that can use for CDS [316]. Nevertheless, the clinical implementation of the CDS systems often hinder the use of questions, the lack of user acceptance and uncertainty about how to effectively implement such system in the existing and diverse operating mode [317]. These issues are particularly relevant in settings where

there are no smart CDS systems with the ability to generate an active order entry based on pharmacogenetics warnings.

In recent years, a significant number of articles published on the development and implementation of pharmacogenetic CDS systems [318-322]. However, most of them are specialized for use within a local or EHR CPOE, and thus their application is limited to the corresponding local health IT infrastructure. In contrast, there are several methods to do pharmacogenetic CDS independent of local infrastructure and opportunities of IT. Examples of such measures include freely available web-based platform that helps to assess the therapeutic dose of warfarin to the patient based on the embodiments, pharmacogenetics and other clinical parameters, such as body weight and medical (www.WarfarinDosing.org). Other mobile solution for CDS genomics includes Genomics Advisor app, which focuses on the prediction of the risk of diabetes and related comorbidities [323].

In recent years began to appear flexible mobile-based system for the CDS pharmacogenetic - guided drug therapy, which can easily integrated into existing processes and health infrastructure, "Drug Safety Code» - «Medication Safety Code» (MSC). MSC system makes it possible to download data on the pharmacogenetics of patients in the compact two-dimensional "quick meeting» - «Quick Response» codes (QR), which can be decoded and interpreted by common smartphones and other devices. QR code can be included in the base paper or the operational messages can printed on personalized cards. Patients can wear these cards in their wallets and make them available to medical professionals when you need to enter or change pharmacotherapy.

After scanning the QR code, a medical professional goes to a web site that provides support for its messaging solutions modificated under the pharmacogenetic profile of the patient. The website provides information about all the medicines for which clinically relevant and current pharmacogenetic information is available by installing the drug for which the specific genetic profile of the patient must point to the top of the deviation from standard therapy. The links below each recommendation enable professionals to study the full text of mainstream and authentic links to Pharmacogenomics Knowledgebase website (PharmGKB). MSC interface screenshot shown in Figure 4.11. Typical MSC QR code, which placed into a personalized credit card-sized card, provides the ability to upload test results pharmacogenetics (i.e., haplotypes and phenotypes) for 20 genes. Generation of the MSC, which loads data on pharmacogenetics for more than 20 genes, it is possible, but requires less compact size QR code. More detailed descriptions of services and substantive Medication Safety Code technology can found in the following publications [324, 325].

Of the problems that remain solved in the framework of the use of CDS, need to note the following: the uncertainty of the economic costs and the ratio of income-ratio and the preservation of data secrecy.

While a positive effect on the outcome of treatment, as well as the cost-effectiveness of pharmacogenetics - guided drug therapy is only shown for a number of drugs, the situation for other medicines actually is unclear or contradictory [326-329]. However, the parallel development of a proactive approach pharmacogenetics - testing would increase the efficiency and reduce testing costs [330].

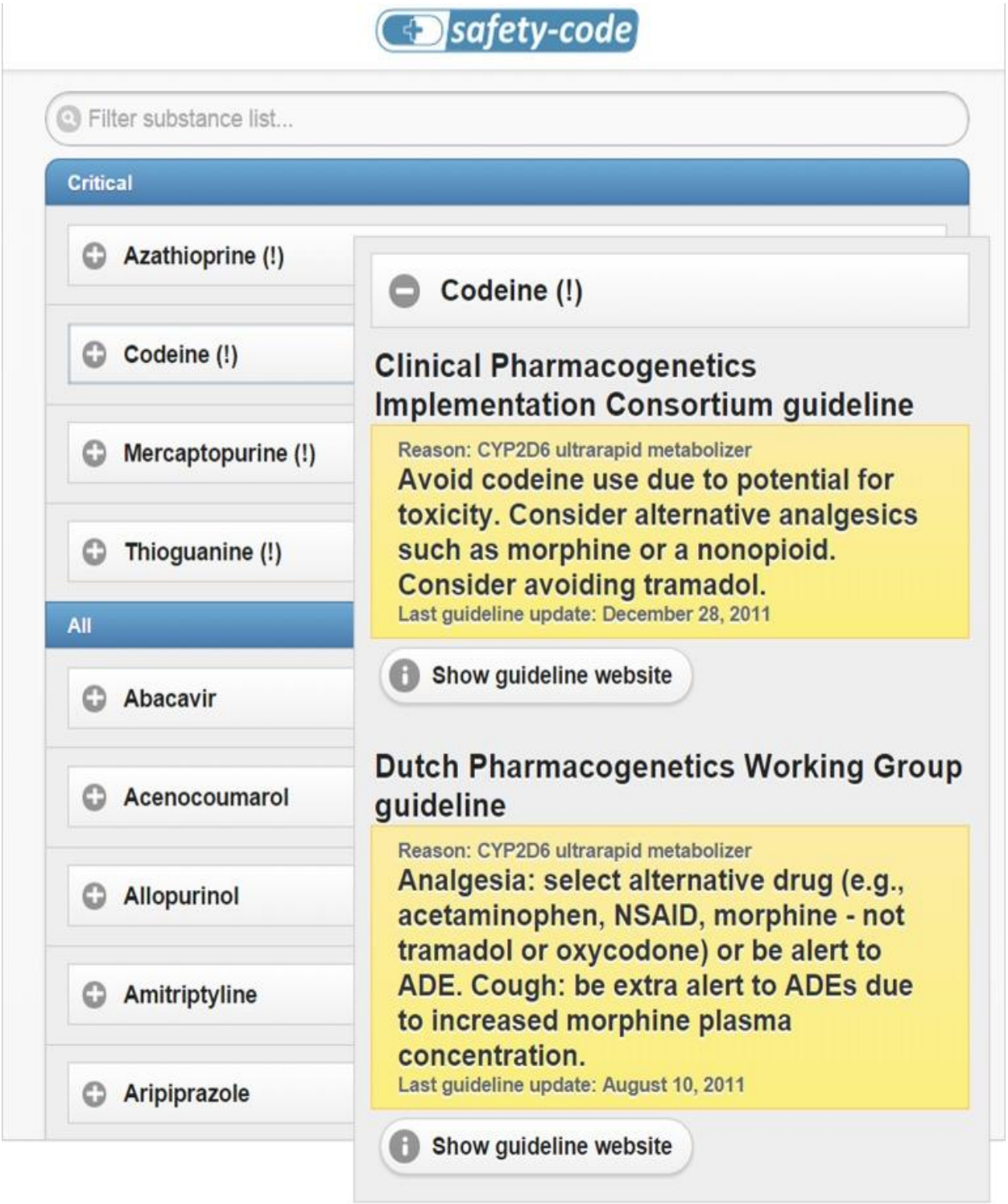


Figure 4.11. The patient-specific guidance for the purpose of codeine.

Note: shows a diagram for a hypothetical patient, on which there are available the results of pharmacogenetic test to identify it as "ultrafast metabolizer for CYP2D6» and «poor metabolizer for TPMT». Screenshot shows a version of the user interface, which used in the pilot interviews with pharmacists. Scheme represented respectively [325].

Although some US regulatory documents, such as: Genetic Information Nondiscrimination Act (GINA) and the Health Insurance Portability and Accountability Act (HIPAA) and similar policies in Europe, concerns about data privacy still when it

comes to testing pharmacogenetics. Concerns that the providers of health insurance will be able to gain access to the results of a genetic test is widespread and it is anticipated the need for educational activities on the legal and regulatory framework, as well as the importance and benefits of testing variations of enzymes of drug metabolism in comparison to testing for the risk and course of the disease [331].

Finally, it is now a wide swing the process of developing a prototype pocket card that fits the expanded use of pharmacogenetic data to support decisions by adjusting various parameters of health. It should be noted that the gene-centered and tabulated presentation of pharmacogenetic profile of the patient based on a pocket card is considered to be the most useful to draw the attention of clinicians and pharmacists to the patient, such as poor metabolizers, and to the existence of a potential need for adaptation of therapy. In addition, there is actual need for information transparency for pharmacogenetic data source (i.e., tested options, laboratory contact details) to make such a system a valuable and acceptable to the pharmacogenetics of professionals.

REFERENCES

1. Corsini A., Bortolini M. Drug-induced liver injury: The role of drug metabolism and transport. J Clin Pharmacol. 2013;53:463–474.

2. Villeneuve JP, Pichette V. Cytochrome P450 and liver diseases. Curr Drug Metab.2004;5:273–282.

3. Krakovsky ME Drug metabolism in animal organs on some experimental pathology. Abstract of dissertation on doctor of medical science– Moscow, 1991.

4. Khakimov ZZ The pharmacological effectiveness of inducer benzonal in correction of monooxygenase system alteration at the pathological states. Abstract of dissertation on doctor of medical science– Tashkent, 1994.

5. Zueva EB Condition of portal-hepatic bloodstream and hepatocytes microsomal system in patients with hepatic cirrhosis, different portal hypertension and drug correction pathways. Abstract of dissertation on doctor of medical science– Tashkent, 2004.

6. Frye RF, Zgheib NK, Matzke GR et al. Liver disease selectively modulates cytochrome P450-mediated metabolism. Clin Pharmacol Ther. 2006;80:235–245.

7. Jeong SW, Jang JY, Chung RT Hepatitis C virus and hepatocarcinogenesis. Clin Mol Hepatol. 2012;18:347–356.

8. Negro F. Hepatitis C in 2013: HCV causes systemic disorders that can be cured. Nat Rev Gastroenterol Hepatol. 2014;11:77–78.

9. Imran M., Manzoor S., Khattak NM et al. Current and future therapies for hepatitis C virus infection: From viral proteins to host targets. Arch Virol. 2014;159:831–846.

10. Cortez KJ, Kottilil S. Beyond interferon: Rationale and prospects for newer treatment paradigms for chronic hepatitis C. Ther Adv Chronic Dis.2015;6:4–14.

11. Martel-Laferriere V., Dieterich DT Treating HCV in HIV 2013: On the cusp of change. Liver Int. 2014;34(Suppl 1):53–59.

12. Komurasaki R., Imaoka S., Tada N. et al. LKM-1 sera from autoimmune hepatitis patients that recognize ERp57, carboxylesterase1 and CYP2D6. Drug Metab Pharmacokinet. 2010;25:84–92.

13. Hintermann E., Holdener M., Bayer M. et al. Epitope spreading of the anti-CYP2D6 antibody response in patients with autoimmune hepatitis and in the CYP2D6 mouse model. J Autoimmun. 2011;37:242–253.

14. Ma Y., Bogdanos DP, Hussain MJ et al. Polyclonal T-cell responses to cytochrome P450IID6 are associated with disease activity in autoimmune hepatitis type 2. Gastroenterology, 2006;130:868–882.

15. Mizutani T., Shinoda M., Tanaka Y. et al. Autoantibodies against CYP2D6 and other drug-metabolizing enzymes in autoimmune hepatitis type 2. Drug Metab Rev. 2005; 37:235–252.

16. Joanne C., Paintaud G., Bresson-Hadni S. et al. Is debrisoquine hydroxylation modified during acute viral hepatitis? Fundam Clin Pharmacol.1994;8:76–79.

17. Girardin F., Daali Y., Gex-Fabry M. et al. Liver kidney microsomal type 1 antibodies reduce the CYP2D6 activity in patients with chronic hepatitis C virus infection. J Viral Hepat. 2012;19:568–573.

18. Ho MT, Kelly EJ, Bodor M. et al. Novel cytochrome P-450-2D6 promoter sequence variations in hepatitis C positive and negative subjects. Ann Hepatol. 2011;10:327–332.

19. Nakai K., Tanaka H., Hanada K. et al. Decreased expression of cytochromes P-450 1A2, 2E1, and 3A4 and drug transporters Na+-taurocholate-cotransporting polypeptide, organic cation transporter 1, and organic anion-transporting peptide-C correlates with the progression of liver fibrosis in chronic hepatitis C patients. Drug MetabDispos. 2008;36:1786–1793.

20. Boelsterli UA, Ho HK, Zhou S., Leow KY. Bioactivation and hepatotoxicity of nitroaromatic drugs. Curr Drug Metab. 2006;7:715–727.

21. Zhou S., Chan E., Duan W. et al. Drug bioactivation, covalent binding to target proteins and toxicity relevance. Drug Metab Rev. 2005;37:41–213.

22. Czaja AJ, Manns MP Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. Gastroenterology, 2010;139:58–72.

23. Bieche I., Asselah T., Laurendeau I. et al. Molecular profiling of early stage liver fibrosis in patients with chronic hepatitis C virus infection. Virology, 2005;332:130–144.

24. Asselah T., Bieche I., Laurendeau I. et al. Liver gene expression signature of mild fibrosis in patients with chronic hepatitis C. Gastroenterology, 2005;129:2064–2075.

25. Leung TM, Nieto N. CYP2E1 and oxidant stress in alcoholic and non-alcoholic fatty liver disease. J Hepatol. 2013;58:395–398.

26. Cederbaum AI CYP2E1–biochemical and toxicological aspects and role inalcohol-induced liver injury. Mt Sinai J Med. 2006;73:657–672.

27. Aubert J., Begriche K., Knockaert L. Increased expression of cytochrome P-450 2E1 in nonalcoholic fatty liver disease: mechanisms and pathophysiological role. Clin Res Hepatol Gastroenterol. 2011;35:630–637.

28. Millonig G., Wang Y., Homann N. et al. Ethanol-mediated carcinogenesis in the human esophagus implicates CYP2E1 induction and the generation of carcinogenic DNA-lesions. Int J Cancer. 2011;128:533–540.

29. Wang Y., Millonig G., Nair J. et al. Ethanol-induced cytochrome P-4502E1 causes carcinogenic etheno-DNA lesions in alcoholic liver disease. Hepatology, 2009; 50:453–461.

30. Krakovsky ME Effect and toxicity peculiarities of drug, that metabolized in the liver, in experimental acute renal failure. Abstract of dissertation on candidate of medical science–Tashkent, 1982.

31. Yuabova JYu The change of hepatocytes microsomal oxidative system activity in some endogenous intoxications. Abstract of dissertation on candidate of biological science– Tashkent, 1991.

32. Barnes KJ, Rowland A., Polasek TM, Miners JO Inhibition of human drug-metabolising cytochrome P-450 and UDP glucuronosyltransferase enzyme activities in vitro by uremic toxins. Eur J Clin Pharmacol. 2014;70(9):1097-1106.

33. Velenosi TJ, Feere DA, Sohi G. et al. Decreased nuclear receptor activity and epigenetic modulation associates with down-regulation of hepatic drug-metabolizing enzymes in chronic kidney disease. FASEBJ. 2014;28(12):5388-5397.

34. Dreisbach AW The influence of chronic renal failure on drug metabolism and transport. Clin Pharmacol Ther. 2009;86:553–556.

35. Dreisbach AW, Lertora JJ The effect of chronic renal failure on drug metabolism and transport. Expert Opin Drug Metab Toxicol. 2008;4:1065–1074.

36. Yeung CK, Shen DD, Thummel KE, Himmelfarb J. Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport. Kidney Int. 2014;85:522–528.

37. Ladda MA, Goralski KB The Effects of CKD on Cytochrome P450–Mediated Drug Metabolism. Advances in Chronic Kidney Disease, 2016;23(2):67-75.

38. Tsujimoto M., Sugimoto S., Nagatomo M. et al. Possibility of decrease in CYP1A2 function in patients with end-stage renal disease. Ther Apher Dial. 2014;18:174–180.

39. Daminov BT Trombocyte and erythrocyte hemostatic systems and liver monooxygenase system in patients with chronic renal failure. Abstract of dissertation on candidate of medical science–Tashkent, 1997.

40. Alidjanov NA The pharmacological correction of hepatic function hidden alteration in patients with uremic stone disease complicated chronic pyelonephritis. Abstract of dissertation on candidate of medical science–Tashkent, 1998.

41. Mavlyanov IR The pharmacokinetics and pharmacodynamics peculiarities of drug, that metabolized in the liver, on burn trauma. Abstract of dissertation on candidate of medical science–Tashkent, 1987.

42. Ashirmetov AKh The effects and toxicity peculiarities of drug, that metabolized in the liver, in experimental peritonitis. Abstract of dissertation on candidate of medical science–Tashkent, 1983.

43. Ahmedov RM The hepatic drug-metabolizing function in elderly and senile age patients with peritonitis. Abstract of dissertation on candidate of medical science–Tashkent, 1987.

44. Finegold DY The pharmacokinetics and pharmacodynamics peculiarities of some drug metabolized in the liver, on acute intestinal obstruction. Abstract of dissertation on candidate of medical science–Tashkent, 1988.

45. Muhtarova MS Hepatic detoxication function in experimental pancreatitis. Abstract of dissertation on candidate of medical science–Tashkent, 1992.

46. Mahkamov KE Hepatic monooxygenase system and surfactant of lungs in experimental skull–brain trauma and pharmacological correction of revealled alteration. Abstract of dissertation on candidate of medical science–Tashkent, 1993.

47. Kaumov TH The change of hepatic drug metabolism in postoperative period. Abstract of dissertation on candidate of medical science–Tashkent, 1986.

48. Ganiev ShA Clinico-pharmacological motivation of inducer benzonal implication in preoperational preparing of patients with chronic nonspecific lungs diseases. Abstract of dissertation on candidate of medical science–Tashkent, 1990.

49. Nakachi K., Imai K., Hayashi S., Kawajiri K. Polymorphisms of the CYP1A1 and glutathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. Cancer Res. 1993;53:2994–2999.

50. Ishibe N., Wiencke JK, Zuo ZF et al. Susceptibility to lung cancer in light smokers associated with CYP1A1 polymorphisms in Mexican- and African-Americans. Cancer Epidemiol Biomarkers Prev. 1997;6:1075–1080.

51. London SJ, Yuan JM, Coetzee GA et al. CYP1A1 I462V genetic polymorphism and lung cancer risk in a cohort of men in Shanghai, China. Cancer Epidemiol Biomarkers Prev. 2000;9:987–991.

52. Shi X., Zhou S., Wang Z. et al. CYP1A1 and GSTM1 polymorphisms and lung cancer risk in Chinese populations: a meta-analysis. Lung Cancer, 2008;59:155–163.

53. Kawajiri K., Watanabe J., Eguchi H., Hayashi S. Genetic polymorphisms of drug-metabolizing enzymes and lung cancer susceptibility. Pharmacogenetics, 1995;5Spec No:S70–S73.

54**.** Lin J., He B., Cao L. et al**.** CYP1A1 Ile462Val polymorphism and the risk of non-small cell lung cancer in a Chinese population. Tumori. 2014;100(5):547-552.

55. Wei XP, Hu J. Cytochrome P-450 1A1 exon 7 polymorphism and susceptibility to lung cancer in the Chinese population: an updated meta-analysis and review.Onco Targets Ther. 2015;8:1611-1618.

56. Diergaarde B., Potter JD, Jupe ER et al. Polymorphisms in genes involved in sex hormone metabolism, estrogen plus progestin hormone therapy use, and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev. 2008;17:1751–1759.

57. Justenhoven C., Hamann U., Schubert F. et al. Breast cancer: a candidate gene approach across the estrogen metabolic pathway. Breast Cancer Res Treat. 2008;108:137–149.

58. Mittal RD, Srivastava DL Cytochrome P-4501A1 and microsomal epoxide hydrolase gene polymorphisms: gene-environment interaction and risk of prostate cancer. DNA Cell Biol. 2007;26:791–798.

59. Silig Y., Pinarbasi H., Gunes S. et al. Polymorphisms of CYP1A1, GSTM1, GSTT1, and prostate cancer risk in Turkish population. Cancer Invest. 2006;24:41–45.

60. Sellers TA, Schildkraut JM, Pankratz VS et al. Estrogen bioactivation, genetic polymorphisms, and ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2005;14:2536–2543.

61. Holt SK, Rossing MA, Malone KE et al. Ovarian cancer risk and polymorphisms involved in estrogen catabolism. Cancer Epidemiol Biomarkers Prev. 2007;16:481–489.

62. Terry KL, Titus-Ernstoff L., Garner EO et al. Interaction between CYP1A1 polymorphic variants and dietary exposures influencing ovarian cancer risk. Cancer Epidemiol Biomarkers Prev. 2003;12:187–190.

63. Moysich KB, Shields PG, Freudenheim JL et al. Polychlorinated biphenyls, cytochrome P-4501A1 polymorphism, and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev. 1999;8:41–44.

64. Chen X., Wang H., Xie W. et al. Association of CYP1A2 genetic polymorphisms with hepatocellular carcinoma susceptibility: a case-control study in a high-risk region of China. Pharmacogenet Genomics, 2006;16:219–227.

65. Pavanello S., B'Chir F., Pulliero A. et al. Interaction between CYP1A2-T2467DELT polymorphism and smoking in adenocarcinoma and squamous cell carcinoma of the lung. Lung Cancer, 2007;57:266–272.

66. Osawa Y., Osawa KK, Miyaishi A. et al. NAT2 and CYP1A2 polymorphisms and lung cancer risk in relation to smoking status. Asian Pac J Cancer Prev. 2007;8:103–108.

67. Agudo A., Sala N., Pera G. et al. Polymorphisms in metabolic genes related to tobacco smoke and the risk of gastric cancer in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev. 2006;15:2427–2434.

68. Li D., Jiao L., Li Y. et al. Polymorphisms of cytochrome P4501A2 and N-acetyltransferase genes, smoking, and risk of pancreatic cancer. Carcinogenesis, 2006;27:103–111.

69. Le Marchand L., Donlon T., Kolonel LN et al. Estrogen metabolism-related genes and breast cancer risk: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev. 2005;14:1998–2003.

70. Mikhailova ON, Gulyaeva LF, Prudnikov AV et al. Estrogen-metabolizing gene polymorphisms in the assessment of female hormone-dependent cancer risk. Pharmacogenomics, 2006;6:189–193.

71. Rossini A., de Almeida Simao T., Albano RM Pinto LF CYP2A6 polymorphisms and risk for tobacco-related cancers. Pharmacogenomics, 2008;9:1737–1752.

72. Miyamoto M., Umetsu Y., Dosaka-Akita H. et al. CYP2A6 gene deletion reduces susceptibility to lung cancer. Biochem Biophys Res Commun. 1999;261:658–660.

73. Loriot MA, Rebuissou S., Oscarson M. et al. Genetic polymorphisms of cytochrome P450 2A6 in a case-control study on lung cancer in a French population. Pharmacogenetics, 2001;11:39–44.

74. Khlifi R., Chakroun A., Hamza-Chaffai A., Rebai A. Association of CYP1A1 and CYP2D6 gene polymorphisms with head and neck cancer in Tunisian patients. Mol Biol Rep. 2014;41:2591–2600.

75. Huang Y., Liu X., Kuang X., Liao D. CYP2D6 T188C variant is associated with lung cancer risk in the Chinese population. Tumour Biol. 2013;34:2189–2193.

76. Li H., Feng L., Xu Y. et al. The association of CYP2D6 *10 polymorphism with breast cancer risk and clinico-pathologic characteristics in Chinese women.Acta Oncol. 2006;45:597–601.

77. Modugno F., Knoll C., Kanbour-Shakir A., Romkes M. A potential role for the estrogen-metabolizing cytochrome P450 enzymes in human breast carcinogenesis. Breast Cancer Res Treat. 2003;82:191–197.

78. Maurya SS, Katiyar T., Dhawan A. et al. Gene-environment interactions in determining differences in genetic susceptibility to cancer in subsites of the head and neck.Environ Mol Mutagen. 2015;56(3):313-321.

79. Leng WD, Zeng XT, Chen YJ et al. Cytochrome P450 2E1 RsaI/PstI polymorphism and risk of esophageal cancer: a meta-analysis of 17 case-control studies. Exp Ther Med. 2012;4:938–948.

80. Wang Y., Yang H., Li L. et al. Association between CYP2E1 genetic polymorphisms and lung cancer risk: a meta-analysis. Eur J Cancer. 2010;46:758–764.

81. Wang YD, Yang HY, Liu J., Wang HY Updated meta-analysis of the association between CYP2E1 RsaI/PstI polymorphisms and lung cancer risk in Chinese population. Asian Pac J Cancer Prev. 2014;15:5411–5416.

82. Tian Z., Li YL, Zhao L., Zhang CL CYP2E1 RsaI/PstI polymorphism and liver cancer risk among east Asians: a HuGE review and meta-analysis. Asian Pac J Cancer Prev. 2012;13:4915–4921.

83. Lu D., Yu X., Du Y. Meta-analyses of the effect of cytochrome P450 2E1 gene polymorphism on the risk of head and neck cancer. Mol Biol Rep. 2011;38:2409–2416.

84. Zhou GW, Hu J., Li Q. CYP2E1 PstI/RsaI polymorphism and colorectal cancer risk: a meta-analysis. World J Gastroenterol. 2010;16:2949–2953.

85. Deng XD, Gao Q., Zhang B. et al. Functional RsaI/PstI polymorphism in cytochrome P450 2E1 contributes to bladder cancer susceptibility: evidence from a meta-analysis. Asian Pac J Cancer Prev. 2014;15:4977–4982.

86. Zhuo W., Zhang L., Wang Y. et al. CYP2E1 RsaI/PstI polymorphism and gastric cancer susceptibility: meta-analyses based on 24 case-control studies. PLoS One, 2012;7:e48265.

87. Liao G., Wang Y., Zhou YQ et al. Host genetic susceptibility to oral cancer: evidence from meta-analyses and pooled analyses. Oral Dis. 2014;20:644–649.

88. Basma HA, Kobeissi LH, Jabbour ME et al. CYP2E1 and NQO1 genotypes and bladder cancer risk in a Lebanese population. Int J Mol Epidemiol Genet. 2013;4:207–217.

89. Cantor KP, Villanueva CM, Silverman DT et al. Polymorphisms in GSTT1, GSTZ1, and CYP2E1, disinfection by-products, and risk of bladder cancer in Spain. Environ Health Perspect. 2010;118:1545–1550.

90. Wang YH, Yeh SD, Shen KH et al. A significantly joint effect between arsenic and occupational exposures and risk genotypes/diplotypes of CYP2E1, GSTO1 and GSTO2 on risk of urothelial carcinoma. Toxicol Appl Pharmacol. 2009;241:111–118.

91. Mittal RD, Srivastava DS Genetic polymorphism of drug metabolizing enzymes (CYP2E1, GSTP1) and susceptibility to bladder cancer in North India. Asian Pac J Cancer Prev. 2005;6:6–9.

92. Yang J., Qian LX, Wu HF et al. Genetic polymorphisms in the cytochrome P450 1A1 and 2E1 genes, smoking, drinking and prostate cancer susceptibility: a case-control study in a Han nationality population in Southern China. Int J Urol. 2006;13:773–780.

93. Yuldashev NM The interlink of hepatic monooxygenase enzymes system with ischemic alteration range of myocardium in process of experimental myocardial infarction. Abstract of dissertation on doctor of biological science–Tashkent, 1997.

94. Elmuradov MT The myocardial infarction development peculiarities on the different level of hepatic monooxygenase system operation. Abstract of dissertation on candidate of medical science–Tashkent, 1994.

95. Djamaldinova PK Actovegine and essentiale influence on hepatic drug biotransformation and free radicals oxydation systems in acute period of myocardial infarction. Abstract of dissertation on candidate of medical science–Tashkent, 1997.

96. Yuldasheva FI The hepatic bloodstream state and drug-metabolizing function in patients with heart ischemic disease and its alteration correction by antianginal drugs treatment. Abstract of dissertation on candidate of medical science–Tashkent, 1993.

97. Hodjaeva RSh The treatment individualization of patients with hypertensive disease in dependence on nervous system typing, hemodynamics and drug-metabolizing peculiarities of organism. Abstract of dissertation on candidate of medical science–Tashkent, 1999.

98. Usmanov RI Pharmacological correction of hepatic monooxygenase system and lung surfactant synthesis in chronical bronchitis. Abstract of dissertation on doctor of medical science– Moscow, 1991.

99. Sultanova KM The pharmacokinetic parameters dynamics of theophylline by verapamil action in patients with chronic obstructive bronchitis. Abstract of dissertation on candidate of medical science–Tashkent, 1995.

100. Zufarov PS Clinico-pharmacological basis of inducer benzonal using in complex therapy of bronchial asthma. Abstract of dissertation on candidate of medical science–Tashkent, 1990.

101. Dostalek M., Akhlaghi F., Puzanovova M. Effect of diabetes mellitus on pharmacokinetic and pharmacodynamic properties of drugs. Clin Pharmacokinet. 2012; 51:481–499.

102. Carvalho TM, Cavalli Rde C., Cunha SP et al. Influence of gestational diabetes mellitus on the stereoselective kinetic disposition and metabolism of labetalol in hypertensive patients. Eur J Clin Pharmacol. 2011;67:55–61.

103. Marques MP, Coelho EB, Dos Santos NA et al. Dynamic and kinetic disposition of nisoldipine enantiomers in hypertensive patients presenting with type-2 diabetes mellitus. Eur J Clin Pharmacol. 2002;58:607–614.

104. Matzke GR, Frye RF, Early JJ et al. Evaluation of the influence of diabetes mellitus on antipyrine metabolism and CYP1A2 and CYP2D6 activity. Pharmacotherapy, 2000;20:182–190.

105. Madacsy L., Barkai L., Santa A., Krikovszky D. Altered distribution of the debrisoquine oxidative phenotypes in children with type 1 diabetes mellitus. Horm Res. 2004;61:176–179.

106. Antunes Nde J., Cavalli RC, Marques MP et al. Influence of gestational diabetes on the stereoselective pharmacokinetics and placental distribution of metoprolol and its metabolites in parturients. Br J Clin Pharmacol. 2015;79:605–616.

107. Poscorcova TV The investigation of treatment efficacy by benzonal addition in complex therapy of patients with type 2 diabetes mellitus. Abstract of dissertation on candidate of medical science–Tashkent, 1990.

108. Nadjimutdinova DK The clinic-experimental investigation of hepatic drug-metabolizing function in thyreotoxicosis. Abstract of dissertation on candidate of medical science–Tashkent, 1987.

109. Lu Y., Qin X., Li S. et al. Quantitative assessment of CYP2D6 polymorphisms and risk of Alzheimer's disease: A meta-analysis. J Neurol Sci. 2014;343:15–22.

110. Golab-Janowska M., Honczarenko K., Gawronska-Szklarz B., Potemkowski A. CYP2D6 gene polymorphism as a probable risk factor for Alzheimer's disease and Parkinson's disease with dementia. Neurol Neurochir Pol. 2007;41:113–121.

111. Singh NK, Banerjee BD, Bala K. et al. Polymorphism in cytochrome P450 2D6, glutathione S-transferases 1 Genes, and organochlorine pesticides in Alzheimer disease: A case-control study in North Indian population. J Geriatr Psychiatry Neurol. 2014;27:119–127.

112. Scordo MG, Dahl ML, Spina E. et al. No association between CYP2D6 polymorphism and Alzheimer's disease in an Italian population. Pharmacol Res. 2006; 53:162–165.

113. Atkinson A., Singleton AB, Steward A. et al. CYP2D6 is associated with Parkinson's disease but not with dementia with Lewy Bodies or Alzheimer's disease. Pharmacogenetics, 1999;9:31–35.

114. Harhangi BS, Oostra BA, Heutink P. et al. CYP2D6 polymorphism in Parkinson's disease: The Rotterdam Study. Mov Disord. 2001;16:290–293.

115. Joost O., Taylor CA, Thomas CA et al. Absence of effect of seven functional mutations in the CYP2D6 gene in Parkinson's disease. Mov Disord.1999; 14:590–595.

116. Stefanovic M., Topic E., Ivanisevic AM et al. Genotyping of CYP2D6 in Parkinson's disease. Clin Chem Lab Med. 2000;38:929–934.

117. Lo HS, Chen CH, Hogan EL et al. Genetic polymorphism and Parkinson's disease in Taiwan: Study of debrisoquine 4-hydroxylase (CYP2D6). J Neurol Sci. 1998; 158:38–42.

118. Persad AS, Stedeford T., Tanaka S. et al. Parkinson's disease and CYP2D6 polymorphism in Asian populations: A meta-analysis.Neuroepidemiology, 2003;22:357–361.

119. Lu Y, Peng Q, Zeng Z. et al. CYP2D6 phenotypes and Parkinson's disease risk: A meta-analysis. J Neurol Sci. 2014;336:161–168.

120. Lu Y, Mo C, Zeng Z. et al. CYP2D6*4 allele polymorphism increases the risk of Parkinson's disease: Evidence from metaanalysis. PLoSOne, 2013;8:e84413.

121. Musaev MU Hepatic monooxygenase system investigation in rheumatoid arthritis and search of the correction variants for revealled alterations. Abstract of dissertation on candidate of medical science–Tashkent, 1991.

122. Abduraimova MM Improvement of pharmacotherapy with provision for functional links of monooxygenase and immune systems in rheumatoid arthritis. Abstract of dissertation on candidate of medical science–Tashkent, 1993.

123. Beyeler C, Daly AK, Armstrong M. et al. Phenotype/genotype relationships for the cytochrome P450 enzyme CYP2D6 in rheumatoid arthritis: Influence of drug therapy and disease activity. J Rheumatol. 1994; 21:1034–1039.

124. Nigmatova GM The monooxygenase enzymes and lipid peroxidation process charactheristics in experimental endometritis and these pharmacological correction. Abstract of dissertation on candidate of medical science–Tashkent, 1997.

125. Alieva LE Clinico-pathogenetic importance of hepatic monooxygenase enzymes system in acute intestinal infections. Abstract of dissertation on candidate of medical science–Tashkent, 1992.

126. Mavlyanov ZI Some premiseses to involvements of cytochrome P-450 system for drug allergy. Terapevticheskiy vestnik Uzbekistana, 2014;4:213.

127. Rahimov AT Study of the benzonal impact on monooxygenase and immune systems interlink in organism. Abstract of dissertation on candidate of biological science–Tashkent, 1987.

128. Harvey RD, Morgan ET Cancer, inflammation, and therapy: Effects on cytochrome p450-mediated drug metabolism and implications for novel immunotherapeutic agents. Clin Pharmacol Ther. 2014;96:449–457.

129. Lee JI, Zhang L., Men AY et al. CYP-mediated therapeutic protein-drug interactions: Clinical findings, proposed mechanisms and regulatory implications. Clin Pharmacokinet. 2010;49:295–310.

130. Shah RR, Smith RL Inflammation-induced phenoconversion of polymorphic drug metabolizing enzymes: Hypothesis with implications for personalized medicine. Drug Metab Dispos. 2015;43:400–410.

131. Headland SE, Norling LV The resolution of inflammation: Principles and challenges. Semin Immunol. 2015;27:149–160.

132. McNab F., Mayer-Barber K., Sher A. et al. Type I interferons in infectious disease. Nat Rev Immunol. 2015;15:87–103.

133. Sokol CL, Luster AD The chemokine system in innate immunity. Cold Spring Harb Perspect Biol. 2015;7:pii:a016303.

134. Aitken AE, Morgan ET Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes. Drug Metab Dispos. 2007;35:1687–1693.

135. Dallas S., Chattopadhyay S., Sensenhauser C. et al. Interleukins-12 and -23 do not alter expression or activity of multiple cytochrome P450 enzymes in cryopreserved human hepatocytes. Drug MetabDispos, 2013;41:689–693.

136. Assenat E., Gerbal-Chaloin S., Larrey D. et al. Interleukin 1 binhibits CAR-induced expression of hepatic genes involved in drug and bilirubin clearance. Hepatology, 2004;40:951–960.

137. Wu H., Liu Z., Ling G. et al. Transcriptional suppression of CYP2A13 expression by lipopolysaccharide in cultured human lung cells and the lungs of a CYP2A13-humanized mouse model. Toxicol Sci. 2013;135:476–485.

138. Patel SA, Bhambra U., Charalambous MP et al. Interleukin-6 mediated upregulation of CYP1B1 and CYP2E1 in colorectal cancer involves DNA methylation, miR27b and STAT3. Br J Cancer, 2014;111:2287–2296.

139. Kurokohchi K., Yoneyama H., Matsuo Y. et al. Effects of interleukin 1α on the activities and gene expressions of the cytochrome P4502D subfamily. Biochem Pharmacol.1992;44:1669–1674.

140. Gorski JC, Hall SD, Becker P. et al. In vivo effects of interleukin-10 on human cytochrome P450 activity. Clin Pharmacol Ther. 2000;67:32–43.

141. Alimhanov KB Vitiligo curation with provision for functional state of hepatic monooxygenase system. Abstract of dissertation on candidate of medical science– Tashkent, 1994.

142. Episheva LV Pathogenetic therapy of atopic dermatitis in children: importance of nervous system typology peculiarities, autonomic reactivity, acetylation phenotype and monooxygenase activity. Abstract of dissertation on candidate of medical science– Moscow, 1992.

143. Tihonova NN Pathogenetic therapy of patients with essential exema on base the nervous system types, autonomic reactivity, acetylation phenotype and monooxygenase activity analysis. Abstract of dissertation on candidate of medical science–S-Peterburg, 1991.

144. Yakubov AV Hepatic drug-metabolizing function in ulcer disease of duodenum and its correction ways. Abstract of dissertation on candidate of medical science– Tashkent, 1989.

145. Yakubov AV The assay of MOS inducers cytoprotective action mechanisms and its implications in stomach ulcer disease treatment. Abstract of dissertation on doctor of medical science– Tashkent, 1998.

146. Shah-Djahan Hepatic monooxygenase system in patients with ferrum-deficitic anemia and its pharmacological correction. Abstract of dissertation on candidate of medical science–Tashkent, 1992.

147. Preissner SC, Hoffmann MF, Preissner R. et al. Polymorphic Cytochrome P450 Enzymes (CYPs) and Their Role in Personalized Therapy. PLoS ONE, 2013;8(12): e82562. doi:10.1371/journal.pone.0082562

148. Campbell MC, Tishkoff SA African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. Annu Rev Genomics Hum Genet. 2008;9:403–433.

149. Pakenham T. The Scramble for Africa, 1876-1912. Weidenfeld and Nicolson: London, 1991.

150. Salas A., Richards M., De la Fe T. et al. The making of the African mtDNA landscape. Am J Hum Genet. 2002;71:1082–1111.

151. Tishkoff SA, Reed FA, Friedlaender FR et al. The genetic structure and history of Africans and African Americans. Science, 2009;324:1035–1044.

152. Schuster SC, Miller W., Ratan A. et al. Complete Khoisan and Bantu genomes from southern Africa. Nature, 2010;463:943–947.

153. Wojnowski L. Genetics of the variable expression of CYP3A in humans. Ther Drug Monit. 2004;26:192–199.

154. Kuehl P., Zhang J., Lin Y. et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet. 2001;27:383–391.

155. Quaranta S., Chevalier D., Allorge D. et al. Ethnic differences in the distribution of CYP3A5 gene polymorphisms. Xenobiotica, 2006;36:1191–1200.

156. Roy JN, Lajoie J., Zijenah LS et al. CYP3A5 genetic polymorphisms in different ethnic populations. Drug Metab Dispos. 2005;33:884–887.

157. Bains RK, Kovacevic M., Plaster CA et al. Molecular diversity and population structure at the Cytochrome P450 3A5 gene in Africa. BMC Genet 2013;14. doi: 10.1186/1471-2156-14-34.

158. Thompson EE, Kuttab-Boulos H., Witonsky D. et al. CYP3A variation and the evolution of salt-sensitivity variants. Am J Hum Genet. 2004;75:1059–1069.

159. Lin YS, Dowling AL, Quigley SD et al. Co-regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism. Mol Pharmacol. 2002;62:162–172.

160. Boobis AR, Edwards RJ, Adams DA et al. Dissecting the function of cytochrome P450. Br J Clin Pharmacol. 1996;42:81–89.

161. Hustert E., Haberl M., Burk O. et al. The genetic determinants of the CYP3A5 polymorphism. Pharmacogenetics, 2001;11:773–779.

162. Lee SJ, Usmani KA, Chanas B. et al. Genetic findings and functional studies of human CYP3A5 single nucleotide polymorphisms in different ethnic groups. Pharmacogenetics, 2003;13:461–472.

163. Xie HG, Wood AJ, Kim RB et al. Genetic variability in CYP3A5 and its possible consequences. Pharmacogenomics, 2004;5:243–272.

164. Li J., Zhang L., Zhou H. et al. Global patterns of genetic diversity and signals of natural selection for human ADME genes. Hum Mol Genet. 2011;20:528–540.

165. Fukuen S., Fukuda T., Matsuda H. et al. Identification of the novel splicing variants for the hPXR in human livers.Biochem Biophys Res Commun.2002; 298:433–438.

166. Chou FC, Tzeng SJ, Huang JD Genetic polymorphism of cytochrome P450 3A5 in Chinese. Drug Metab Dispos. 2001;29:1205–1209.

167. Shih PS, Huang JD Pharmacokinetics of midazolam and 1’-hydroxymi-dazolam in Chinese with different CYP3A5 genotypes. Drug Metab Dispos. 2002;30:1491–1496.

168. Fukuen S., Fukuda T., Maune H. et al. Novel detection assay by PCR-RFLP and frequency of the *CYP3A5* SNPs, *CYP3A5*3* and *6, in a Japanese population. Pharmacogenetics, 2002;12:331–334.

169. Qiu H., Mathas M., Nestler S. et al. The unique complexity of the CYP3A4 upstream region suggests a nongenetic explanation of its expression variability. Pharmacogenet Genomics, 2010;20:167–178.

170. Chen X., Wang H., Zhou G. et al. Molecular population genetics of human CYP3A locus: signatures of positive selection and implications for evolutionary environmental medicine. Environ Health Perspect. 2009;117:1541–1548.

171. Westlind-Johnsson A., Hermann R., Huennemeyer A. et al. Identification and characterization of CYP3A4*20, a novel rare CYP3A4 allele without functional activity. Clin Pharmacol Ther. 2006;79:339–349.

172. Walker AH, Jaffe JM, Gunasegaram S. et al. Characterization of an allelic variant in the nifedipine-specific element of CYP3A4: ethnic distribution and implications for prostate cancer risk. Mutations in brief no. 191.Online. Hum Mutat. 1998;12:289.

173. Rebbeck TR, Jaffe JM, Walker AH et al. Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4. J Natl Cancer Inst. 1998;90:1225–1229.

174. Westlind A., Lofberg L., Tindberg N. et al. Interindividual differences in hepatic expression of CYP3A4: relationship to genetic polymorphism in the 50-upstream regulatory region. Biochem Biophys Res Commun. 1999;259:201–205.

175. Shi Y., Li Y., Tang J. et al. Influence of CYP3A4, CYP3A5 and MDR-1 polymorphisms on tacrolimus pharmacokinetics and early renal dysfunction in liver transplant recipients. Gene, 2013;512:226–231.

176. Naoe T., Takeyama K., Yokozawa T. et al. Analysis of genetic polymorphism in NQO1, GST-M1, GST-T1, and CYP3A4 in 469 Japanese patients with therapy-related leukemia/ myelodysplastic syndrome and *de novo* acute myeloid leukemia. Clin Cancer Res.2000;6:4091–4095.

177. Chen X., Wang H., Zhou G. Molecular Population Genetics of Human CYP3A Locus: Signatures of Positive Selection and Implications for Evolutionary Environmental Medicine. Environ Health Perspect. 2009;117:1541–1548.

178. van Schaik R.H., de Wildt SN, Brosens R. et al. The CYP3A4*3 allele: is it really rare? Clin Chem. 2001;47:1104–1106.

179. Sata F., Sapone A., Elizondo G. et al. CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: evidence for an allelic variant with altered catalytic activity. Clin Pharmacol Ther. 2000;67:48–56.

180. Hsieh KP, Lin YY, Cheng CL et al. Novel mutations of *CYP3A4* in Chinese. Drug Metab Dispos.2001;29:268–273.

181. Garcia-Martin E., Martinez C., Pizarro RM et al. CYP3A4 variant alleles in white individuals with low CYP3A4 enzyme activity. Clin Pharmacol Ther. 2002; 71:196–204.

182. Ingelman-Sundberg M., Sim SC, Gomez A. et al. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther. 2007;116:496–526.

183. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J. 2005;5:6–13.

184. Teh LK, Bertilsson L. Pharmacogenomics of CYP2D6: molecular genetics, interethnic differences and clinical importance. Drug Metab Pharmacokinet. 2012;27:55–67.

185. Sistonen J., Fuselli S., Palo JU et al. Pharmacogenetic variation at CYP2C9, CYP2C19, and CYP2D6 at global and microgeographic scales. Pharmacogenet Genomics, 2009;19:170–179.

186. Sistonen J, Sajantila A., Lao O. et al. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenet Genomics, 2007;17:93–101.

187. Dandara C., Masimirembwa CM, Magimba A. et al. Genetic polymorphism of CYP2D6 and CYP2C19 in east- and southern African populations including psychiatric patients. Eur J Clin Pharmacol. 2001;57:11–17.

188. Masimirembwa C., Persson I., Bertilsson L. et al. A novel mutant variant of the CYP2D6 gene (CYP2D6*17) common in a black African population: association with diminished debrisoquine hydroxylase activity. Br J Clin Pharmacol. 1996;42:713–719.

189. Speed WC, Kang SP, Tuck DP et al. Global variation in CYP2C8-CYP2C9 functional haplotypes. Pharmacogenomics J. 2009;9:283–290.

190. Garcia-Martin E., Martinez C., Ladero JM et al. Interethnic and intraethnic variability of CYP2C8 and CYP2C9 polymorphisms in healthy individuals. Mol Diagn Ther.2006;10:29–40.

191. Kudzi W., Dodoo AN, Mills JJ Characterisation of CYP2C8, CYP2C9 and CYP2C19 polymorphisms in a Ghanaian population. BMC Med Genet. 2009;10:124.

192. Limdi N., Goldstein J., Blaisdell J. et al. Influence of CYP2C9 Genotype on warfarin dose among African American and European Americans. Per Med. 2007;4:157-169.

193. Scott SA, Jaremko M., Lubitz SA et al. CYP2C9*8 is prevalent among African-Americans: implications for pharmacogenetic dosing. Pharmacogenomics, 2009;10:1243-1255.

194. Pechandova K., Buzkova H., Matouskova O. et al. Genetic polymorphisms of CYP2C8 in the Czech Republic. Genet Test Mol Biomarkers, 2012;16:812–816.

195. 1000 Genomes Project Consortium, Abecasis GR, Auton A., Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA; An integrated map of genetic variation from 1,092 human genomes. Nature, 2012;491:56–65.

196. Suarez-Kurtz G., Genro JP, de Moraes MO et al. Global pharmacogenomics: Impact of population diversity on the distribution of polymorphisms in the CYP2C cluster among Brazilians. Pharmacogenomics J. 2012;12:267–276.

197. Martis S., Peter I., Hulot JS et al. Multiethnic distribution of clinically relevant CYP2C genotypes and haplotypes. Pharmacogenomics J. 2013;13:369–377.

198. Roco A., Quinones L., Agundez JA et al. Frequencies of 23 functionally significant variant alleles related with metabolism of antineoplastic drugs in the chilean population: comparison with caucasian and asian populations. Front Genet. 2012;3:229.

199. Vicente J., Gonzalez-Andrade F., Soriano A. et al. Genetic polymorphisms of CYP2C8, CYP2C9 and CYP2C19 in Ecuadorian Mestizo and Spaniard populations: a comparative study.Mol Biol Rep. 2014;41:1267–1272.

200. Backman JT, Filppula AM, Niemi M., Neuvonen PJ Role of Cytochrome P450 2C8 in Drug Metabolism and Interactions. Pharmacol Rev. 2016;68:168–241.

201. Minhas S., Setia N., Pandita S. et al. Prevalence of CYP2C8 polymorphisms in a North Indian population. Genet Mol Res. 2013;12:2260–2266.

202. Wu X., Zuo J., Guo T., Yuan L. CYP2C8 polymorphism frequencies among Han, Uighur, Hui, and Mongolian Chinese populations. Genet Test Mol Biomarkers, 2013;17:104–108.

203. Staehli Hodel EM, Csajka C., Ariey F. et al. Effect of single nucleotide polymorphisms in cytochrome P450 isoenzyme and N-acetyltransferase 2 genes on the metabolism of artemisinin-based combination therapies in malaria patients from Cambodia and Tanzania. Antimicrob Agents Chemother. 2013;57:950–958.

204. Arnaldo P., Thompson RE, Lopes MQ et al. Frequencies of cytochrome P450 2B6 and 2C8 allelic variants in the mozambican population. Malays J Med Sci. 2013; 20:13–23.

205. Arun Kumar AS, Kumar SS, Umamaheswaran G. et al. Association of CYP2C8, CYP2C9 and CYP2J2 gene polymorphisms with myocardial infarction in South Indian population. Pharmacol Rep. 2015;67:97–101.

206. Vargens DD, Petzl-Erler ML, Suarez-Kurtz G. Distribution of CYP2C polymorphisms in an Amerindian population of Brazil. Basic Clin Pharmacol Toxicol. 2012;110:396–400.

207. Lerena A., Naranjo MEG, Rodrigues-Soares F. et al. Interethnic variability of CYP2D6 alleles and of predicted and measured metabolic phenotypes across world populations. Expert Opin Drug Metab Toxicol. 2014;10:1569–1583.

208. Ingelman-Sundberg M., Daly AK, Nebert DW Home Page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee. 2010. Available from: http://www.cypalleles.ki.se/

209. Zhou SF, Zhou ZW, Huang M. Polymorphisms of human cytochrome P450 2C9 and the functional relevance. Toxicology, 2010;278(2):165-188.

210. Gulati S., Yadav A., Kumar N. et al. Frequency distribution of high risk alleles of CYP2C19, CYP2E1, CYP3A4 genes in Haryana population. Environ Toxicol Pharmacol. 2014;37(3):1186-1193.

211. Pedersen RS, Brasch-Andersen C., Sim SC et al. Linkage disequilibrium between the CYP2C19*17 allele and wildtype CYP2C8 and CYP2C9 alleles: identification of CYP2C haplotypes in healthy Nordic populations. Eur J Clin Pharmacol. 2010;66:1199-1205.

212. Miura J., Obua C., Abbo C. et al. Cytochrome P450 2C19 genetic polymorphisms in Ugandans. Eur J Clin Pharmacol. 2009;65:319-320.

213. Sim SC, Risinger C., Dahl ML et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther. 2006;79:103-113.

214. World population statistics. Available at: www.worldpopulationstatistics. com (accessed 1 May 2014).

215. Henn BM, Feldman MW The great human expansion. Proc Natl Acad Sci USA, 2012;109:17758–17764.

216. Hsu H-L, Woad KJ, Woodfield DG, Helsby NA A high incidence of polymorphic CYP2C19 variants in archival blood samples from Papua New Guinea. Hum Genomics, 2008;3:17–23.

217. Yusuf Irawan, Djojosubroto MW, Rika Wan et al. Ethnic and geographical distributions of CYP2C19 alleles in the populations of Southeast Asia. In: Marzuki S., Verhoef .J, Snippe H. (eds). Tropical Diseases. Springer:New York, USA, 2003, pp 37–46.

218. Kaneko A., Lum JK, Yaviong L. et al. High and variable frequencies of CYP2C19 mutations: medical consequences of poor drug metabolism in Vanuatu and other Pacific islands. Pharmacogenetics, 1999;9:581–590.

219. Griese EU, Ilett KF, Kitteringham NR et al. Allele and genotype frequencies of polymorphic cytochromes P4502D6, 2C19 and 2E1 in aborigines from western Australia. Pharmacogenetics, 2001;11:69–76.

220. Masta A., Lum JK, Tsukahara T. et al. Analysis of Sepik populations of Papua New Guinea suggests an increase of CYP2C19 null allele frequencies during the colonization of Melanesia. Pharmacogenetics, 2003;13:697–700.

221. Wanwimolruk S., Bhawan S., Coville PF, Chalcroft SC Genetic polymorphism of debrisoquine (CYP2D6) and proguanil (CYP2C19) in South Pacific Polynesian populations. Eur J Clin Pharmacol. 1998;54:431–435.

222. Wanwimolruk S., Pratt EL, Denton JR et al. Evidence for the polymorphic oxidation of debrisoquine and proguanil in a New Zealand Maori population. Pharmacogenetics, 1995;5:193–198.

223. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138:103–141.

224. Clinical Pharmacogenetics Implementation Consortium (CPIC). CYP2C19. Pharmacogenomics Knowledge Database. Available at: ttps://www.pharmgkb.org/ cpic/alleles (accessed 20 March 2014).

225. Rudberg I., Mohebi B., Hermann M. et al. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther. 2008;83:322–327.

226. Bauer T., Bouman HJ, van Werkum JW et al. Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. BMJ, 2011;343:d4588.

227. Sugimoto K., Uno T., Yamazaki H., Tateishi T. Limited frequency of the CYP2C19*17 allele and its minor role in a Japanese population. Br J Clin Pharmacol.2008;65:437–439.

228. Payan M., Rouini MR, Tajik N. et al. Hydroxylation index of omeprazole in relation to CYP2C19 polymorphism and sex in a healthy Iranian population. Daru, 2014; 22:81.

229. Kaneko A., Bergqvist Y., Taleo G. et al. Proguanil disposition and toxicity in malaria patients from Vanuatu with high frequencies of CYP2C19 mutations. Pharmacogenetics, 1999;9:317–326.

230. Wu AH, WhiteSam MJ, Burchard E. The Hawaii clopidogrel lawsuit: the possible effect on clinical laboratory testing. Per Med. 2015;12:179–181.

231. Fricke-Galindo I., Cespedes-Garro C., Rodrigues-Soares F. et al. Interethnic variation of CYP2C19 alleles, 'predicted' phenotypes and 'measured' metabolic phenotypes across world populations The Pharmacogenomics Journal, 2016;16:113 – 123.

232. Chang TK, Bandiera SM, Chen J. Constitutive androstane receptor and pregnane X receptor gene expression in human liver: interindividual variability and correlation with CYP2B6 mRNA levels. Drug Metab Dispos. 2003;31:7–10.

233. Ekins S., Vandenbranden M., Ring BJ et al. Further characterization of the expression in liver and catalytic activity of CYP2B6. J Pharmacol Exp Ther. 1998;286:1253–1259.

234. Hanna IH, Krauser JA, Cai H. et al. Diversity in mechanisms of substrate oxidation by cytochrome P450 2D6.Lack of an allosteric role of NADPH-cytochrome P450 reductase in catalytic regioselectivity. J Biol Chem. 2001;276:39553–39561.

235. Stresser DM, Kupfer D. Monospecific antipeptide antibody to cytochrome P-450 2B6. Drug Metab Dispos.1999;27:517–525.

236. Faucette SR, Hawke RL, Lecluyse EL et al. Validation of bupropion hydroxylation as a selective marker of human cytochrome P450 2B6 catalytic activity. Drug Metab Dispos. 2000;28:1222–1230.

237. Lang T., Klein K., Fischer J. et al. Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. Pharmacogenetics, 2001;11:399–415.

238. Hiratsuka M., Hinai Y., Konno Y. et al. Three novel single-nucleotide polymorphisms (SNPs) of the CYP2B6 gene in Japanese individuals. Drug Metab Pharmacokinet. 2004;19:155–158.

239. Xu X., Kelsey KT, Wiencke JK et al. Cytochrome P450 CYP1A1 MspI polymorphism and lung cancer susceptibility.Cancer Epidemiol Biomarkers Prev. 1996; 5:687–692.

240. Gunes A., Dahl ML Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms. Pharmacogenomics, 2008;9:625-637.

241. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev. 2009;41:289-295

242. Aklillu E., Carrillo JA, Makonnen E. et al. Genetic polymorphism of CYP1A2 in Ethiopians affecting induction and expression: characterization of novel haplotypes with single-nucleotide polymorphisms in intron 1. Mol Pharmacol. 2003;64:659-669.

243. Han XM, Ouyang DS, Chen XP et al. Inducibility of CYP1A2 by omeprazole in vivo related to the genetic polymorphism of CYP1A2. Br J Clin Pharmacol. 2002;54:540-543.

244. Sachse C., Brockmoller J., Bauer S. et al. Functional significance of a C-- > A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol. 1999;47:445-449.

245. Ingelman-Sundberg M., Sim SC, Nebert DW Coffee, myocardial infarction, and CYP nomenclature. Jama, 2006;296:764-765.

246. Cornelis MC, El-Sohemy A., Kabagambe EK et al. Coffee, CYP1A2 genotype, and risk of myocardial infarction. Jama, 2006;295:1135-1141.

247. Gentile G., Borro M., Lala N. et al. Genetic polymorphisms related to efficacy and overuse of triptans in chronic migraine. J Headache Pain, 2010;11:431-435.

248. Browning SL, Tarekegn A., Bekele E. et al. CYP1A2 is more variable than previously thought: a genomic biography of the gene behind the human drug-metabolizing enzyme. Pharmacogenet Genomics, 2010;20:647–664.

249. Yi B., Yang JY, Yang M. Past and future applications of CYP450-genetic polymorphisms for biomonitoring of environmental toxicants. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2007;25:353-377.

250. Mwenifumbo JC, Al Koudsi N., Ho MK et al. Novel and established CYP2A6 alleles impair in vivo nicotine metabolism in a population of Black African descent. Hum Mutat. 2008;29:679-688.

251. Mwenifumbo JC, Zhou Q., Benowitz NL et al. New CYP2A6 gene deletion and conversion variants in a population of Black African descent. Pharmacogenomics, 2010;11:189-198.

252. Park SL, Tiirikainen MI, Patel YM et al. Genetic determinants of CYP2A6 activity across racial/ethnic groups with different risks of lung cancer and effect on their smoking intensity. Carcinogenesis. 2016;37(3):269-279.

253. Moolchan ET, Franken FH, Jaszyna-Gasior M. Adolescent nicotine metabolism: ethnoracial differences among dependent smokers. Ethn Dis. 2006;16:239-243.

254. Nakajima M., Kuroiwa Y., Yokoi T. Interindividual differences in nicotine metabolism and genetic polymorphisms of human CYP2A6. Drug Metab Rev. 2002;34:865-877.

255. Schoedel KA, Hoffmann EB, Rao Y. et al. Ethnic variation in CYP2A6 and association of genetically slow nicotine metabolism and smoking in adult Caucasians. Pharmacogenetics, 2004;14:615-626.

256. McGraw JE Sr, Waller DP Specific human CYP 450 isoform metabolism of a pentachlorobiphenyl (PCB-IUPAC#101). Biochem Biophys Res Commun. 2006;344:129-133.

257. McGraw JE, Waller DP The role of African American ethnicity and metabolism in sentinel polychlorinated biphenyl congener serum levels. Environ Toxicol Pharmacol. 2009;27:54-61.

258. Wang H., Tompkins LM CYP2B6: new insights into a historically overlooked cytochrome P450 isozyme. Curr Drug Metab. 2008;9:598-610.

259. Hofmann MH, Blievernicht JK, Klein K. et al. Aberrant splicing caused by single nucleotide polymorphism c.516G > T [Q172H], a marker of CYP2B6*6, is responsible for decreased expression and activity of CYP2B6 in liver. J Pharmacol.Exp Ther. 2008;325:284-292.

260. Guan S., Huang M., Chan E. et al. Genetic polymorphisms of cytochrome P450 2B6 gene in Han Chinese. Eur J Pharm Sci. 2006;29:14-21.

261. Guan S., Huang M., Li X. et al. Intra and inter-ethnic differences in the allele frequencies of cytochrome P450 2B6 gene in Chinese. Pharm Res. 2006;23:1983-1990.

262. Puthanakit T., Tanpaiboon P., Aurpibul L. et al. Plasma efavirenz concentrations and the association with CYP2B6-516G>T polymorphism in HIV-infected Thai children. Antivir Ther. 2009;14:315-320.

263. Ramachandran G., Ramesh K., Hemanth Kumar AK et al. Association of high T allele frequency of CYP2B6 G516T polymorphism among ethnic south Indian HIV-infected patients with elevated plasma efavirenz and nevirapine. J Antimicrob Chemother. 2009;63:841-843.

264. Veiga MI, Asimus S., Ferreira PE et al. Pharmacogenomics of CYP2A6,CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and MDR1 in Vietnam. Eur J Clin Pharmacol. 2009;65:355-363.

265. Xu BY, Guo LP, Lee SS et al. Genetic variability of CYP2B6 polymorphisms in four southern Chinese populations. World J Gastroenterol. 2007;13:2100-2103.

266. Rohrbacher M., Kirchhof A., Geisslinger G. et al. Pyrosequencing-based screening for genetic polymorphisms in cytochrome P450 2B6 of potential clinical relevance. Pharmacogenomics, 2006;7:995-1002.

267. King LM, Ma J., Srettabunjong S. et al. Cloning of CYP2J2 gene and identification of functional polymorphisms. Mol Pharmacol.2002;61:840–852.

268. Polonikov AV, Ivanov VP, Solodilova MA et al. Promoter polymorphism G-50T of a human CYP2J2 epoxygenase gene is associated with common susceptibility to asthma. Chest, 2007;132:120–126.

269. Polonikov AV, Ivanov VP, Solodilova MA et al. A common polymorphism G-50T in cytochrome P450 2J2 gene is associated with increased risk of essential hypertension in a Russian population. Dis Markers, 2008;24:119–126.

270. Dreisbach AW, Japa S., Sigel A. et al. The Prevalence of CYP2C8, 2C9, 2J2, and soluble epoxide hydrolase polymorphisms in African Americans with hypertension. Am J Hypertens.2005;18:1276–1281.

271. King LM, Gainer JV, David GL et al. Single nucleotide polymorphisms in the CYP2J2 and CYP2C8 genes and the risk of hypertension. Pharmacogenet Genomics, 2005;15:7–13.

272. Lee CR, North KE, Bray MS et al. CYP2J2 and CYP2C8 polymorphisms and coronary heart disease risk: The Atherosclerosis Risk in Communities (ARIC) study. Pharmacogenet Genomics, 2007;17:349–358.

273. Lee SS, Jeong HE, Liu KH et al. Identification and functional characterization of novel CYP2J2 variants: G312R variant causes loss of enzyme catalytic activity. Pharmacogenet Genomics, 2005;15:105–113.

274. Wu SN, Zhang Y., Gardner CO et al. Evidence for association of polymorphisms in CYP2J2 and susceptibility to essential hypertension. AnnHumGenet.2007;71:519–525.

275. Fava C., Montagnana M., Almgren P. et al. The common functional polymorphism -50G4T of the CYP2J2 gene is not associated with ischemic coronary and cerebrovascular events in an urban-based sample of Swedes. J Hypertens. 2010;28:294–299.

276. Marciante KD, Totah RA, Heckbert SR et al. Common variation in cytochrome P450 epoxygenase genes and the risk of incident nonfatal myocardial infarction and ischemic stroke. Pharmacogenet Genomics, 2008;18:535–543.

277. Jie Z., Hong K., Jianhong T. et al. Haplotype analysis of the CYP2J2 gene associated with myocardial infarction in a Chinese Han population. Cell Biochem Funct. 2010;28:435–439.

278. Liahovich VV, Vavilin VA, Grishanova AYu et al. Pharmacogenetics and current medicine. Vestnik RAMN, 2004;10:40-45.

279. Kukes VG, Grachev SV, Sichev DA, Ramenskaya GV The drug-metabolism. Scientific bases of personalized medicine: physician manual Moscow: GEOTAR – Media, 2008. – 304p.

280. Makeeva O., Stepanov V., Puzyrev V. et al. Global pharmacogenetics: genetic substructure of Eurasian populations and its effect on variants of drug-metabolizing enzymes. Pharmacogenomics, 2008;9(7):847-868.

281. Zarukian AA Ethnic peculiarities of warfarin using in Stavropol Edges inhabitants: clinic and pharmacogenetic aspects. Abstract of dissertation on candidate of medical science–Volgograd, 2015.

282. Duzhak T., Mitrofanov D., Ostashevskii V. et al. Genetic polymorphisms of CYP2D6, CYP1A1, GSTM1 and p53 genes in a unique Siberian population of Tundra Nentsi. Pharmacogenetics, 2000;10(6):531-537.

283. Korchagina RP, Osipova LP, Vavilova NA et al. Genetic polymorphisms of participating in drug metabolism cytochrome P450 2C9 in North Sibirian scolded inhabitants populations. Bulliten SO RAMN, 2011;31(6):39 - 46.

284. Gasanov NA Pharmacogenetic basis severe drug adverse reactions in Azerbaidjan respublic inhabitants: genetic polymorphism of xenobiotic detoxication system. Abstract of dissertation on doctor of medical science– Moscow, 2008.

285. Eliseeva MP, Hamidullaeva GA, Srodjidinova NZ et al. The molecular-genetic aspects of essential hypertension. Tashkent "Shark", 2009. – 272p.

286. Kurbanov RD, Zakirov NU, Irisov DB et al. The impact of CYP2C9 genetic polymorphisms to warfarin efficacy in uzbek nationality patients with long existing atrium fibrillation. Medicinskie novosti, 2012;9:35-38.

287. Dolgosheva A. We are overestimated of drugs and underestimated of specialists for them. S-Peterburg vedomosti – 08.10.2008

288. Suleimanov SSh, Abrosimova NV, Kirpichnikova NV, Gorbach AA The problem of pharmacotherapy safety within the framework of responsible autotreatment in far eastern region. Klinicheskaya pharmacologia i terapia, 2009;6(supplement) P.14.

289. Morozova TE, Andrushishina TB The polypragmasy problem in multiprofile hospital. Klinicheskaya pharmacologia i terapia, 2009;6(supplement) P.18.

290. Zurdinov AZ Place and importance of clinical pharmacology teaching in realization of drug rational using concepts. Klinicheskaya pharmacologia i terapia, 2009; 6(supplement) P.14.

291. Marzevich SU, Suhanov YV, Belolipezkaya VG, Kutishenko NP Bioequivalence assay as a way of original agent and agent-generic identity evidence. Rossiyskiy kardiologicheskiy jurnal, 2005;12(52):76-78.

292. Clinico-pharmacological assay of using therapy - assay method of practical experience on clinical pharmacology /Metodicheskaya rekomendacia Tashkent. -2005. 8p.

293. Kirchmair J., Williamson MJ, Tyzack JD et al. Computational Prediction of Metabolism: Sites, Products, SAR, P450 Enzyme Dynamics, and Mechanisms. J Chem Inf Model. 2012;52(3):617–648.

294. Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. Trends Pharmacol Sci. 2004;25(4):193–200.

295. Wu Z., Zhang X., Shen L. et al. A Systematically Combined Genotype and Functional Combination Analysis of CYP2E1, CYP2D6, CYP2C9, CYP2C19 in Different Geographic Areas of Mainland China – A Basis for Personalized Therapy. PLoS ONE, 2013;8(10):e71934. doi:10.1371/journal.pone.00719

296. Phillips KA, Veenstra DL, Oren E. et al. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. JAMA. 2001;286(18):2270–2279.

297. Samer CF, Lorenzini KI, Rollason V. et al. Applications of CYP450 testing in the clinical setting. Mol Diagn Ther. 2013;17(3):165–184.

298. Daly AK Pharmacogenetics of the major polymorphic metabolizing enzymes. Fundam Clin Pharmacol. 2003;17(1):27–41.

299. Wilkinson GR Drug metabolism and variability among patients in drug response. N Engl J Med. 2005;352(21):2211–2221.

300. The human cytochrome P450 (CYP) allele nomenclature database. Available at: http://www.cypalleles.ki.se.Accessed 14 Apr 2015.

301. Hughes S. Vanderbilt now also routinely gene testing for clopidogrel metabolizer status. The Heart.Org [website on the Internet]. Montreal: TheHeart.Org; 2010. Available from: http://www.theheart.org/article/1139495.do. Accessed August 11, 2011.

302. Relling MV, Altman RB, Goetz MP, Evans WE Clinical implementation of pharmacogenomics: overcoming genetic exceptionalism. Lancet Oncol. 2010;11(6):507–509.

303. Tai-Ming Ko, Chih-Shung Wong, Jer-Yuarn Wu, Yuan-Tsong Chen Pharmacogenomics for personalized pain medicine. Acta Anaesthesiologica Taiwanica, 2016;54:24-30.

304. Caudle EK, Klein TE, Hoffman JM et al. Incorporation of Pharmacogenomics into Routine Clinical Practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Current Drug Metabolism, 2014;15(2):209–217.

305. Pirmohamed M., Burnside G., Eriksson N. et al. EU-PACT Group A randomized trial of genotype-guided dosing of warfarin. The New England Journal of Medicine.2013;369(24):2294–2303.

306. Swen JJ, Nijenhuis M., de Boer A. et al. Pharmacogenetics: from bench to byte–an update of guidelines. Clinical Pharmacology and Therapeutics. 2011;89(5):662–673.

307. Hoffman JM, Haidar CE, Wilkinson MR et al. PG4kds: a model for the clinical implementation of pre-emptive pharmacogenetics. American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 2014;166(1):45–55.

308. Gottesman O., Scott SA, Ellis SB et al. The CLIPMERGE PGx Program: clinical implementation of personalized medicine through electronic health records and genomics-pharmacogenomics. Clinical Pharmacology and Therapeutics, 2013;94(2):214–217.

309. O'Donnell PH, Danahey K., Jacobs M. Adoption of a clinical pharmacogenomics implementation program during outpatient care–initial results of the

University of Chicago “1,200 Patients Project” American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 2014;166C(1):68–75.

310. Pulley JM, Denny JC, Peterson JF et al. Operational implementation of prospective genotyping for personalized medicine: the design of the vanderbilt PREDICT project. Clinical Pharmacology and Therapeutics, 2012;92(1):87–95.

311. Haga SB, Burke W., Ginsburg GS et al. Primary care physicians’ knowledge of and experience with pharmacogenetic testing. Clinical Genetics, 2012;82(4):388–394.

312. Varonen H., Kortteisto T., Kaila M. EBMeDS Study Group What may help or hinder the implementation of Computerized Decision Support Systems (CDSSs): a focus group study with physicians. Family Practice, 2008;25(3):162–167.

313. Zaidi STR, Marriott JL, Nation RL The role of perceptions of clinicians in their adoption of a web-based antibiotic approval system: do perceptions translate into actions? International Journal of Medical Informatics, 2008;77(1):33–40.

314. Jaspers MWM, Smeulers M., Vermeulen H., Peute LW Effects of clinical decision-support systems on practitioner performance and patient outcomes: a synthesis of high-quality systematic review findings. Journal of the American Medical Informatics Association, 2011;18(3):327–334.

315. Bright TJ, Wong A., Dhurjati R. et al. Effect of clinical decision-support systems: a systematic review. Annals of Internal Medicine, 2012;157(1):29–43.

316. Boyce RD, Freimuth RR, Romagnoli KM et al. Toward semantic modeling of pharmacogenomic knowledge for clinical and translational decision support. AMIA Joint Summits on Translational Science Proceedings AMIA Summit on Translational Science, 2013;2013:28–32.

317. Kawamoto K. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. British Medical Journal, 2005;330(7494):765.

318. Goldspiel BR, Flegel WA, DiPatrizio G. et al. Integrating pharmacogenetic information and clinical decision support into the electronic health record. Journal of the American Medical Informatics Association, 2014;21(3):522–528.

319. Hicks JK, Crews KR, Hoffman JM et al. A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. Clinical Pharmacology and Therapeutics, 2012;92(5):563–566.

320. Rasmussen-Torvik LJ, Stallings SC, Gordon AS et al. Design and anticipated outcomes of the eMERGE-PGx project: a multicenter pilot for preemptive pharmacogenomics in electronic health record systems. Clinical Pharmacology and Therapeutics, 2014;96(4):482–489.

321. Devine EB, Lee C-J, Overby CL et al. Usability evaluation of pharmacogenomics clinical decision support aids and clinical knowledge resources in a computerized provider order entry system: a mixed methods approach. International Journal of Medical Informatics, 2014;83(7):473–483.

322. Overby CL, Tarczy-Hornoch P., Kalet IJ et al. Developing a prototype system for integrating pharmacogenomics findings into clinical practice. Journal of Personalized Medicine, 2012;2(4):241–256.

323. Alterovitz G., Warner J., Zhang P. et al. SMART on FHIR Genomics: facilitating standardized clinico-genomic apps. Journal of the American Medical Informatics Association, 2015;22(6):1173–1178.

324. Samwald M., Adlassnig K-P. Pharmacogenomics in the pocket of every patient? A prototype based on quick response codes. Journal of the American Medical Informatics Association, 2013;20(3):409–412.

325. Miñarro-Giménez JA, Blagec K., Boyce RD et al. An ontology-based, mobile-optimized system for pharmacogenomic decision support at the point-of-care.PLoS ONE, 2014;9(5):e1671

326. Verhoef TI, Redekop WK, de Boer A., Maitland-van der Zee AH. EU-PACT group Economic evaluation of a pharmacogenetic dosing algorithm for coumarin anticoagulants in The Netherlands.Pharmacogenomics, 2015;16(2):101–114.

327. Thompson AJ, Newman WG, Elliott RA et al. The cost-effectiveness of a pharmacogenetic test: a trial-based evaluation of TPMT genotyping for azathioprine. Value in Health: Journal of the International Society for Pharmacoeconomics and Outcomes Research,2014;17(1):22–33.

328. Lala A., Berger JS, Sharma G. et al. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost-effectiveness analysis. Journal of Thrombosis and Haemostasis, 2013;11(1):81–91.

329. Olgiati P., Bajo E., Bigelli M. et al. Should pharmacogenetics be incorporated in major depression treatment? Economic evaluation in high- and middle-income European countries. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2012;36(1):147–154.

330. Schildcrout JS, Denny JC, Bowton E. et al. Optimizing drug outcomes through pharmacogenetics: a case for preemptive genotyping.Clinical Pharmacology and Therapeutics, 2012;92(2):235–242.

331. Tuteja S., Haynes K., Zayac C. et al. Community pharmacists' attitudes towards clinical utility and ethical implications of pharmacogenetic testing. PersonalizedMedicine, 2013;10(8):793–800.

CONCLUSION

Adverse drug reactions are a major hindrance in the development of generic drugs and for the treatment of specific diseases, as each person reacts differently to the same medicine. Most of the drugs used in clinical practice, to date, only effective in 25-60% of patients, whereas the adverse reactions of drugs as a result of drug therapy is estimated at billions of US dollars and tens of thousands of deaths.

A meta-analysis of several studies showed that of the 2.2 million people who have been hospitalized for treatment, approximately 100,000 people die every year due to complications arising from adverse drug reactions. These reactions have a negative impact on health and quality of life were also the reason for the return back of a number of potentially revolutionary drug from the market. Occurrence of adverse drug reactions is largely dependent on changes in the parameters of pharmacokinetics.

However, all stages of pharmacokinetics and drug substances, such as absorption, distribution, metabolism, excretion are controlled by the respective genes, thus different gene polymorphism may affect all pharmacokinetic processes. However, as shown by studies conducted in the last decade, the greatest clinical significance had polymorphisms of genes controlling the synthesis and activity of drug biotransformation enzymes, particularly its phase 1 with the participation of cytochrome P-450 (CYP).

The catalytic mechanism of CYP is similar due to the stable functioning of hemethiolate, but the amino acid variations in the substrate-binding sites determined component-, regio-, and stereoselectivity of metabolism. Over 90% of the oxidation of drugs in humans can be classified as follows CYP: 1A2 (4%), 2A6 (2%), 2C9 (10%), 2C19 (2%), 2E1 (2%), 2D6 (30%) and 3A4 (50%). With the identification of a greater number of substrates of various CYP, this picture may change. In humans, about 50% of the total elimination of commonly used drugs may be assigned to one or more of various CYP enzymes. CYP activity varies among individuals of a given population. The variability in the composition and activity of CYP can have a profound impact on people in vivo response to drugs. Most of CYP are exposed the induction and inhibition, and genetic mutation play an important or a dominant role in many variations of CYP enzyme activity, in particular: CYP2A6, 2C9, 2C19 and 2D6. Genetic polymorphisms in CYP, mainly affect the metabolism of drugs that are substrates for the specific enzymes that are likely to lead to differences in the response to the drug, in addition, an increased risk of adverse drug reactions. Most of the CYP family's members are polymorphic (see. Http://www.imm.ki.se/CYPalleles) and allelic variants ending altered protein expression or activity have important effects in drug disposition and can cause disease phenotypically. Genetic polymorphism defined as the stabile variation in transmitted locus of genetic sequence that found in 1% or greater volume specific population. The most common genetic mutation in human genes are considered to be the only CYP-nucleotide polymorphism (SNP) and nonsynonymous SNP, which are functionally important SNP, if they occur in the coding region and cause the amino acid variations in corresponding CYP. It was found that each human CYP gene contains an average of 14.6 nonsynonymous SNP and many of them are associated with altered metabolism of drugs or susceptibility to certain diseases.

In recent years, have accumulated evidence that the SNP study to CYP human genes have to also take into account the ethnic variations in response to the many therapeutic

agents, since ethnicity - an important factor that promotes individual variability in response to drugs. Genetic influences that because the appearance of racial/ethnic differences in the CYP450 phenotypic activity has yet not fully characterized; however, current research approaches and methods provide a good tool for the promotion of research opportunities in this area. Available data on clinically relevant alleles of CYP genes will optimize pharmacotherapy based on ethnic characteristics.

It well known that the CYP activity is influenced by clinical factors, various inducers and inhibitors, drug-drug interactions, as well as other genetic polymorphisms in genes associated with the organism's response to the medication. Because most of the studies cited the results of drug reactions after genotyping only common alleles, variants, which not detected, could missed. Most amounts of SNP-candidates may improve the process. A limited number of genotyping with ongoing research can be a consequence of a lack of data on the functional significance (in vitro or in vivo) allele and low or uncertain allele frequency in the population.

Therefore, information about the functional significance of the different alleles should help the researcher to include more candidates for the SNP-genotyping in their clinical studies. This should ultimately improve the quality of clinical settings and serve as an initial step in personalized medicine, because doctors could easily communicate with patients, using a biological response to the confirmation of the forecast for the drug, instead of explaining the statistical risk their biological value.

Begins with the observation of differences in drug metabolism between racial/ethnic groups, pharmacogenetics is now developed into a scientific discipline, which is already producing concrete results in practice. For example, the FDA in the US now promotes, where necessary, use of pharmacogenomic information label pharmaceutical products. Many of these labels contain information about the role and the effect of CYP polymorphisms in drug metabolism.

If pharmacogenetics is considered as a study of the influence of genetic factors on individual variation in response to drugs that pharmacogenomics - a global definition and involves a study of the whole range of genes and their contribution to the variability in the effectiveness of drugs and toxicity using gene-enhanced approach. Therefore, using pharmacogenomics is possible to ensure a better pharmacotherapy personalized for each individual patient in order to pick it suitable dosage most appropriate medication.

As large-scale genome-associated, as well as smaller-scale studies, candidate gene approach is widely used to study genes involved in metabolism, transport and receptor binding drugs, help our understanding of the basic mechanisms of efficacy and manifestations of the adverse drug action. The next generation of whole genome sequencing, which provides a variety of genomic map of many populations, will be useful for future pharmacogenetic studies. These studies, in an effort to detect and replicate new pharmacogenetic loci that have clinical significance, should take into account the ancestral genetic structure, complex haplotypes intragenic interaction and rare variants.

A distinctive feature of the genetic factors is their constancy throughout life, so the identification of the genetic characteristics of patients allows predicting the pharmacological response to the drug, and thus improving the efficiency and security of their applications. The use of this approach in clinical practice, where the identification of the relevant allelic variants, resulting in changes of the pharmacokinetics in patients requiring therapy adjustment, allows individualized pharmacotherapy.

Personalized medicine aims to rebuild the health, using molecular analysis and tailoring individualized medical approach and treatment according to the patient's genetic information. Selection of suitable individual and optimal therapy is based in part on the genetic status of the patient. This successful application of pharmacogenomics to the application of therapy, which based primarily on the assessment of the presence or absence of specific CYP. Personalized medicine can be used to predict the risk of a particular disease for a person based on the presence or absence of a specific gene. With regard to drug therapy, drug selection and dosage employed may be due, in part, the type and the presence of CYP polymorphisms identified. Furthermore, existing knowledge and CYP polymorphic forms may be useful to include or exclude certain individuals in Clinical Trials for the study of new drugs and to increase the safety and may reduce adverse effects caused by the test drug.

In the near future it will be possible widespread use of pharmacogenetic tests to identify individuals at pharmacotherapy of patients with affordable medicines, which will greatly reduce the risk of treatment-related adverse events. Attempts to minimize such adverse effects require further research in structural and functional terms CYP enzymes, further information on the links between the polymorphism of CYP and disease/toxicity, identification of specific substrates for orphan CYP and developing bioinformatic models to predict - whether certain drugs and chemical substances are toxic or carcinogenic, or act as inducers of CYP.

Pharmacotherapy thus could benefit in the case of participation in addition to the responsibility of clinicians, pharmacists and laboratory specialists, which would lead to a reduction in the therapeutic errors, adverse drug reactions and health costs.

ATTACHMENT

Table 1

Selected genetic polymorphisms of human cytochromes P-450 and POR (Data are presented respectively by Bains*)

CYP allele designation[a]	Key mutation(s)[b] rs number	Location, protein effect	Functional effect	Clinical correlations	Allele frequencies[c]								
					gMAF	Ca	Af	As	AA	Hs	Pc	SA	Ar
CYP1A1 *2C	2454A>G (rs1048943)	I462V	↑ Activity (17β-estradiol and estrone)	↑ Lung cancer risk in Chinese; ↑ breast cancer risk in Caucasians; ↑ prostate cancer risk	0.120	0.03–0.07	0.0–0.04	0.20–0.26	0.0–0.04	0.18–0.43	0.17		
CYP1A2 *1C	−3860G>A (rs2069514)	Promoter	↓ Inducibility (smokers)	May influence susceptibility to certain cancers	0.188	0.01–0.08	0.26–0.40	0.21–0.27	0.26–0.40	0.20–0.30	0.21–0.27		
CYP1A2 *1F	−163C>A (rs762551)	Intron 1	↑ Inducibility (smokers, omeprazole)	↑ Susceptibility to cancer in Caucasians; ↑ oral clearance olanzapine; possible modifier for risk of coronary heart disease	0.35 (A>C)	0.5–0.8	0.5–0.8	0.5–0.8	0.5–0.8	0.5–0.8	0.5–0.8		
CYP1B1 *6	142C>G (rs10012); 355G>T (rs1056827); 4326C>G (rs1056836)	R48G A119S L432V	↑ Km, ↓ Vmax (17β-estradiol)	↑ Prostate cancer risk for L432V in Asians	0.32–39	0.23–0.40	0.5–0.85	0.09–0.13	0.5–0.85				
CYP2A6 *2	1799T>A (rs1801272)	L160H	No activity	↓ Nicotine metabolism & influence on cigarette consumption, nicotine dependence, smoking cessation response; ↑ lung cancer risk in Caucasians; ↓ oral clearance of tegafur	0.013	0.04–0.10	0.00–0.01	0.00–0.025	0.00–0.01				
CYP2A6 *4A to *4H	Recombination	CYP2A6 deleted	Null allele			0.01–0.04		0.05–0.24	0.01–0.02				
CYP2A6 *7	6558T>C (rs5031016)	I471T	↓ Activity		0.04	0.00	0.00	0.06–0.13	0.00				

CYP2A6 *9	−48T>G (rs28399433)	Promoter, TATA-box	↓ Activity		0.13	0.04–0.05	0.04–0.12	0.16–0.27	0.04–0.12				
CYP2A6 *17	5065G>A (rs28399454)	V365M	↓ Activity		0.025	0.00–0.02	0.04–0.50	0.00	0.04–0.50				
CYP2B6 *4	18053A>G (rs2279343)	K262R (isolated)	↑ Expression & activity	↑ Drug clearance (bupropion, efavirenz,cyclophosphamide)	0.26	0.04	0.00	0.05–0.12	0.00				
CYP2B6 *5	25505C>T (rs3211371)	R487C	↑ Expression & activity	Possibly decreased drug clearance	0.05	0.09–0.12	0.01–0.04	0.01–0.04	0.01–0.04				
CYP2B6 *6	15631G>T (rs3745274); 18053A>G (rs2279343)	Q172H K262R	↓ Expression ↓ Activity (efavirenz, nevirapine) ↑ Activity (cyclophosphamide)	↓ Drug clearance & ↑ adverse events including treatment discontinuation (efavirenz, nevirapine, S-methadone)	0.27	0.14–0.27	0.33–0.5	0.10–0.21	0.33–0.5		0.62		
CYP2B6 *18	21011T>C (rs28399499)	I328T	↓↓ Expression & activity		0.02	0.00	0.05–0.12	0.00	0.04–0.08	0.01	0.00		
CYP2B6 *22	−82T>C (rs34223104)	Promoter, TATA-box	↑ Expression & activity ↑ Inducibility	Possibly increased drug clearance	0.012	0.024	0.00–0.025	0.00–0.025	0.00–0.025	0.024			
CYP2C8 *2	11054A>T (rs11572103)	I269F	↓ Activity	Controversial clinical effects	0.039	0.00	0.10–0.22	0.00	0.10–0.22				
CYP2C8 *3	2130G>A (rs11572080); 30411A>G (rs10509681)	R139K K399R	↓ Activity (paclitaxel) ↑ Activity (antidiabetics)		0.065	0.65–0.14	0.00	0.00	0.00	0.65–0.14			
CYP2C8 *4	11041C>G (rs1058930)	I264M	↓ Activity (paclitaxel)		0.026	0.03–0.07	0.00–0.01	0.00–0.01	0.00–0.01	0.03–0.07	0.00–0.01		
CYP2C9 *2	3608C>T (rs1799853)	R144C	↓ Activity	↓ Drug clearance & ↑ risk of bleeding (anticoagulants warfarin, acenocoumarol, phenprocoumone); ↓ drug clearance & ↑ adverse events	0.069	0.10–0.17	0.00–0.02	0.00–0.02	0.00–0.02	0.065	0.00–0.02		

				(sulfonylurea hypoglycemic drugs, NSAIDS); ↓ drug clearance & ↑ adverse events									
CYP2C9 *3	42614A>C (sulfonylurea hypoglycemic drugs, NSAIDS)(rs1057910)	I359L	↓↓ Activity		0.043	0.06	0.00 – 0.01	0.02–0.06	0.00 – 0.01				
CYP2C19*2	19154G>A (rs4244285)	Splicing defect	Null allele	↓ Clearance & ↑ efficacy of PPIs in Helicobacter pylori eradication therapy; ↓ anticoagulation effect of clopidogrel & ↑ cardiovascular events; ↓ clearance & ↑ risk of ADRs for antidepressants (amitriptypine, citalopram, clomipramine, moclobemide), antimalarials (proguanil), antifungals	0.199	0.06 – 0.15	0.10 – 0.17	0.22–0.32	0.10 – 0.17	0.15	0.22 – 0.32		
CYP2C19*3	17948G>A (voriconazole) (rs4986893)	W212X	Null allele		0.014	0.00 – 0.01	0.00 – 0.01	0.03–0.07		0.00–0.01	0.03 – 0.07		
CYP2C19*17	−806C>T (rs12248560)	Promoter	↑ Expression & activity	↑ Clearance of PPIs & risk of subtherapeutic concentrations; ↑ risk of bleeding with clopidogrel	0.15	0.21 – 0.25	0.15 – 0.27	0.00–0.02	0.15 – 0.27				
CYP2D6 *3	2549delA (rs35742686)	Frameshift	Null allele	↓ Clearance & ↑ risk of ADRs for many antiarrhythmics, antidepressants, antipsychotics; ↓ metabolic activation & analgesic effect of opioids (codeine, dihydrocodeine, oxycodone, tramadol); ↓ metabolic activation & efficacy of tamoxifen	0.009	~0.01	~0.01	~0.01	~0.01	~0.01	~0.01		

CYP2D6 *4	1846G>A (rs3892097)	Splicing defect	Null allele		0.106	0.15–0.25	0.01–0.10	0.01–0.10	0.01–0.10	0.01–0.10			
CYP2D6 *5	Recombination	Deletion	Null allele			0.03–0.06	0.03–0.06	0.03–0.06	0.03–0.06	0.03–0.06	0.03–0.06		
CYP2D6 *6	1707delT (rs5030655)	Frameshift	Null allele		0.01	~0.01	~0.01	~0.01	~0.01	~0.01	~0.01		
CYP2D6 *10	100C>T (rs1065852)	P34S	↓ Expression & activity		0.26	0.02	0.08–0.12	0.40–0.70	0.08–0.12				
CYP2D6 *17	1023C>T (rs28371706); 2850C>T (rs16947)	T107I R296C	↓ Expression & activity		0.049 (для 1023C>T)	0.00	0.14–0.24	0.00					
CYP2D6 *41	2988G>A (rs28371725)	Splicing defect	↓ Expression & activity		0.055	0.09	0.01–0.06	0.01–0.06		0.01–0.06	0.01–0.06		
CYP2D6 *Nxn	Recombination	Copy number variations	↑ Expression & activity	↑ Toxicity of opioids		0.01–0.09	Up to 0.30						Up to 0.3
CYP2J2 *7	−76G>T (rs890293)	SP1-binding to promoter decreased	↓ Expression & activity	No conclusive clinical associations	0.073	0.055–0.08	0.10–0.17	0.02–0.13	0.10–0.17				
CYP3A4 *1B	−392A>G (rs2740574)	Promoter	Probably no effect on transcription	↑ Prostate cancer disease progression	0.20	0.03–0.05	0.50–0.82	0.00	0.50–0.82	0.03–0.05		0.03–0.05	
CYP3A4 *22	15389 C>T (rs35599367)	Intron 6	↓ Expression & activity	↓ Metabolism of simvastatin & ↑ lipid-lowering response; ↓ daily-dose requirement for tacrolimus	0.021	0.025–0.08		0.043	0.043				
CYP3A5 *3	6986A>G (rs776746)	Intron 3, splicing defect	↓↓ Expression & activity	↓ Metabolism & dose requirements for selected drugs with a preference for metabolism by CYP3A5 over CYP3A4 (e.g., tacrolimus, saquinavir)	0.312	0.88–0.97	0.12–0.35	0.66–0.75	0.37	0.66–0.75			

CYP3A5 *6	14690A>G (rs10264272)	Exon 6, K208, splicing defect	↓↓ Expression & activity		0.045	0.00	0.15 – 0.25	0.00	0.12	0.00			
POR*28	31696C>T (rs1057868)	A503V	Various substrate- and CYP-dependent effects in vitro	↓ Enzyme activity of major CYP enzymes in patients with rare POR deficiency; ↑ CYP3A4 enzyme activity with midazolam	0.287	0.29 – 0.33	0.08 – 0.50	0.38–0.42	0.08 – 0.50		0.32 – 0.35		

a According to the CYPallele nomenclature homepage (http://www.cypalleles.ki.se).
b Genomic positions are given with corresponding rs numbers in parentheses.
c gMAF, global allele frequency of the minor allele as reported in the 1000Genome phase 1 genotype data (released May 2011). Selected frequencies of individual ethnicities (AA, African American; Af African; As Asian; Ar, Arab; Ca Caucasian;
Hs, Hispanic; In, Indian; Pc, Pacific; SA, South American) were compiled from dbSNP (build 137) at http://www.ncbi.nlm.nih.gov/projects/SNP/; from the Allele Frequency Database ALFRED at http://alfred.med.yale.edu/alfred/index.asp; and from the references cited in the text.

*Bains R.K.African variation at Cytochrome P-450 genes Evolutionary aspects and the implications for the treatment of infectious diseases Evolution, Medicine, and Public Health 2013 pp. 118–134, doi:10.1093/emph/eot010

Table 2

Substrates (drugs, metabolites, endogenous and exogenous compounds) undergoing of metabolism by different CYP isoforms

CYP isoforms	Substrates	Class substances or therapeutic use	Metabolic pathways	Other CYP isoforms involved in metabolism
CYP1A2	Acetanilide	Chemical compound	4-hydroxylation	CYP 2E1
	Caffeine	Psychostimulant	N3-demethylation	
	Chlorpromazine	Antipsychotic	N-demethylation and 5-sulfoxidation	CYP3A4
	Clozapine	Antipsychotic	N-demethylation	CYP 3A4/5
	Estradiol	Hormone	2-hydroxylation	CYP 3A4/5, 1A1
	7-ethoxyresorufin	Chemical compound	O-deethylation (in vitro)	
	Flutamide	Anticancer, antiandrogen	2-hydroxylation	CYP 3A4/5, 2C19
	Genistein	Anticancer, PKI	3′hydroxylation	CYP 2E1
	Guanabenz		N-hydroxylation	
	Lidocaine	Antiarrhythmic	N-deethylation and 3′-hydroxylation	CYP 3A4, 2B6
	Melatonin	Endogenous compound	6-hydroxylation	CYP 1A1, 2C19
	Mianserin	Tetracyclic antidepressant	N-demethylation+N-oxidation	CYP 3A4/5
	Nabumetone	Chemical compound	6-methoxy-2-naphthylacetic acid formation	
	Naproxen	NSAIDs	O-demethylation	CYP 2C9, 2C8
	Olanzapine	Antipsychotic	N-demethylation+2-/7-hydroxylation	CYP 2D6
	Perphenazine	Antipsychotic	N-dealkylation	CYP 3A4/5, 2C9/19, 2D6
	Phenacetin	Analgesic	O-deethylation	CYP 1A1, 2A13
	Propafenone	Anesthetic	N-dealkylation	CYP 3A4/5
	Propranolol	β-blocker	N-desisopropylation	

	Riluzole		N-hydroxylation	
	Tacrine	Cholinesterase inhibitor	1-hydroxylation	
	Theophylline	Psychostimulant	8-hydroxylation and N3-demethylation	
	Triamterene	Diuretic	4′-hydroxylation	
CYP2A6	Bilirubin	Endogenous compound	oxidation to biliverdin	
	Cotinine	Endogenous compound	3′-hydroxylation	
	Coumarin	Anticoagulant	7-hydroxylation	
	1,7-dimethylaxanthine	Endogenous compound	8-hydroxylation	
	Efavirenz	Antiviral	7-hydroxylation	CYP 2B6
	Letrozole		carbinol formation	CYP 3A4/5
	Nicotine	Natural compound	5′-oxidation and N-demethylation	CYP 2B6
	Pilocarpine	Stimulant	3-hydroxylation	
	Tegafur	Anticancer, prodrug	5-fluorouracil formation	CYP 1A2, 2C8
CYP2B6	Artemether		O-demethylation	CYP 3A4/5
	Artemisinin		reductive cleavage	CYP 3A4/5
	Benzphetamine	Antipsychotic	N-demethylation	
	7-Benzyloxyresorufin	Chemical compound	O-debenzylation	CYP 3A4/5
	Bupropion		4-hydroxylation	
	Chlorpyrifos	Pesticide	desulfuration	CYP 3A4/5, 1A2, 2C9/19
	Cyclophosphamide	The anticancer alkylating agent	4-hydroxylation	CYP 2C19, 3A4/5, 2C9, 2A6
	N,N-diethyl-m-toluamide	Chemical compound	(DEET) ring methyl hydroxylation	
	Efavirenz	Antiviral	8-hydroxylation	CYP 1A2, 3A4/5
	Endosulfan		S-oxidation	CYP 3A4
	(7-EFC) 7-ethoxy-4-trifluoromethylcoumarin	Chemical compound	O-deethylation	

	Hexane	Chemical compound	2-hydroxylation	CYP 2E1
	Ifosfamide	The anticancer alkylating agent	4-hydroxylation	CYP 3A4/5
	Ketamine	Analgesic	N-demethylation	CYP 3A4/5, 2C9
	S-mephenytoin	Drug metabolite	N-demethylation	CYP 2C9
	S-mephobarbital	Drug metabolite	N-demethylation	
	Meperidine		N-demethylation	CYP 3A4/5, 2C19
	Methadone	Opioid receptor inhibitor	N-demethylation	CYP2C, 3A4
	Methamphetamine	Drug of abuse	4-hydroxylation and N-demethylation	
	Nevirapine	Non-nucleoside reverse transcriptase inhibitor	3-hydroxylation	
	Propofol	Anesthetic	hydroxylation	CYP2C9
	Selegiline	Anti-Parkinson	N-demethylation and N-depropargylation	CYP 1A2
	Sertraline	SSRI	N-demethylation	CYP 2C19, 2C9, 3A4/5
	Temazepam	Sedative, benzodiazepine	N-demethylation	
	Testosterone	Hormone	16α- and 16β-hydroxylation	CYP 3A4/5
	Tramadol	Opioid analgesic	N-demethylation	CYP 3A4/5
CYP2C8	Amodiaquine	Antimalarial	N-deethylation	CYP1A1, CYP1B1
	Cerivastatin (acid, parent)	Antilipidemic, HMGCoA reductase inhibitor	6-hydroxylation (M-23),demethylation (M-1)	CYP3A4
	Daprodustat (GSK1278863)	Antianaemia, prolylhydroxylase inhibitor		CYP3A4
	Dasabuvir (ABT-333)	Antiviral, NSB5 inhibitor	M1 formation	CYP3A4, CYP2D6
	Enzalutamide	Anticancer Antiandrogen	Hydroxylation (M6), N-demethylation (M2)	CYP3A4/5
	Montelukast	Anti-asthmatic, LTRA	36-hydroxylation (M6), 25-hydroxylation	CYP3A4, CYP2C9

			(M3), M4 formation	
	Pioglitazone	Antidiabetics	Hydroxylation	CYP3A4/5, CYP1A1
	Repaglinide	Antidiabetics, meglitinide analogue	M2 and M4 formation	CYP3A4
Metabolism of 20–70%	9cUAB30	Anticancer, retinoid	M1-M5 formation	CYP2C9, CYP2C19, (CYP1A2, CYP2B6)
	Acotiamide (Z-338)	Acetylcholinesterase inhibitor	Deisopropylation (M-4)	CYP1A1, CYP3A4
	Alitretinoin (9-cisretinoicacid)	Antipsoriatic, retinoid	4-hydroxylation	CYP2C9, CYP3A4, CYP26A1
	Amiodarone	Antiarrhythmic	N-deethylation	CYP3A4, (CYP1A2, CYP2C19, CYP2D6)
	Chloroquine	Antimalarial	N-deethylation	CYP3A4/5, (CYP2D6)
	(2)(+)-Cisapride	Gastroprokynetic, 5-HT4 receptor agonist	N-dealkylation, 4-hydroxylation, 2-hydroyxlation	CYP3A4, CYP2B6
	Dabrafenib	Anticancer, PKI	Hydroxylation	CYP3A4/5, (CYP2C9,CYP2C19)
	Fenretinide	Anticancer, retinoid	49-hydroxylation, 49-oxidation	CYP3A4/5
	R/S-Fluoxetine	SSRI	N-demethylation	CYP2C9, CYP2D6
	R-Ibuprofen	NSAIDs	2-hydroxylation, 3-hydroxylation	CYP2C9
	Imatinib	Protein tyrosine kinase inhibitor	N-demethylation	CYP3A4/5
	Irosustat	SSRI	M9 and M13 formation	CYP2C9, CYP3A4/5,(CYP2E1)
	Isotretinoin (13-cisretinoic acid)	Antiacne, retinoid	4-hydroxylation	CYP3A4

	Loperamide	Opioid analgesic	N-demethylation	CYP3A4, CYP2B6, CYP2D6
	Olanzapine	Antipsychotic	N-demethylation	CYP1A2, CYP2D6, CYP3A4
	Olodaterol	Anti-asthmatic, LABA	O-demethylation	CYP2C9, (CYP3A4)
	Paclitaxel (taxol)	Antineoplastic	6a-hydroxylation	CYP3A4
	Paritaprevir (ABT-450)	Antiviral, NS3-4A inhibitor		CYP3A4
	Propanoic acid dronedarone	Drug metabolite	Hydroxylation (M10 andM11)	CYP1A1
	R483	Antidiabetics, PPAR-g agonist	M1 and M4 formation	CYP2C19, CYP3A4,(CYP2C9)
	Rosiglitazone	Antidiabetics, PPAR-g agonist	p-hydroxylation, N-demethylation	CYP2C9
	Simvastatin acid	Antilipidemic, HMG CoA reductase inhibitor	Oxidation (M1-M3)	CYP3A4/5
	Tazarotenic acid	Antipsoriatic, metabolite drugs (active)	Sulfoxidation	
	Tozasertib (MK 0457, VX6, VX 680)	Anticancer, PKI	N-demethylation	CYP3A4
	Treprostinil	Antihypertensive		CYP2C9
	Troglitazone	Antidiabetics, PPAR-g agonist	Quinone metabolite formation	CYP3A4
	R/S-Verapamil	Antihypertensive, CCB	N-dealkylation, Ndemethylation, Odemethylation	CYP3A4/5, (CYP2E1)
	Vidupiprant (AMG 853)	Anti-asthmatic, PGD2receptor antagonist	t-butyl hydroxylation (M2), cyclopropyl hydroxylation (M3)	CYP2J2, CYP3A
	Zopiclone	Sedative, GABA receptor agonist	N-demethylation, N-oxidation	CYP3A4, CYP2C9

Metabolism of <20%	7-Epi-10-deacetylpaclitaxel	Paclitaxel derivative	Hydroxylation	CYP3A4
	7-Epi-cephalomannine	Paclitaxel derivative	M-2 formation	CYP3A4
	7-Epi-paclitaxel	Paclitaxel epimer	M-2 formation	CYP3A4
	10-Deacetylpaclitaxel	Paclitaxel derivative	6-hydroxylation	CYP3A4
	17a-Ethinylestradiol	Contraceptive	2-hydroxylation	
	17b-Estradiol (estradiol)	Hormone	2-hydroxylation, 4-hydroxylation	CYP1A1, CYP1B1
	Aminophenazone (aminopyrine)	Analgesic	N-demethylation	CYP2C19, CYP2B6, CYP2D6
	Amitriptyline	Antidepressant, TCA	N-demethylation	CYP3A4/5, CYP2C19
	Anastrozole	Anticancer, Aromatase inhibitor	Hydroxylation	CYP3A4, CYP3A5
	Apixaban	The antithrombotic, factor Xa inhibitor	O-demethylation	CYP3A4, CYP1A2, CYP2C9, CYP2C19, CYP2J2
	Apremilast	Antipsoriatic, PDE4ingibitor	M5 formation	CYP3A4, CYP2A6, (CYP1A2, CYP2C9,CYP2E1)
	Artelinic acid	Antimalarial	3-hydroxylation	CYP3A4/5
	Atorvastatin (acid,parent)	Antilipidemic, HMGCoA reductase inhibitor	p-hydroxylation	CYP3A4/5
	Azilsartan	Antihypertensive, ARB	Decarboxylation (M-I), O-dealkylation (M-II)	CYP2C9, CYP2B6
	Bedaquiline	Antibiotic, ATP synthase inhibitor	N-demethylation	CYP3A4, CYP2C19
	Brinzolamide	Antiglaukoma, carbonic anhydrase inhibitor		CYP3A4, CYP2A6, CYP2B6, CYP2C9
	Brivaracetam	Antiepileptic	Hydroxylation	CYP2C9, CYP3A4

	Buprenorphine	The opioid analgesic	N-dealkylation, M1 formation	CYP3A4
	Buspirone	Anxiolytic		CYP3A4
	BYZX	Antidementia	N-deethylation (M3)	CYP3A4
	BYZX M2	Drug metabolite	N-deethylation (M1)	CYP3A4
	Cabazitaxel	Anticancer	RPR 112698 formation	CYP3A4/5
	Caffeine	Psychostimulant	N-demethylation, C-8-hydroxylation	CYP3A4, CYP1A2, CYP2C9
	Capravirine	Antiviral, NNRTI	Sulfoxidation (C23), N-oxidation (C26), hydroxylation (C19)	CYP3A4, CYP2C9, CYP2C19
	Carbamazepine	Antiepileptic	10,11-epoxidation, 3-hydroxylation	CYP3A4
	Cerlapirdine	Antidementia, 5-HT6 receptor antagonist	Demethylation	CYP3A4
	Cilostazol	The antithrombotic, PDE3 inhibitor	OPC-13217 formation	CYP3A4/5, CYP1B1, CYP2C19
	Cinitapride	Gastroprokynetic, 5-HT4 receptor agonist		CYP3A4
	E-Clomiphene	Ovulation Stimulator, SERM	Deethylation, hydroxylation	CYP3A4/5, CYP2D6
	Clozapine	Antipsychotic	N-demethylation, oxidation	CYP1A2,(CYP3A4)
	Cyamemazine	Antipsychotic	N-demethylation	CYP1A2, CYP3A4, CYP2C9
	Cyclophosphamide	Anticancer alkylating agent	4-hydroxylation	CYP2C9, CYP2A6, CYP2B6, CYP3A4
	Cyclosporine	Immunosuppressants, calcineurin inhibitor		CYP3A4
	Dapsone	Antileprotic	N-hydroxylation	CYP2C9

	Diazepam	Anxiolytic	N-demethylation, 3-hydroxylation	CYP2C9, CYP3A4, CYP2C19
	Dibenzylfluorescein	Fluorescent probe	O-debenzylation	CYP3A4, CYP2C19,CYP2C9, CYP3A5,CYP3A7
	Diclofenac	Anti-inflammatory, NSAIDs	49-hydroxylation, 5-hydroxylation	CYP2C9, CYP3A4, CYP2C18/19
	Diltiazem	Antihypertensive, CCB	N-demethylation	CYP3A4, CYP2C9, CYP2D6
	Docetaxel	Anticancer, taxane Baccatin	ring hydroxylation	CYP3A4
	Dovitinib	Anticancer, PKI		CYP1A1/2, CYP2D6,CYP3A4
	Eltrombopag	Antihemorrhagic, c-mpl receptor agonist	Monooxygenation (J and M6)	CYP1A2
	Elzasonan	Antidepressant	N-demethylation (M4)	CYP3A4
	Erlotinib	Anticancer, PKI		CYP3A4/5, CYP1A2, CYP1A1, CYP1B1
	Ethanol	Alcohol	Acetaldehyde formation	CYP2E1, CYP1A2
	Etodolac	Anti-inflammatory antiphlogistic	NSAID 6-hydroxylation, 7-hydroxylation	CYP2C9
	Evatanepag	Prostaglandin EP2 receptor agonist	Formation of M3, M4, M20,M22-M6	CYP3A4/5
	Everolimus	Immunosuppressants, PKI	Hydroxylation	CYP3A4/5
	Febuxostat	Antihyperuricogen, XO inhibitor	Hydroxylation (67M-2)	CYP1A2, CYP2C9
	Felodipine	Antihypertensive, CCB		CYP3A4
	Flutamide	Anticancer Antiandrogen	Flu-1-G2 formation	CYP1A2, CYP3A4, CYP2C9

	Fluvastatin (acid, parent)	Antilipidemic, HMGCoA reductase inhibitor	5-hydroxylation	CYP2C9, CYP1A1, CYP2D6, CYP3A4
	Gallopamil	Antiarrhythmic, CCB	Oxidation	CYP3A4, CYP2D6
	Genistein	Anticancer, PKI	39-hydroxylation	CYP1A2, CYP2E1
	Gliclazide	Antidiabetic sulfonylureas	6b-hydroxylation, 7bhydroxylation	CYP2C9, CYP2C19
	Glyburide (glibenclamide)	Antidiabetic sulfonylureas	4-trans- (M1) and 3-cishydroxycyclohexyl (M2b) glyburide formation	CYP3A4, CYP2C9, CYPC19
	Halofantrine	Antimalarial	N-debutylation	CYP3A4/5
	Ibrolipim	Antilipidemic	O-deethylation (M2)	CYP3A4
	Ifosfamide	The anticancer alkylating agent	4-hydroxylation	CYP2C9, CYP2A6, CYP2B6, CYP3A4
	Karenicetin	Anticancer		CYP3A4, CYP2D6
	Lansoprazole	Antiulcer, PPI	5-hydroxylation	CYP2C19, CYP3A4
	Lapatinib	Anticancer, PKI	O-dealkylation, Ndealkylation	CYP3A4/5, CYP2C19
	Licofelone	Anti-inflammatory, NSAIDs	Hydroxylation (M2 and M4)	CYP2C9, CYP2C19, CYP2D6, CYP2J2, CYP3A4
	Lonafarnib	Anticancer, FTI	Hydroxylation (M4)	CYP3A4/5, CYP1A1
	Macitentan	Antihypertensive, ERA	Depropylation	CYP3A4, CYP2C9,CYP2C19
	Mavoglurant	Anti-Parkinson, mGLUR5 antagonist	M7 formation	CYP3A4, CYP1A1
	Methadone	Opioid analgesic	N-demethylation	CYP2B6, CYP3A4
	Mirodenafil	Erectogenic, PDE5 inhibitor	N-dealkylation	CYP3A4, CYP2D6
	Mirtazapine	Antidepressant, NaSSA	N-demethylation	CYP2D6, CYP1A2, CYP3A4
	Morphine	Opioid analgesic	N-demethylation	CYP3A4

	Muraglitazar	Antidiabetics, PPAR-g agonist	O-demethylation, Odealkylation hydroxylation, N-acetylimide metabolite formation	CYP2C9, CYP2C19, CYP2D6, CYP3A4
	(2)(+)-Naftopidil	Antihypertensive	M1-M5 formation	CYP2C9, CYP2C19
	Nalfurafine	Opioid	Decyclopropylmethylation	CYP3A4, CYP2C9, CYP2C19
	Naproxen	Anti-inflammatory, NSAIDs	O-demethylation	CYP2C9, CYP1A2
	Nicotine	Natural compound	5-hydroxylation	CYP2A6, CYP2B6
	Nifedipine	Antihypertensive, CCB		CYP3A4/5
	Nilotinib	Anticancer, PKI		CYP3A4, CYP1A1/2,CYP2J2
	R/S-Norverapamil	Drug metabolite	O-demethylation, N-dealkylation	CYP3A4/5
	Odanacatib	Cathepsin K enzyme inhibitor	Methyl hydroxylation (M8)	CYP3A4/5
	Ombitasvir	Antiviral, NS5A inhibitor		CYP3A4, CYP3A5
	Omeprazole	Antiulcer, PPI	5-hydroxylation	CYP2C19, CYP3A4
	Pafuramidine maleate	Antiparasitic	O-demethylation (M1)	CYPF4
	Pazopanib	Anticancer, PKI	Mono-oxygenation	CYP3A4, CYP1A2
	Perospirone	Antipsychotic	MX 1, 10-11614, CO-UK2 and CO-UK3 formation	CYP3A4, CYP2D6, (CYP1A1)
	Perphenazine	Antipsychotic	N-dealkylation	CYP1A2, CYP3A4, CYP2C19, CYP2D6, (CYP2C18)
	Phenazone (antipyrine)	Analgesic	N-demethylation, 3-hydroxylation, 4-hydroxylation	CYP3A4, CYP1A2, CYP2C9
	Phenprocoumon	The antithrombotic, VKA	S-49-hydroxylation	CYP2C9, CYP3A4
	Phenytoin	Antiepileptic	4-hydroxylation	CYP2C9, CYP2C19

	Piperaquine	Antimalarial		CYP3A4
	Pitavastatin acid	Antilipidemic		CYP2C9
	Ponatinib	Anticancer, PKI		CYP3A4, CYP2D6, CYP3A5
	Progesterone	Hormone		CYP2C19, CYP3A4
	Propofol	Anesthetic	4-hydroxylation	CYP2C9, CYP1A2, CYP2B6
	Riociguat	Antihypertensive	N-demethylation	CYP1A1, CYP3A4, CYP2J2
	Rotigotine	Anti-Parkinson, dopamine agonist	Desthienylethyl rotigotine formation	CYP1A2, CYP2C9, CYP3A4
	Sarizotan	Antipsychotic	M203, EMD148107, EMD 329989, and M364d formation	CYP3A4, CYP2C9, CYP1A2
	Selegiline	Anti-Parkinson, MAO-B inhibitor	N-demethylation	CYP2B6, CYP2C19
	Semagacestat	Antidementsiya, g-secretase inhibitor	Benzylic hydroxylation (M3)	CYP3A4/5
	Seratrodast	Anti-asthmatic, TXRA	5-methyl hydroxylation, 49-hydroxylation	CYP3A4/5, CYP2C9
	Sildenafil	Erectogenic, PDE5 inhibitor		CYP3A4, CYP2C9
	Simeprevir	Antiviral, protease inhibitor	M21 and M2 formation	CYP3A4/5,CYP2C19
	Sipoglitazar	Antidiabetics, PPAR-g agonist	Hydroxylation (M-II)	
	Sirolimus	Immunosuppressant	Hydroxylation	CYP3A4/5
	Sitagliptin	Antidiabetics, DPP-4 inhibitor	M2 and M5 formation	CYP3A4
	Sulfadiazine	Antibacterial	N-hydroxylation	CYP2C9
	Sunitinib	Anticancer, PKI	N-deethylation	CYP3A4, CYP2B6, CYP2C9/19
	Tacrolimus	Immunosuppressant		CYP3A4/5
	Tamoxifen	Anticancer, SERM	M-I formation	CYP3A4/5, CYP2D6

	Tamoxifen N-oxide	Drug metabolite	Reduction to tamoxifen	CYP2A6, CYP1A1, CYP3A4
	Tegafur	Anticancer, prodrug	5-hydroxylation	CYP1A2, CYP2A6
	Temazepam	Sedative, benzodiazepine	N-demethylation	
	Terbinafine	Antifungal	N-demethylation, side chain oxidation	CYP2C9, CYP1A2, CYP3A4
	Testosterone	Hormone		CYP3A4/5, CYP2B6
	Tienilic acid	Diuretic	5-hydroxylation	CYP2C9
	Tipifarnib	Anticancer, FTI		CYP3A4, CYP2C19,CYP2A6, CYP2D6,CYP2C9
	R-Tofisopam	Anxiolytic	M3 formation	CYP3A4, CYP2C9, (CYP3A5, CYP2C19)
	Tolbutamide	Antidiabetic sulfonylureas	p-methyl hydroxylation	CYP2C9, CYP2C19
	Torsemide (torasemide)	Diuretic	Methyl hydroxylation	CYP2C9
	Trabectedin	Anticancer	N-demethylation	CYP3A4, CYP2D6
	Tretinoin (all-transretinoic acid)	Antiacne, retinoid	4-hydroxylation, 18-hydroxylation, 5,6-epoxy metabolite formation	CYP26A1,CYP3A4/5, CYP2B6, CYP1A2, CYP26, CYP2C9
	Trimethadione	Antiepileptic	N-demethylation	CYP2E1, CYP3A4, CYP2C9
	Vanoxerine	Antiarrhythmic, DRI		CYP3A4, CYP2E1
	R-Warfarin	Antithrombotic, VKA	4-hydroxylation, 7-hydroxylation	CYP3A4,CYP1A1,CYP2C19, CYP1A2
	Vitamin A (retinol)	Antiacne, retinoid	Hydroxylation	CYP1A1, CYP1A2,CYP1B1, CYP2D6,CYP3A4

	Vortioxetine	Antidepressant, SMS	Sulfoxide (M4a) formation	CYP2D6, CYP3A4/5,CYP2C19, CYP2C9,CYP2A6
	Zidovudine	Antiviral, NRTI	Reduction	CYP2C9
CYP2C9	Acenocoumarol	Drug metabolite	6- and 7-hydroxylation	CYP 1A2, 2C19
	Candesartan		O-deethylation	
	Chlorpropamide	Antidiabetic	2-hydroxylation	CYP 2C19
	Celecoxib	NSAIDs	methylhydroxylation	CYP 3A4/5
	Dapsone	Antibacterial	N-hydroxylation	CYP 2C8
	Diclofenac	Anti-inflammatory, NSAIDs	4′-hydroxylation	
	Etodolac	Antiphlogistic	6- and 7-hydroxylation	
	Fluoxetine	Antidepressant, SMS	N-demethylation	CYP 2D6, 2C19, 3A4/5
	Flurbiprofen	NSAIDs	4′-hydroxylation	
	Glibenclamide	Antidiabetics	hydroxylation	
	Glimepiride		hydroxylation	
	Ibuprofen	NSAIDs	2- and 3-hydroxylation	CYP 2C8, 3A4/5
	Indomethacine	NSAIDs	O-demethylation	CYP 2C8
	Irbesartan	Antipsychotic	hydroxylation	
	Ketobemidone		N-demethylation	CYP 3A4/5
	Lornoxicam		5′-hydroxylation	
	Losartan		2-step oxidation –CH2OH	CYP 3A4/5
	Meloxicam		5′-methylhydroxylation	CYP 3A4/5
	Phenobarbital	Antiepileptic	p-hydroxylation	CYP 2C19
	Phenytoin	Antiepileptic	4-hydroxylation	CYP 2C19
	Piroxicam		5′-hydroxylation	
	Rosuvastatin	Antilipidemic	N-demethylation	
	Sulfamethoxazole	Antibacterial	N-hydroxylation	
	S-warfarin	Anticoagulant	7-hydroxylation	CYP 4F2
	Tetrahydrocannabinol	Chemical compound	11-hydroxylation	CYP 3A4/5

	Tienilic acid	Diuretic	S-oxidation	
	Tolbutamide	Antidiabetic	4′-hydroxylation	CYP 2C19
	Valproic acid	NSAIDs	4-hydroxylation	CYP 2B6, 2A6
	Valsartan		4-hydroxylation	
	Zaltoprofen		sulfoxidation	
CYP2C19	Amitriptyline	Antidepressant, TCA	N-demethylation	CYP 2C8, 2C9
	Clomipramine		8-hydroxylation	CYP 1A2
	Clopidogrel	The antithrombotic	2-oxo-clopidogrel formation	CYP 3A4/5, 2B6, 1A2
	Hexobarbital	Hypnotic	3′-hydroxylation	
	Imipramine	Antidepressant	N-demethylation	
	Lansoprazole		5-hydroxylation	CYP 3A4/5
	Melatonin	Endogenous compound	O-demethylation	CYP 1A2
	Nelfinavir	Antiviral	tert-butylamide-hydroxylation (M8)	
	Omeprazole	Antiulcer, PPI	5-hydroxylation	CYP 3A4/5
	Pantoprazole	Antiulcer, PPI	sulfoxidation	CYP 3A4/5
	Progesterone	Hormone	21-hydroxylation	CYP 2C9, 3A4/5
	Proguanil	Antimalarial	isopropyl oxidation and cyclization cycloguanil	CYP 3A4/5
	R-mephobarbital	Drug metabolite	4-hydroxylation	CYP 2B6
	Ranitidine	Antiulcer, PPI	N-demethylation	CYP 1A2, 2D6
	S-mephenytoin	Drug metabolite	4′-hydroxylation	
	Venlafaxin		N-demethylation	CYP 2C9, 3A4/5
	Voriconazole	Antifungal	N-oxidation	CYP 3A4/5
CYP2D6	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine	Neurotoxin	N-demethylation	
	1,2,3,4-Tetrahydroquinoline	Neurotoxin	Oxidation	

	4-Chloromethyl-7-ethoxycoumarin	Chemical compound	O-deethylation	
	5-Methoxyindolethylamine	Endogenous compound	O-demethylation	
	7-Methoxy-4-(aminomethyl)-coumarin	Fluorescent probe	O-dealkylation	
	7,8-Dihydroxybenzo [a]pyrene	Chemical compound	Tetrols and triols formation	
	7.12-Dimethylbenzo [a]anthracene	Chemical compound	Methyl hydroxylation and diol formation	
	17a-Hydroxyprogesterone	Hormone	21-Hydroxylation	
	17b-Estradio1	Estrogen	2-Hydroxylation (C4-hydroxylation)	
	Acetaminophen	NSAIDs	Oxidation	
	Allopregnanolone	Neurosteroid	21-Hydroxylation	
	Almotriptan	5-HT1B / 1D receptor agonist is	N-demethylation	
	Amiflamine	MAO-A inhibitor	N-demethylation	
	Aminopyrine	NSAIDs	N-demethylation	
	Amiodarone	Antiarrhythmic	Deethylation	
	Amitriptyline	Tricyclic antidepressant	E-10-hydroxylation	CYP 3A4/5
	Amodiaquine	Antimalarial	Deethylation	
	Anandamide	Endocannabinoid	Hydroxylation	
	Antipyrine	NSAIDs	N-demethylation	
	Aprindine	Antiarrhythmic	Hydroxylation	
	Aripiprazole	Antipsychotic	Dehydrogenation	CYP 3A4/5
	Artelinic acid	Antimalarial	3-Hydroxylation	
	Atomoxetine	Norepinephrine reuptake inhibitor	4-Hydroxylation	
	Azelastine	H1 receptor blocker	N-demethylation	

	Benzo[a]pyrene	Chemical compound	3- and 9-Hydroxylation	
	Bicifadine	Non-narcotic analgesic	Methyl hydroxylation	
	Bisoprolol	β1-blocker	O-deisopropylation	
	Bortezomib	Anticancer agent	Deboronation and dehydrogenation	
	Bufuralol	β-blocker	1,2-Ethenylation and 1-hydroxylation	CYP 1A2, 2C19
	Bunitrolol	Antiarrhythmic	4-Hydroxylation	
	Carbamazepine	Psychotolytic	10, 11-Epoxidation	
	Carvedilol	β-blocker	40- and 50-Hydroxylation	
	Cerivastatin	HMG-CoA reductase inhibitor	O-demethylation and 60-methyl hydroxylation	
	Chloroquine	Antimalarial	N-deethylation	
	Chlorpheniramine	H1-receptor antagonist	N-demethylation	
	Chlorpromazine	Antipsychotic	7-Hydroxylation	CYP 1A2
	Cibenzoline	Antiarrhythmic	p-Hydroxylation and 4,5-dehydrogenation	
	Cinnarizine	Antihistamine	p-Hydroxylation	
	Cisapride	5-HT4 Receptor agonist	5 N-dealkylation and fluorophenyl ring hydroxylation	
	Citalopram	SSRI	Demethylation and N-oxidation	
	Clomipramine	Tricyclic antidepressant	8-Hydroxylation	
	Clomiphene		4-hydroxylation	CYP 2B6
	Clozapine	Antipsychotic	N-demethylation and N-oxidation	
	Codeine	Antimigraine (opioid)	O-demethylation	
	Cyclophosphamide	Antineoplastic	C4-hydroxylation	

	Dapsone	Antileprotic	N-hydroxylation	
	Debrisoquine	Cardiovascular agent	4-Hydroxylation	
	Delavirdine	Non-nucleoside reverse transcriptase Inhibitor	Dealkylation	
	Desipramine	Tricyclic antidepressant	2-Hydroxylation	CYP 2C19, 1A2
	Desmethylclomipramine	Tricyclic antidepressant	8-Hydroxylation	
	Dextromethorphan	Antitussive	N-demethylation and O-demethylation	CYP 2C9/19
	Diazepam	Sedative	N-demethylation and C3-hydroxylation	
	Diclofenac	NSAIDs	40- and 50-Hydroxylation	
	Dihydrocodeine	Analgesic and antitussive	O-demethylation	
	Diltiazem	Calcium channel blocker	O-demethylation	
	Diphenhydramine	Antihistamine	N-demethylation	CYP 1A2, 2C9, 2C19
	Disulfoton	Thioether pesticide	Sulfoxidation	
	Diuron	Herbicide	N-demethylation	
	Dolasetron	5-HT3 receptor antagonist	Hydroxylation	CYP 3A4/5
	Donepezil	Cholinesterase inhibitor	500- and 600-Demethylation and O-dealkylation	CYP 3A4/5
	Doxepin	Tricyclic antidepressant	2-Hydroxylation	
	Droloxifene	Selective estrogen receptor modulator	Ortho-hydroxylation	
	Duloxetine	Antidepressant	4-, 5-, 6-Oxidation of naphthyl ring	CYP 1A2
	Eletriptan	5-HT1B/1D receptor agonist	N-demethylation	
	Encainide	antiarrhythmic	O-demethylation	
	Enclomifene	Selective estrogen receptor modulator	Hydroxylation and N-demethylation	

	Etoricoxib	COX-2 inhibitor	60-Methyl hydroxylation and 10-N-oxidation	
	Estrone	Estrogenic hormone	2-Hydroxylation	
	Ezlopitant	Antiemetic	Dehydrogenation	
	Flecainide	Antiarrhythmic	m-O-dealkylation	CYP 1A2
	Flunarizine	Antihistamine	p-Hydroxylation	
	Fluoxetine	SSRI	N-demethylation	
	Fluvastatin	HMG-CoA reductase inhibitor	5-Hydroxyltion	
	Fluvoxamine	SSRI	Demethylation and N-acetylation	
	Galantamine	Tertiary alkaloid	O-demethylation	
	Gepirone	5-HT1A agonist	30- and 5-Hydroxylation	
	Halofantrine	Antimalarial	N-debutylation	
	Haloperidol	Antipsychotic	N-dealkylation	
	Harmaline	b-Carboline alkaloids	O-demethylation	
	Harmine	b-Carboline alkaloids	O-demethylation	
	Hydrocodone	Opioid	O-demethylation	
	Ibogaine	Plant alkaloid	O-desmethylation	
	Ibuprofen	NSAIDs	2- and 3-Hydroxylation	
	Ifosfamide	Antineoplastic	4-Hydroxylation	
	Iloperidone	Antipsychotic	Hydroxylation	
	Imatinib	protein tyrosine kinase inhibitor	N-demethylation	
	Imipramine	TCA	2-Hydroxylation	CYP 2C19, 1A2
	Indinavir	HIV protease inhibitor	Indanyl group oxidation	
	Indomethacin	NSAIDs	O-demethylation	
	Lansoprazole	Proton pump inhibitor	5-Hydroxylation	
	Lasiocarpine	Pyrrolizidine alkaloid	Oxidation	
	Lasofoxifene	Estrogen receptor modulator	Oxidation	

	Lauric acid	Fatty acid	!-1-Hydroxylation	
	Licofelone	COX-1, COX-2 and 5-lipoxygenase inhibitor	Hydroxylation	
	Lidocaine	Antiarrhythmic	3-Hydroxylation	
	Loratadine	H1 receptor antagonist	Decarboethoxylation	CYP 3A4/5
	Maprotiline	Tricyclic antidepressant	Demethylation	
	Mequitazine	H1 receptor antagonist	Hydroxylation and S-oxidation	
	Methadone	Opioid receptor inhibitor	N-demethylation	
	Methamphetamine	Drug of abuse	N-demethylation and aromatic 4-hydroxylation	
	Methilcarb	Thioether pesticide	Sulfoxidation	
	Methoxychlor	Insecticide	O-demethylation	
	Methylenedioxymethamphetamine	Drug of abuse	Demethylation	
	Metoclopramide	Antiemetic	N-dealkylation	CYP 3A4/5
	Metoprolol	B-1 blocker	a-Hydroxylation and O-demethylation	
	Mexiletine	Antiarrhythmic	p- and m-Hydroxylation	CYP 1A2
	Mianserin	Tetracyclic antidepressant	8-Hydroxylation, N-demethylation and N-oxidation	CYP 2B6, 3A4/5
	Mirtazapine	Antidepressant	8-Hydroxylation, N-demethylation and N-oxidation	CYP 1A2, 3A4/5
	Monocrotaline	Pyrrolizidine alkaloid	Oxidation	
	Naphthalene	Chemical compound	Ring hydroxylation	
	Naproxen	NSAIDs	O-demethylation	

	Nevirapine	Non-nucleoside reverse transcriptase inhibitor	8- and 12-Hydroxylation	
	Nicardipine	Calcium channel blocker	Oxidation	
	Nicergoline	Vasodilator	Hydroxylation	
	Nicotine	Natural compound	50-Oxidation	
	Nortriptyline	Tetracyclic antidepressant	E-10-hydroxylation and demethylation	CYP 3A4/5
	Norverapamil	Calcium channel blocker	O-demethylation and N-demethylation	
	Olanzapine	Antipsychotic	N-demethylation and 2-hydroxymethylation	
	Omeprazole	Proton pump inhibitor	5-Pyridinyl methyl hydroxylation	
	Ondansetron	5-HT3 receptor antagonist	6-, 7- and 8-hydroxylation	CYP 3A4/5
	Oxatomide	Antihistamine	N-dealkylation	
	Oxybutynin	Anesthetic	Oxidation	
	Oxymorphone	The opioid analgesic	O-demethylation	
	Oxysophocarpine	Toxic quinolizidine alkaloid	Reduction	
	Paclitaxel	Antineoplastic	6-a-Hydroxylation	
	Pactimibe	acyl coenzyme A: cholesterol acyltransferase inhibitor	!-1-Oxidation	
	Palmatine	Protoberberine alkaloid	O-demethylation and hydroxylation	
	Paroxetine	SSRI	Demethylation	
	Perphenazine	Antipsychotic	N-dealkylation; sulfoxidation and 7-hydroxylation	
	Phenformin	Antimalarial prodrug	p-Hydroxylation	
	Phenoxypropoxybiguanide	Antidiabetic	Oxidation	

	Phenytoin	Antiepileptic	40-Hydroxylation	
	Pinoline	b-Carboline alkaloids	O-demethylation	
	Perhexiline	Antianginal agent	Hydroxylation	
	Perphenazine	Antipsychotic	N-dealkylation, sulfoxidation and 7-hydroxylation	
	Pranidipine	Calcium channel blocker	De-esterification	
	Prasugrel	ADP-receptor antagonist	Ring-open reaction	
	Procainamide	Antiarrhythmic	N-hydroxylation	
	Progesterone	Hormone	16a- and 21-Hydroxylation	
	Promazine	Antipsychotic	5-Sulphoxidation and N-demethylation	
	Propafenone	Antiarrhythmic	Aromatic ring hydroxylation	
	Propofol	General anesthetic	4-Hydroxylation	
	Propranolol	β-blocker	4-, 5- and 7-Hydroxylation	
	Retinoic acid	Dermatological agent	40-, 4- and 7-Hydroxylation, 18- and 4-oxo-formation and 5,6-epoxidation	
	Retinol	Nutritional agent	4-Hydroxylation	
	Risperidone	Antipsychotic	9-Hydroxylation	CYP 3A4/5
	Ritonavir	HIV protease inhibitor	N-demethylation	
	Rosiglitazone	Antidiabetic	p-Hydroxylation and N-demethylation	
	Saquinavir	HIV protease inhibitor	Oxidation	
	Selegiline	Antiparkinsonism agent	N-demethylation and N-depropargylation	
	Seratrodast	Thromboxane A2 receptor antagonist	5-Methyl hydroxylation and 40-Hydroxylation	
	Sertraline	SSRI	N-demethylation	
	Sparteine	Tricyclic antidepressant	N1-oxidation	

	Sildenafil	Phosphodiesterase type 5 inhibitor	N-desmethylation	
	Styrene	Chemical compound	Oxidation	
	Sulfadiazine	Antibacterial	N-Hydroxylation	
	Tacrine	Centrally-acting cholinesterase inhibitor	1-Hydroxylation	
	Tamoxifen	Estrogen receptor modulator	4- and 40-Hydroxylation and N-demethylation	CYP 2C9
	Tandospirone	Antipsychotic	Pyrimidine ring hydroxylation	
	Tegafur	Antineoplastic	50-Hydroxylation	
	Temazepam	Sedative	N-demethylation	
	Terbinafine	Antifungal	N-demethylation and side chain oxidation	
	Terfenadine	H1 receptor antagonist	t-Butyl hydroxylation	
	Testosterone	Hormone	2b-, 6b- and 17-hydroxylation	
	Tetrahydrocannabinol	Natural compound	Oxidation	
	Thebaine	CNS drug	O-demethylation	
	Thioridazine	Antipsychotic	Oxidation	CYP 3A4/5
	Tiaramide	NSAID	N-dealkylation and N-oxidation	
	Ticlopidine	P2RY12 receptor inhibitor	Dihydrogenation and S-oxidation	
	Tienilic acid	Diuretic	5-Hydroxylation	
	Timolol	β-blocker	Hydroxylation	CYP 2C19
	Tolbutamide	Antidiabetic	p-Methyl hydroxylation	
	Tolterodine	Antimuscarinic	5-Hydroxymethylation	
	Toluene	Chemical compound	p-hydroxylation and methyl hydroxylation	
	Torasemide	Loop diuretic	Methyl tolyl hydroxylation	

	Tramadol	Opioid analgesic	O-demethylation	
	Trimethadione	Antiepileptic	N-demethylation	
	Trimethoprim	Antibacterial	40-O-demethylation	
	Trimipramine	Tricyclic antidepressant	2-Hydroxylation and 2,10- and 2,11-dihydroxylation	
	Troglitazone	Antidiabetic	Quinone formation	
	Tropisetron	5-HT3 antagonist	5- and 6-Hydroxylation	CYP 3A4/5
	Venlafaxine	Antidepressant	O- and N-demethylation	CYP 2C19, 2C9
	Verapamil	Calcium channel blocker	N- and O-demethylation	
	Warfarin	Anticoagulant	40- and 7-Hydroxylation	
	Zopiclone	Cyclopyrrolone sedative	N-demethylation and N-oxidation	
	Zolpidem	Hypnotic	Oxidation of C-methyl groups and hydroxylation	
	Zuclopenthixol	Antipsychotic	Sulphoxidation; N-dealkylation	CYP 3A4/5
CYP2E1	Aniline	Chemical compound	4-hydroxylation	
	Arachidonic acid	Fatty acid	ω-1-hydroxylation	CYP 1A1, 2D6
	Benzene	Chemical compound	hydroxylation and hydrochinone formation	
	Butadiene	Chemical compound	1,2-epoxidation	CYP 2A6
	Chlorzoxazone	Chemical compound	6-hydroxylation	CYP 1A2
	N,N-dimethylnitrosamine	Chemical compound	N-demethylation	CYP 2A6
	Enflurane	Inhaled anesthetic	oxidation and dehalogenation	
	Ethanol	Alcohol	oxidation	major: ADH1
	Halothane	Inhaled anesthetic	hydroxylation	CYP 2A6, 3A4/5
	Isoflurane	Inhaled anesthetic	Dehalogenation	
	Lauric acid	Fatty acid	(ω-1)-hydroxylation	CYP 4A11
	Para-nitrophenol	Chemical compound	2-hydroxylation	

	Salicylic acid	Analgesic	5-hydroxylation	CYP 3A4/5
	Sevoflurane	Inhaled anesthetic	Hydroxylation	
	Styrene	Chemical compound	7,8-epoxidation	
	Tetrachloromethane	Chemical components	dehalogenation	CYP 3A4/5
	Toluene	Chemical compound	benzylic hydroxylation	CYP 2B6, 2C8, 1A2
	Vinylchloride	Chemical compound s	epoxidation	
CYP2J2	Albendazole	Antiparasitic	S-oxidation, ω-Hydroxylation	CYP3A4
	Amiodarone	Antiarrhythmic	4-hydoxylation	CYP1A2, 3A4, 2C8,2C19
	Apixaban	Antithrombotic, factor Xa inhibitor	O-demethylation	CYP1A2, 3A4
	Arachidonic acid	Eicosanoid	Epoxygenation	
	Astemizole	Antiparasitic	O-demethylation	CYP2D6, 4F12
	Benzphetamine	Antipsychotic	N-demethylation	
	Cyclosporine A	Immunosuppressants, calcineurin inhibitor	hydroxylation	major: 3A4/5
	Ebastine		t-butyl hydroxylation	3A4/5) CYP4F12
	Eicosapentaenoic acid	Eicosanoid	Epoxygenation (major) ω-1 Hydroxylation (minor)	
	Eperisone		ω-Hydroxylation	CYP2D6, 3A4, 4F12, 1A2, 2C9
	Danazol		hydroxylation	CYP3A4
	Docosahexaenoic acid	Eicosanoid	Epoxygenation (major) ω-1/ω Hydroxylation (minor)	
	Mesoridazine		sulfoxidation	major: CYP3A4
	Nitroglycerin	Vasodilator	NO formation	CYP2E1, 2A6, 3A4, 2D6,2C9, CYP1A2
	Linoleic acid	Fatty acid	Epoxygenation	CYP1A2, 2C8, 2C9,2C19, 3A4
	Tamoxifen	Anticancer, SERM	N-demethylation	CYP3A4

	Terfenadine	H1 receptor antagonist	Hydroxylation	CYP3A4, 2D6, 4F12
	Thioridazine	Antipsychotic	Sulfoxidation	CYP3A4
	Vitamin D3	Vitamin	25-Hydroxylation	CYP2R1
	Vitamin D2	Vitamin	25-Hydroxylation	CYP3A4, 2R1
	Vorapaxar		Hydroxylation	CYP3A4
CYP3A 4/5	L-α-acetylmethadol (LAAM)	Drug metabolite	N-demethylation	CYP 2B6
	Aflatoxin B1	Toxine	3α-hydroxylation and 8,9-epoxidation	CYP 1A2
	Alfentanil	The opioid analgesic	N-dealkylation	
	Alprazolam	Antiparasitic	α-hydroxylation	
	Antipyrine	Analgesic	4-hydroxylation	CYP 1A2
	Aprepitant		N- and O-dealkylation	CYP 1A2, 2C19
	Atorvastatin	Antilipidemic	o- and p-hydroxylation	
	Budesonide	Anticancer	6β-hydroxylation	
	Buprenorphine	The opioid analgesic	N-demethylation	CYP 2C8
	Buspirone		6′-hydroxylation	
	Carbamazepine	Antiepileptic	10,11-epoxidation	CYP 2C8
	Cholesterol	Endogenous component	4β-hydroxylation	
	Cisapride		N-dealkylation	CYP 2A6
	Citalopram	Antipsychotic	N-demethylation	CYP 2C19, 2D6
	Clarithromycin	Antibacterial	14-(R)-hydroxylation and N-demethylation	
	Clindamycin	Antibacterial	S-oxidation	
	Codeine	Opioid	N-demethylation	CYP 2B6
	Cortisol	Hormone	6β-hydroxylation	
	Cyclosporine A	Immunosuppressants, calcineurin inhibitor	hydroxylation (M1 and M17 formation)	
	Dasatinib	Anticancer	N-dealkylation	

	Dexamethasone	Hormonal drug	6-hydroxylation	
	Dextromethorphan	Antitussive	N-demethylation	CYP 2B6, 2C9/19
	Dextropropoxyphene	Antitussive	N-demethylation	
	Diazepam	Anxiolytic, benzodiazepine	3-hydroxylation and N-demethylation	CYP 2C19
	Dihydrocodeine	Drug metabolite	N-demethylation	
	Diltiazem	Antihypertensive, CCB	N-demethylation	CYP 2C8, 2C9
	Donezepil		O-dealkylation	CYP 2D6
	Ebastine		N-dealkylation	
	Erlotinib	Anticancer	O-demethylation	CYP 1A1/2
	Erythromycin	Antibacterial	N-demethylation	CYP 2B6
	17α-ethinyl estradiol	Contraceptive	2-hydroxylation	
	Felodipine	Antihypertensive, CCB	oxidation to pyridine	
	Fenofibrate	Cholesterol-lowering	deesterification	
	Fentanyl	Opioid analgesic	N-dealkylation	
	Gefitinib	Anticancer	O-demethylation	CYP 1A1/2D6
	Glyburide	Antidiabetic	hydroxylation	CYP 2C9
	Granisetron		N-demethylation	
	Haloperidol	Antipsychotic	N-dealkylation	CYP 2D6
	Hydromorphone	Opioid analgesic	N-demethylation	CYP 2C9
	Ifosfamide	The anticancer alkylating agent	N-dechloroethylation	CYP 2B6
	Isotretinoin	Antiacne, retinoid	(13-cis- retinoic acid) 4-hydroxylation	CYP 2C8
	Lithocholic acid	Bile acid	6α-hydroxylation	
	Lopermide		N-demethylation	CYP 2B6
	Midazolam	Antipsychotic	1′-hydroxylation	
	Mifepristone		N-demethylation	

	Mirtazapine	Antidepressant	N-demethylation and N-oxidation	
	Morphine	Opioid analgesic	N-demethylation	CYP 2C8
	Nevirapine	Non-nucleoside reverse transcriptase inhibitor	2-hydroxylation	
	Nifedipine	Antihypertensive , CCB	oxidation to pyridine	
	Oxycodone	Opioid analgesic	N-demethylation	
	Paracetamol	Non opioid analgesic	oxidation to NAPQI	CYP 2E1, 2A6, 1A2, 2D6,2C9/19
	Quetiapine	NSAIDs	N-dealkylation	
	Quinine	Antimalarial	3- hydroxylation	
	Quinidine	antiarrhythmic	3-hydroxylation and N-oxidation	
	Sildenafil	phosphodiesterase type 5 inhibitor,	N-demethylation	CYP 2C9
	Simvastatin	Antilipidemic	6′-β-hydroxylation	CYP 2C8
	Sirolimus		16-O- and 39-O-demethylation	
	Tacrolimus		O-demethylation	
	Teniposide	Immunosuppressants	O-demethylation	
	Testosterone	Hormone	6β-hydroxylation	CYP 2C9, 1A1
	Tetrahydrocannabinol	Natural compound	7- and 8-hydroxylation	
	Tilidine	Natural compound	N-demethylation	
	Tramadol	Opioid analgesic	N-demethylation	CYP 2B6
	Trazodone	Opioid analgesic	N-dealkylation to mCPP	
	Triazolam	Tricyclic antidepressant	α- and 4-hydroxylation	
	Verapamil	Calcium channel blocker	N-demethylation to norverapamil	CYP 2C8
	Vincristine	Antineoplastic	M1-formation	CYP 3A5>3A4
	Zolpidem	Hypnotic	hydroxylation	CYP 1A2

Table 3

Inhibitors and inducers of CYP isoforms

Isoforms	Inhibitors	Inductors
CYP1A2	α- naphthoflavone	Aminoglutethimide
	Cimetidine	Antipyrine
	Disulfiram	Bilirubin
	Furafylline	Carbamazepine
	Ciprofloxacin	Coffee
	Enoxacin	Nelfinavir
	Fluvoxamine	Omeprazole
	Mexiletine	Phenobarbital
	Moricizine	Phenytoin
	Oral contraceptives	2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
	Tolfenamic acid	Primaquine
		Rifampicin
		Ritonavir
		Sulfinpyrazone
		Cruciferous vegetables (broccoli)
		Polychlorinated biphenyls
		Polycyclic aromatic hydrocarbons (PAH, smoked meat or grilled on coals, cigarette smoke)
CYP2A6	Decursinol angelate	Artemisinin
	(R)-(+) menthofuran	Carbamazepine
	8-methoxypsoralen	Dexamethasone
	Pilocarpine	Phenobarbital
	Selegiline	Rifampicin
	Tranylcypromine	Estrogens
CYP2B6	Bergamottin	Artemisinine-type antimalarials
	Clopidogrel	Baicalin
	Clotrimazole	Carbamazepine
	Imidazoles	Cyclophosphamide
	2-phenyl-2-(1-piperdinyl) propane	N,N-diethyl-m-toluamide (DEET)
	(RU486)	Efavirenz
	Mifepristone	17-α-ethinylestradiol
	Raloxifene	Hyperforin
	Sertraline	Nelfinavir
	thioTEPA	Metamizole
	Ticlopidine	Phenobarbital
		Phenytoin
		Rifampicin
		Ritonavir

		Statins (e.g. atorvastatin)
		Vitamin D
		St. John's Wort
		Nevirapine
CYP2C8	Gemfibrozil 1-O-bglucuronide	Cyclophosphamide
	Trimethoprim	Dexamethasone
	Amiodarone	Fibrates (e.g. gemfibrozil)
	17a-Ethinylestradiol	Hyperforin
	Bosutinib	Clofibric acid
	Isoniazid	Nilotinib
	Nortriptyline	Lithocholic acid
	Desethylamiodarone	Nelfinavir
	Fluoxetine	Paclitaxel
	Phenelzine	Idelalisib
	Verapamil	Ifosfamide
	Raloxifene	Phenobarbital
		Phenytoin
		Rifampicin
		Ritonavir
		Progesterone
		Tasimelteon
CYP2C9	Amiodarone	Aprepitant
	Fluconazole	Avasimibe
	Naringenin	Barbiturates
	Sulphaphenazole	Bosentan
	Tienylic acid	Carbamazepine
	Voriconazole	Cyclophosphamide
		Dexamethasone
		Glutethimide
		Hyperforin
		Nelfinavir
		Nifedipine
		Norethindrone
		Phenobarbital
		Prednisone
		Rifampicin
		Ritonavir
		Statins (e.g. atorvastatin)
		St. John's Wort
CYP2C19	(−)-N-3-benzyl-phenobarbital	Artemisinin-type antimalarials
	Clopidogrel	Acetylsalicylic acid
	Fluoxetine	Antipyrine

	Fluvoxamine	Baicalin
	Naringenin	Barbiturates
	Omeprazole	Carbamazepine
	Ticlopidine	Dexamethasone
	Voriconazole	Efavirenz
	(+)-N-3-benzyl-nirvanol	Hyperforin
		Nelfinavir
		Rifampicin
		Ritonavir
		St. John's Wort
CYP2D6	Bupropion	Inductors are absent
	Celecoxib	
	Flecainide	
	Fluoxetine	
	Haloperidol	
	Methadone	
	Paroxetine	
	Quinidine	
CYP2E1	Clomethiazole	Acetone
	Disulfiram	Ethanol
	4-methylpyrazole	Isoniazid
	Orphenadrine	Pyrazole
	Diethyldithiocarbamate	Various organic solvents
CYP2J2	Arachidonic acid	Unknown
	α-naphthoflavone	
	Ketoconazole	
	Danazol	
	Hydroxyebastine	
	Metoprolol	
	Nifedipine	
	Terfenadone	
	Troglitazone	
	Tranylcypromine	
	Flunarizine	
	Haloperidol	
	Telmisartan	
	Verapamil	
CYP3A4/5	Grapefruit juice	Artemisinine-type antimalarials
	Azamulin	Amprenavir
	Claritromycin	Aprepitant
	Diltiazem	Avasimibe
	Erythromycin	Baicalin
	Ethinylestradiol	Baribiturates
	Irinotecan	Bosentan

	Ketoconazole	Carbamazepine
	Mibefradil	Dexamethasone
	Mifepristone (RU486)	Efavirenz
	Naringenin	Etravirine
	Nicardipine	Ginkgo biloba
	Ritonavir	Glucocorticoids
	Troleandomycin	Hyperforin
	Verapamil	Imatinib
	Voriconazole	Miconazole
		Mitotane
		Moricizine
		Nafcillin
		Nevirapine
		Oxcarbazepine
		Phenobarbital
		Phenylbutazone
		Rifabutin
		Rifampicin
		Rifapentin
		Ritonavir
		Statins
		St. John's Wort
		Sulfinpyrazone
		Topiramate
		Troglitazone
		Valproic acid
		Vinblastine
		Phenytoin

CYTOCHROME P-450: genetic and population aspects
Scientific monograph

Mavlyanov Iskander Rahimovich
Ashirmetov Abdurashid Khamidovich
Mavlyanov Zafar Iskanderovich
Jarilkasinova Gavhar Januzakovna

Publisher: Pavol Jozef Šafárik University in Košice
Technical Advice: University Library at Pavol Jozef Šafárik University in Košice
http://www.upjs.sk/pracoviska/univerzitna-kniznica
Year: 2017
Pages: 223
Author's sheets: 11,15
Edition: first
Available at: https://unibook.upjs.sk/en/15-medicine
Publication date: September 2017

ISBN 978-80-8152-526-1