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Review

GENETIC POLYMORPHISM OF METABOLIC ENZYMES P450 (CYP) AS A SUSCEPTIBILITY FACTOR FOR DRUG RESPONSE, TOXICITY, AND CANCER RISK

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The polymorphic P450 (CYP) enzyme superfamily is the most important system involved in the biotransformation of many endogenous and exogenous substances including drugs, toxins, and carcinogens. Genotyping for *CYP* polymorphisms provides important genetic information that help to understand the effects of xenobiotics on human body. For drug metabolism, the most important polymorphisms are those of the genes coding for CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, which can result in therapeutic failure or severe adverse reactions. Genes coding for CYP1A1, CYP1A2, CYP1B1, and CYP2E1 are among the most responsible for the biotransformation of chemicals, especially for the metabolic activation of pre-carcinogens. There is evidence of association between gene polymorphism and cancer susceptibility. Pathways of carcinogen metabolism are complex, and are mediated by activities of multiple genes, while single genes have a limited impact on cancer risk. Multigenic approach in addition to environmental determinants in large sample studies is crucial for a reliable evaluation of any moderate gene effect. This article brings a review of current knowledge on the relations between the polymorphisms of some CYPs and drug activity/toxicity and cancer risk.

KEY WORDS: *cancer risk, cytochrome P450, drug metabolism, genotyping, pharmacogenomics, polymorphic allele, xenobiotics*

The traditional toxicity assessment has been using descriptive means, finding links between chemicals in different doses and tissue pathology at the site of action, system-level toxicity, and overt mortality. It has been providing a framework for understanding the toxicity of a chemical. Progress in biological research calls for the understanding of the mechanisms of toxicity at the molecular level. Here the essential role is played by genomic information at the pharmacokinetic and pharmacodinamic level. For example, the genotype of an individual can significantly influence the disposition of a chemical, and determine their susceptibility to its toxicity (1). In addition, exposure to chemicals can result in different gene expression, which in turn can lead to different pharmacodynamic effects. The Human Genome Project (HUGO) has provided a number of genetic information that helps us understand the effects of xenobiotics on biological systems. New scientific fields have developed. Pharmacogenomics studies the role of gene variants in interactions between drugs and drug-exposed organisms (2-5). Ecogenetics investigates dynamic interactions between a specific individual genotype and different compounds from the environment such as industrial chemicals and nutrition products (6, 7). Toxicogenomics studies individual

predisposition to carcinogenic, teratogenic, and other toxic effects of drugs and other xenobiotics (8). Integration of genomics into toxicological research can provide a better understanding of how various xenobiotics act in the human body (9).

Main proteins involved in xenobiotic disposition in the body are classified as either phase I (oxidative), or phase II (conjugative) metabolising enzymes, or phase III transporters involved in efflux mechanisms. The major enzymes of phase I metabolism are heme thiolate proteins of the cytochrome P450 superfamily (CYPs).

Phase I enzymes generate functional groups that may subsequently serve as a site for conjugation catalysed by phase II enzymes UDP-glucuronosyltransferases (UGT), Sulfotransferases (SULT), Glutathione S-transferases (GST), and N-acetiltransferases (NAT). These enzyme reactions are necessary fo a lipophilic compound to biotransform into a watersoluble product that can be excreted in urine. Phase III transporters like, P-glycoprotein (Pgp), multidrug resistance-associated proteins (MRPs), and organic anion transporting polypeptide 2 (OATP2) are expressed in many tissues such as the liver, intestine, kidney, and brain, and play a crucial role in xenobiotic absorption, distribution, and excretion. Along with phase I and phase II enzyme induction/inhibition, pretreatment with different inducers or inhibitors has been shown to alter the expression of phase III transporters, with the final results of altered excretion of xenobiotics. Orphan nuclear receptors like pregnane X-receptor (PXR) and constitutive androgen receptor (CAR) are often termed "xenosensors". They interact with various exogenous drugs and toxins, and mediate cellular response to toxic insult by acting as transcription factors for the members of the secretory detoxification system, including efflux transporters and metabolic enzymes (10, 11). Exposure to phase I, phase II, and phase III inducers may trigger cellular stress response leading to increase in gene expression, which ultimately enhances the elimination and clearance of these xenobiotics.

Chemical carcinogenesis is a complex multistage process that includes three main steps: initiation, promotion, and progression. Each stage depends on a number of factors that can promote or prevent carcinogenesis. The genotoxic impact of carcinogen exposure is heavily influenced by a complex array of metabolic pathways. Carcinogenesis induced by genotoxic xenobiotics is related to polymorphisms of phase I and phase II enzyme systems responsible for metabolic activation/detoxification of carcinogenic substances. Along with carcinogen dose and exposure time, these factors influence the outcome of a malignant process. Carcinogenic agents are divided into direct carcinogens such as N-nitrosoalkylurea, ethyl-and methylmethanesulfonate, N-methyl-N-nitronitrosoguanidine, sulphur mustard, diepoxybutane, β-propiolactone, and ethyleneimine, and procarcinogens which are metabolised in the cell in two steps catalysed by various phase I and II enzymes. In the first step, procarcinogens are activated and converted into electrophilic derivatives. In the second step, metabolic products are neutralised by conjugation (12). The main activating enzymes include CYPs isoforms, and to a lesser degree, oxidases, hydroxylases, epoxygenases reductases, flavin-containing monooxygenases, peroxidases, dehydrogenases, hydrolases, and some other enzymes. Conjugation enzymes include epoxidases, acyltransferases, sulfotransferases, gluthatione-S-transferases, UDP-glucuronyl transferases, and transaminases. For some carcinogens, second-stage reactions are a necessary intermediate step and a prerequisite to further activation.

The majority of currently known procarcinogens are hydrophobic CYP substrates (Table 1). Most hydrophobic substrates are polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, and dioxin-like compounds. More hydrophilic compounds include nitrosoureas, aminoazo dyes, biphenyls, fluorenes, and heterocyclic amine (13). Some enzymes influence carcinogenesis indirectly i.e. by metabolising a number of endogenous compounds such as sex hormones, corticosteroids, cholesterol, bile acids, and retinoic acid. Mutations in the corresponding genes may promote carcinogenesis and progression of tumours (14). Habits like cigarette smoking, are yet another source of exposure relevant for cancer development in some tissues and organs such as large bowel, and lung. Estimations of cancer risk should always take into account the interplay between dietary habits, environmental exposure, and expression of particular isoforms of metabolic enzymes.

CYTOCHROMES P450 (CYPs)

Overview

Among the enzymes of phase I biotransformation, CYPs exhibit considerable catalytic diversity. This

enzyme superfamily, existing in over 50 forms, is the most important enzyme system involved in the biotransformation of many endogenous and exogenous substances including drugs. CYPs are variably distributed in different tissues. Most can be found in the membrane of the endoplasmatic reticulum in the liver, although CYPs are found in almost all tissues and organs (intestine, lung, kidney, brain, lymphocytes, and placenta). Physiological substrates of these enzymes include steroids, fatty acids, prostaglandins, leukotrienes, and biogene amines, while xenobiotic substrates include drugs, herbal toxins and toxic chemicals from the environment. CYPs predominantly catalyse oxidative reactions, insertion of an atom from molecular oxygen into a substrate, i.e. a typical activating (or Phase I) reaction, serving as monooxygenases, oxidases and peroxidases, although they can act in reduction reactions too. CYPs are divided in three major groups. The first includes CYP families 5 to 51 with a high affinity for endogenous substrates, which have remained well conserved throughout evolution. The second group includes CYP families 1 to 3, that have lower affinity for their substrates and have been less conserved evolutionarily. The third group includes CYP family 4 which metabolise fatty acids, related substrates, and some xenobiotics. CYP families 1 to 3 are responsible for 70 % to 80 % of all phase I- dependent metabolism of clinically used drugs (9), and participate in the metabolism of a huge number of xenobiotic chemicals (Table 2) (15). Most of the enzymes in CYP families 1 to 3 exhibit interindividual variability in catalytic activity. This is either due to genetic polymorphisms or to variability in expression levels.

Each CYP isoform has its own set of metabolised substrates. The same xenobiotic can be metabolised by different isoforms into similar or different metabolic products. For enzymes belonging to CYP families 1 to 4 overlapping substrate specificity is known.

The most important enzymes for drug metabolism are CYP2C9*, CYP2C19, CYP2D6 and CYP3A4, whereas the most important isoforms responsible for the biotransformation of chemicals and especially for the metabolic activation of pre-carcinogens are CYP1A, CYP1A2, CYP1B1, CYP2A6, CYP2E1 and again CYP3A4. In CYP families 2 and 3 HUGO has found new genes like *CYP2R1, CYP2S1, CYP2U1* and *CYP3A43*. Their function and importance are still investigated.

* Enzymes are written in capital letters, and coding genes in italics.

There is no apparent relationship between the amount of hepatic CYPs and their relative importance for drug metabolism. This might indicate that highly expressed CYPs play an important role in food metabolism and a relatively minor role in drug metabolism.Most CYP enzymes are preferentially expressed in the centrilobular area of the liver (16). This has toxicological implications, as the centrilobular area is more sensitive to damage by drugs and ethanol, which are CYP substrates.

Most CYPs involved in the biotransformation of xenobiotics are inducible (17). An exception is CYP2D6 in which multiple gene copies are responsible for increased detoxifying potential of the enzyme (18). Induction is an important adaptive reaction against environmental toxins from the past. CYP expression can be controlled at the transcriptional, mRNA, translational and posttranslational levels. Transcriptional control is highly important and three crucial cytosolic receptors detect the concentration of environmental xenobiotics, namely the pregnane X-receptor (PXR), constitutive androgen receptor (CAR) and aryl hydrocarbon receptor (AhR). AhR regulates CYP1A1, CYP1A2 and CYP2S1; PXR regulates CYP2C9 and CYP3A4 and CAR regulates CYP2B6, CYP2C9, and CYP3A4. Activation of CYPs as well as phase II and phase III proteins is stimulated by increased cellular amounts of environmental xenobiotics, which may result in higher protein expression and subsequently in lower amounts of xenobiotics. It is evident that these transcriptional factors are involved in the control of most human drug metabolising CYPs.

Polymorphisms of receptors CAR, PXR, and AhR have also been described in literature. For example more than 10 mutations in the AhR gene have been identified to be able to modulate CYP activity (19, 20).

Of special interest are interaction studies in human liver microsomes using CYP- specific inhibitors, which give important information of the role of CYPs in the biotransformation of different xenobiotics (21-26). *In vitro* systems can reliably predict enzyme specificity and drug clearance, provided that the drug is not metabolised in phase II reactions. In addition, knockout mouse and transgenic models provide many advantages in studying physiological and toxicological roles of different CYPs.

Herbs with the potential to significantly modulate the activity of drug-metabolising enzymes, notably CYPs and drug transporter P-glycoprotein, include

garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), echinacea (*Echinacea purpurea*), ginseng (*Panax ginseng*), St John' s wort (*Hypericum perforatum*), kava (*Piper methysticum*), and grapefruit (*Citrus paradisi*). All of these products can participate in pharmacokinetic interactions (27-29).

Cytochrome P450 genes

The nomenclature for cytochrome P450 (CYPs) uses designation "CYP" followed by a number indicating the gene family (for a gene to be in the same family, its aminoacid sequence should be identical in over 40 %), followed by a letter indicating the subfamily (over 55 % of identical amino acid sequence) and the gene number (30). The same gene number means that genes have the same function and are highly conserved. Human genome sequence has revealed about 107 human P450 genes: 59 active and about 48 pseudogenes (31). The majority of hepatic drug metabolising enzymes are polymorphic. A gene is considered to be polymorphic when the frequency of a variant allele in normal population is at least 1 %.

Genes encoding xenobiotic metabolism (*CYP1-3*) differ in their characteristics from genes important for the metabolism of predominantly endogenous compounds (CYP4-CYP51). The first group includes a number of pseudogenes, that is, genes encoding chemical metabolism that have been inactivated as a result of adaptation to the environment. In CYP families 1 to 3, the majority of genes are also functionally polymorphic, with the exception of *CYP1A1, CYP2E1*, and *CYP3A4*, which are relatively well-conserved. The reason for this conservation might be that these enzymes have some endogenous substrates in addition to the exogeneous. Pseudogenes are also present in some CYPs involved in endogenous metabolism (*CYP21P*), but there is significantly less variability than in CYP families 1 to 3. Inter-ethnic and inter-racial differences in frequencies of polymorphic gene variants are also worth noting (32).

Genetic polymorphism is an important reason for variations in drug response of the human body. In terms of drug metabolism, there are four specific phenotypes that can be determined by either

Table 1 *Participation of various human cytochrome P450 enzymes in the metabolic activation of pre-carcinogenes (9)*

CYP1A1	CYP1A2	CYP1B1	CYP2A6	CYP2E1	CYP3A4
Benzo(a)pyrene	2-Acetyl-aminofluorene	Benzanthracene	Aflatoxin B1	Benzene	Aflatoxin B1
	4-Amino-biphenyl	Benzo(a)pyrene	DEN	Chloroform	Aflatoxin G1
	GluP-1	DMBA	IQ	DEN	6-Amino-chrysene
	IQ	1-Ethynyl-pyrene	MOCA	Ethyl carbamate	Benzo(a)pyrene
	MeIQ	3-Methyl-cholantrene	MeIQ	Methylene chloride	1-Nitropyrene
	MeIQx	Oestradiol	NNK	N-nitroso-dimethylamine	Oestradiol
	N-nitroso-diethylamine			N-nitroso-nicotine	Senecionine
	NNK			NNK	Stergmato-cystine
	PhIP			Styrene	
	Trp P-2			Vinyl chloride	
				Vinyl bromide	

DMBA dimethylbenzanthrazene,
DEN 3-amino-1-methyl-5H-pyrido(4,3-b)indole,
DMN N-nitrosodimethylamine,
GluP-1 2-amino-6,-methyl-dipyrido-(1,2-a:3',2'-d)imidazole,
IQ 2-amino-3-methylimidazo(4,5-f)quinoxaline,
MeIQ 2-amino-3,4 dimethylimidazo(4,5-f)quinoxaline,
MOCA 4,4'-methylene-bis(2-choloroaniline),
NNK 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone
PhIP 2-amino-1-methyl-6 phenylimidazo(4,5-b)pyridine,
Trp P-2, 2-aminodipyrido(1,2-a: 3',2'-d)imidazole

phenotyping or genotyping: a poor metaboliser (PM), intermediate metaboliser (IM), extensive metaboliser (EM), and ultrarapid metaboliser (UM). Phenotyping involves administration of a test drug whose metabolism dependens only on the enzyme involved, followed by the estimation of the metabolic ratio (MR, defined as the ratio of the parent/unchanged drug to its metabolite measured in serum or urine). Drug concentration is often measured using methods like HPLC, GC-MS or LC-MS (33). Phenotyping is very useful in pharmacokinetic studies, as it reveals the extent of drug-drug interactions or impairments in drug biotransformation. On the other hand, phenotyping has several disadvantages, which include complicated test protocols, risk of adverse drug reactions, and the risk of incorrect phenotype designation due to coadministration of drugs or confounding effects of a disease. Genotyping involves identification of defined genetic mutations that result in specific drug metabolism. These mutations can be genetic alterations that lead to overexpression (gene multiplication), absence of an active protein product (null allele), or production of a mutant protein with diminished catalytic capacity (inactivating allele). Genotyping is predominantly based on polymerase chain reaction (PCR) methods. An important technological advance in genetic testing is the DNA microarray, which allows for simultaneous testing of thousands of DNA sequences (34).

A poor metaboliser lacks active allele and may experience more adverse events at usual doses due to reduced metabolism and increased drug concentration. If individuals lacking the active allele receive a prodrug, they may not respond due to a lower-than-expected concentration of the active metabolite. Individuals with intermediate metabolic phenotype are homozygous for two reduced activity alleles or are heterozygous for an inactive allele. They may experience some, or a lesser degree of the consequences of the poor metaboliser. Extensive metaboliser has two fully active alleles and shows the expected response to a standard dose. Ultraextensive metabolisers are individuals with more than two copies of active gene. They may not reach therapeutic concentrations at usual, recommended drug doses due to increased metabolism. When a prodrug is administered, they may experience adverse effects due to higher-than-expected concentrations of active metabolite.

Adverse drug reactions (ADRs) pose substantial difficulties in drug treatment and drug development. It has been estimated that ADRs cause more than 100,000 deaths a year in the US alone (35), up to 7 % of all hospital admissions in the UK, and 13 % of all admissions to internal medicine clinics in Sweden (36). ADR burden in the US is about US$ 100 billion a year (35).

The knowledge that enzyme systems take the central role in developing ADRs is crucial for drug therapy. About 59 % of drugs cited in ADR studies are metabolised by polymorphic phase I enzymes, and among those CYPs account for 86 %. By contrast, only 20 % of drugs that are non-polymorphic enzyme substrates are included in ADR reports (37). Clinically the most important polymorphisms are of the *CYP2C9*, *CYP2C19*, and *CYP2D6* genes.

Understanding of the genetics and biology of phase I and II enzymes can help to predict a lot of events related to the metabolic activation of carcinogens and the relative risk for toxic or carcinogenic effects of other xenobiotics. Table 3 summarises the functional profile of polymorphic CYPs involved in the biotransformation of xenobiotics.

This article has focused on some of phase I CYPs participating in the metabolism of xenobiotics.

CYP1A1

CYP1A1 is mainly expressed in extrahepatic organs, especially in epithelial tissues. A relevant feature of this enzyme is its ability to catalyse the first step in the metabolism of polycyclic aromatic hydrocarbons (PAHs, also present in tobacco smoke), which may lead to a formation of electrophilic carcinogenic molecules. CYP1A1 also catalyses oxidation of several xenobiotic chemicals such as 7-ethoxyresorufin, theophylline, caffeine, 7-ethoxycoumarin, and chlorzoxazone, and of endogenous chemicals such as 17β-estradiol and estrone (38). *CYP1A1* polymorphism affects both CYP1A1 regulation and structure. Regulation begins with the binding between the inducing agent (xenobiotic substrate to be metabolised) and intracellular arylhydrocarbon receptor (AhR). This high-affinity receptor is associated with high *CYP1A1* inducibility. The AhR complex can also interact with the activity of a variety of components of the endocrine system (tumour necrosis factor α, epidermal growth factor receptor, or glucocorticoid and estrogen receptors). There are genetic polymorphisms in the *AhR* gene in humans, and interindividual differences in AhR phenotype have been observed (39). About one-tenth of the population have the high-affinity AhR phenotype and highly inducible CYP1A1 (40).

More than 11 alleles of *CYP1A1* have been identified, (41) of which *CYP1A1*2B, *2C, *3, *4, *5, *6, *7, *8, *9, *11* show amino acid changes. However, it is unclear whether these amino acid changes alter catalitic activities in oxidation of xenobiotics, including PAHs. There is evidence of race-related differences in the genetic polymorphism of *CYP1A1*(42, 43); *CYP1A1*2A* and *CYP1A1*2C* variant alleles are more frequent in Asian (Japanese) than Caucasian populations. *CYP1A1*3* allele is specific for African blacks, and has not been found in either Asian or Caucasian populations. This polymorphism has been reported to increase the risk for African-Americans of adenocarcinoma (44). Other studies do not support this finding (45). Most investigations on cancer risk arising from *CYP1A1* polymorphism have studied the effects of modified CYP1A1 in association with deficient phase II enzymes (predominantly GST) and other gene variants that affect activation and detoxification of CYP1A1 substrates (46). GST detoxifies many of activated carcinogens that are produced during the Phase I metabolism. There are numerous conflicting epidemiological studies addressing correlations between cytochrome CYP1A1 genetic polymorphisms and lung cancer susceptibility, with associations plausibly linked to alterations in carcinogen bioactivation. Some studies showed that a combination between overexpressed CYP1A1 and deficient GST highly increased lung cancer risk after exposure to PAHs (47, 48). Moreti at al. (49) published results of a cross-sectional study that aimed to evaluate whether genetic polymorphisms for *CYP1A1, EPHX* (epoxide hydrolase), and *GSTM1* genes that affect PAH activation and detoxification might influence the extent of primary DNA damage in PAH-exposed workers. They showed that molecular epidemiology, that is cross-sectional study of genotoxicity biomarkers, can help identify common genetic risk markers and associate effects with measured exposure data. Shah et al. (50) reported that lung cancer risk increased two to four times in patients carrying the genotype combination of *CYP1A1*2A* and *GSTM1* (deletion polymorphisms), which suggests that lung cancer susceptibility may depend on interactions between genes. In the same study, tobacco smoking or chewing and alcohol consumption were also found to interact with *CYP1A1* genotypes in terms of increased risk, which further confirmed a role of gene-environment interaction in the development of lung cancer.

Other published data (51) also gave evidence of gene-gene interactions which include *CYP1A1* in lung carcinogenesis. A population-based study (52) found that Caucasians but not African Americans with *IIe/Val (CYP1A1*2C)* genotype were at a lower risk of developing lung cancer than those with *lle/lle (*1/*1*) genotype, after adjusting for age at diagnosis, sex, years of smoking and family history of cancer. A recent study (53) pointed to a potential role of oestrogen in lung cancer susceptibility. Authors evaluated 11 *SNPs* in genes involved in tobacco and oestrogen metabolism (*CYP1A1*2A, CYP1A1*2C, CYP1B1*3, CYP17, CYP19A1, XRCC1 Gln(399)Arg*, *COMT Val(158)Met*, *NQO1 Pro(187)Ser*, *GSTM1*, *GSTT1*, and *GSTP1 Ile(105)Val*. The study included 504 women aged 18 to 74, diagnosed with non-small cell lung cancer (NSCLC) and 527 controls. Lung cancer risk associated with individual *SNP* was established for *GSTP1* (*A* allele) and *XRCC1* (*A/A* genotype) in white women smokers and for *CYP1B1* (*G* allele) in black women smokers. White women smokers carrying two risk genotypes at the following loci - *CYP17* and *GSTM1*, *COMT* and *GSTM1*, *CYP17* and *GSTT1, XRCC1* and *GSTP1, CYP1B1* and *XRCC1,* and *COMT* and *XRCC1* - were at a higher risk of lung cancer than individuals not carrying risk alleles at these loci. This suggests that even the most parsimonious model of lung cancer risk assessment in white smoking women should include age, family history of lung cancer, history of chronic lung disease, pack-years, BMI, *XRCC1 A/A* genotype, *GSTM1* null, and *COMT A/G* or *G/G* genotype. These findings also support the need for continued study of oestrogen in relation to lung cancer risk.

Shi et al. (54) summarised data from 46 studies and conducted a meta-analysis of *CYP1A1* and *GSTM1* polymorphisms and lung cancer risk in Chinese populations. They confirmed the association between the *CYP1A1*2C* allele variant and *GSTM1* with increased risk of lung cancer. For the same polymorphisms, an eightfold increase in susceptibility to lung cancer was demonstrated in a north Indian population (55). A Korean group (56) investigated the association between *CYP1A1*2C, CYP1B1*3, GSTP1 Ile105Val,* and *MPO G-463A* polymorphisms and lung cancer risk in never-smoking Korean women. They found *CYP1A1*2C* polymorphism associated with a significantly lower risk of lung adenocarcinoma. However, a combination of risk gene variant *CYP1B1*3* with *CYP1A1*2C* was associated with a higher risk of lung adenocarcinoma as well as of overall lung cancer. Variability assessment of tobacco metabolism, oestrogen metabolism, and

DNA repair pathways could be useful in developing more predictive models for individual cancer risk in connection with *CYP1A1* polimorphism.

Other published data (57) suggest that *CYP1A1* polymorphisms could be useful predictors of breast cancer risk as well as of some tumour characteristics. Variant allele *6235C* carriers at the 3' noncoding region, and variant allele *462Val* carriers at the codon 462 polymorphism showed a significantly reduced breast cancer risk than noncarriers. Another study found that carriers of *CYP19 (TTTA)7(-3bp*) and *CYP1A1 C6235T* polymorphisms had a significantly increased risk of ER-positive breast cancers, which could be a useful information in

Table 2 *General properties of human cytochrome P450 enzymes in families 1-3 (9)*

Enzyme	Marker substrate reaction	Substrate specificity	Main tissue localisation	Comments
CYP1A1	EthoxyresorufinO-deethylation	Pre-carcinogens, PAHs	Extrahepatic	Inducible by PAHs, endogenous role in cell growth
CYP1A2	Phenacetin O-deethylation ethoxyresorufin O-deethylation	Aromatic amines, PAHs	Liver	Inducible by PAHs and some drugs
CYP1B1	Estradiol-4-hydroxylation	DMBA, oestradiol	Extrahepatic	Inducible by PAHs, high affinity for some PAHs
CYP2A6	Coumarin 7-hydroxylation	Nicotine	Liver	The major nicotine oxidase, active on some drugs and carcinogens
CYP2A13	Coumarin 7-hydroxylation		Olfactory mucosa	
CYP2C8	Taxol hydroxylation		Liver	Might have a role in hepatic drug metabolism
CYP2C9 *see Table 4*	Tolbutamide methylhydroxylation, losartan hydroxylation, S-warfarin 7-hydroxylation	Many drugs	Liver	Very important for drug metabolism
CYP2C18	?	Some drugs	Extrahepatic	Highly polymorphic
CYP2C19 *see Table 5*	S-mephenytoin 4-hydroxylationomeprazole 5-hydroxylation	Many drugs	Liver	Highly polymorphic, very important for drug metabolism
CYP2D6 *see Table 6*	Dextromethorphan O-deethylation; bufuranol 1-hydroxylation, debrisoquine 4-hydroxylation	Many drugs	Liver	Very important for drug metabolism
CYP2E1	Chlorzoxazone 6-hydroxylation	Solvents, many drugs, precarcinogens	Liver	The main enzyme which metabolises organic solvents, highly inducible
CYP2F1			Lung	Active?
CYP2J2	Arachidonic acid hydroxylation	Fatty acids	Extrahepatic	
CYP2R1	Vitamin D25 hydroxylase	Vitamin D	Extrahepatic	The function recently revealed
CYP2S1	Trans-retinol oxidation	Small aromatic hydrocarbons	Extrahepatic	Inducible by UV-light in skin
CYP3A4 *see Table 7*	Testosterone 6β-hydroxylation, midazolam 1'-hydroxylation, erythromycin N-demethylase	Many drugs, pre-carcinogens, dietary components	Liver, intestine	The most important P450 in drug metabolism
CYP3A5	Same as CYP3A4	Similar as CYP3A4	Liver, intestine	Expressed in some individuals
CYP3A7	Same as CYP3A4	Similar as CYP3A4	Liver, intestine	Mainly expressed in fetal liver
CYP3A43	Not known	Not known	Liver	Tiny expression, active?

screening for chemoprevention with tamoxifen (58). Some studies (59) confirmed earlier reports that *CYP1A1*2C*-containing genotypes modified the association between PCB exposure and risk of breast cancer. They presented additional evidence suggesting that *CYP1A1*3*-containing genotypes modified the effects of PCB exposure among African American women. A Russian group (60) estimated the frequency of *CYP1A1, CYP1A2, CYP1B1, CYP19*, and *SULT1A1* allele variants in a female population of the Novosibirsk district and their associations with higher risk of breast (BC), ovarian (OC), and endometrial (EC) cancers. It found significant differences in allele distributions for *CYP1A1*2A* polymorphism between patients with BC and controls. Furthermore, significant differences were found in the allele and genotype distributions for *CYP1A2*1F* polymorphism between patients with BC and OC. The frequency of a mutant *CYP19* heterozygote genotype *C/T* was higher in patients with OC and EC than in healthy women. These results support the hypothesis that the susceptibility gene of oestrogen-metabolising enzymes may involve different risk of hormone-dependent cancers in women. Report on the association between a combination of *CYP1A1* and *SULT* gene polymorphisms and endometrial cancer suggests that decreased variant allele *CYP1A1*2A* and increased variants of *SULT1A1*(*Arg213His, 14A/G, 85C/T*) and *SULT1E1-64G/A* may be risk factors for endometrial cancer in Caucasians (61). Oestrogens have also been proposed to act as tumour promoters and inducers of hepatocarcinogenesis. We observed a significant association between the risk of hepatocellular carcinoma and the polymorphisms of the oestrogen receptor alpha (*ESR1*) gene. A Chinese group (62) confirmed the association between hepatocellular carcinoma (HCC) and four variants of *CYP1A1* in a study that included 1006 pathologically confirmed HCC patients and 1015 cancer-free controls from Han population. Another Chinese study (63) could not confirm these results and concluded after stratification by common confounding factors of

Table 3 *Functional importance of polymorphism in human P450 enzymes involved in xenobiotic metabolism*

Enzyme	Substrate	Frequency of variant alleles	Functional effects	Clinical effects
CYP1A1	Carcinogens	Relatively high	Unproven	No
CYP1A2	Many drugs Carcinogens	High	Polymorphic induction Rare allels yielding less expr	Yes
CYP1B1	Carcinogens Oestrogens	Rare null alleles Frequent missense mutations	7 haplotypes with similar activity	Yes, glaucoma
CYP2A6	Nicotine, drugs, carcinogens	High in orientals Les frequent in Caucasians	Nicotine metabolism	
CYP2B6	Many drugs	Relatively low	Reduced drug metabolism	Yes
CYP2C8	Some drugs	High	Taxol metabolism	Yes
CYP2C9 *See Table 4*	Many drugs	Relatively low	Very significant	Yes
CYP2C19 *See Table 5*	Many drugs	High	Very significant	Yes
CYP2D6 *See Table 6*	Many drugs	Very significant	Yes	Yes
CYP2E1	Carcinogens, solvents, some drugs	High	Not shown	No
CYP3A4 *See Table 7*	Many drugs Carcinogens	Low	No importance of polymorphism	No
CYP3A5	Many drugs	High	No expression	No

hepatocellular carcinoma, that the polymorphisms in enzymes involved in the biogenesis (CYP17,CYP19), bioavailability (CYP1A1, CYP1B1), and degradation (catechol-O-methyltransferase) of oestrogens were not associated with the risk of hepatocellular carcinoma. Furthermore, no signs of gene-gene interactions were observed for any of the combinations of the seven polymorphisms. Recent findings (64) suggest that common variants in hormone-related genes contribute to the risk of biliary tract cancers and stones, possibly by modulating hormone metabolism. Genotyping 18 SNPs in 9 genes involved in steroid hormone biosynthesis, metabolism, and transport revealed that *CYP1A1 IVS1 + 606 (rs2606345) T* allele had a possible impact on gallbladder and bile duct cancers, while the *CYP1A1 Ex7 + 131 (rs1048943) G* allele was associated with ampulla of Vater cancer.

Other studies partly support that polymorphic variations in *CYP1A1 (*2A, *2C, *4)* may play a role in colorectal cancer (65-67).

CYP1A2

CYP1A2 is mainly expressed in the liver. The level of CYP1A2 protein is 10 % to 15 % of total P450 in human adult liver. Expression levels vary about 40 times between individuals.

CYP1A2 catalyses metabolic activation of a variety of aryl- and heterocyclic amines such as 2-aminoanthracene and 2-acetylaminofluorene (Tables 1 and 2). CYP1A2 catalyses the activation of PAH-diols to reactive metabolites at much slower rates than CYP1A1 and 1B1. CYP1A2 oxidizes other xenobiotic chemicals including acetaminophen, antipyrine, caffeine, 7- ethoxyresorufin, lidocaine, phenacetin, theophylline, and *R*-warfarin. More than 16 CYP1A2 polymorphic alleles have been identified (41). Alleles *CYP1A2*2-*16* show amino acid changes (68, 69). *In vitro* studies revealed that the *CYP1A2*11* allele variant decreases 7-ethoxyresorufin *O*-deethylation activity (70) The *CYP1A2*7* allele contains a splicing defect (*G3534A*), which is responsible for a decrease in clozapine (an atypical antipsychotic) concentrations *in vivo* (69). *CYP1A2*1F* (*-163C>A*) is associated with a high inducibility of CYP1A2 in smokers. Some reports (71) described cases where smoking patients did not respond to clozapine treatment and had low drug plasma levels at normal doses. A discontinuation in smoking might lead to elevated clozapine plasma concentrations and severe side effects (72). As schizophrenic patients have a high frequency of smokers and a high frequency of the *-163C>A* polymorphism, *CYP1A2* genotyping could have important clinical implications. Reports described patients with *CYP1A2*1F CC* genotype treated for rheumatoid arthritis, who had a 9.7 times higher risk of overall leflunomide-induced toxicity than did the carriers of the *CYP1A2*1F A* allele (73). It is not fully understood whether *CYP1A2* gene polymorphism relates to cancer susceptibility in humans. Some findings indicate that the association between cigarette smoking and colorectal carcinogenesis can be modified by the *CYP1A2* genotype (74). Significant associations were found between the *CYP1A2*1F* and the risk of colorectal adenomas (75). Aromatic amines, N-nitroso compounds and heterocyclic amines are suspected human pancreatic carcinogens. Study (76) results of association between the interaction of the *CYP1A2, SULT1A1* and *NAT* gene polymorphisms with smoking and dietary mutagen intake in modifying pancreatic cancer risk revealed that *CYP1A2* and *NAT1* genotypes exhibited significant interactions with heavy smoking in women, but not in men. These data indicate a sex-specific susceptibility to tobacco carcinogen and dietary mutagen exposure in pancreatic cancer. They are in agreement with other published data (77). Some reports suggest that the *CYP1A2*1F* polymorphism has an important role in lung carcinogenesis, especially in squamous cell carcinoma among smokers (78). Ninety-five percent of caffeine is metabolised by cytochrome CYP1A2, and caffeine induce the enzyme. A common *A* to *C* polymorphism at position 163 in the *CYP1A2* gene has been associated with decreased enzyme inducibility and enzymatic activity, resulting in the slower metabolism of caffeine (79-81). Some studies reported that among breast cancer susceptibility gene (*BRCA1*) mutation carriers, the consumption of caffeinated coffee was associated with a significant reduction in breast cancer risk (82). Another study indicated that *CYP1A2* genotype did not affect breast cancer risk. However, among women with at least one variant *C* (*AC* or *CC*, at position 163), those who consumed coffee had a 64 % lower breast cancer risk than women who never consumed coffee (83).

Increased risk of myocardial infarction with increasing coffee consumption has been reported among carriers of the variant *C* of the *CYP1A2* gene (84). The authors attributed this to the prolonged presence of caffeine in the circulation among the slow metabolisers due to lower enzyme inducibility.

CYP1B1

CYP1B1 is expressed in the endoplasmatic reticulum of extrahepatic organs, predominantly in

the steroidogenic tissues of the uterus, breast, ovary, testis, prostate and adrenal gland. It is also expressed in many other extrahepatic tissues including the lung, kidney, thymus, spleen, brain, heart, colon and intestine. Higher levels are found in a wide range of human cancers including cancers of the skin, brain, testis (85) and breast (86). CYP1B1 converts oestrogen to 4-hydroxylated metabolites (87) that may initiate breast cancer in humans (88). The enzyme also plays an important role in activating diverse procarcinogens including PAHs, aryl and heterocyclic amines and nitroarenes to reactive metabolites that cause DNA damage (Table 1) (89, 90).

More than 26 polymorphisms of CYP1B1 have been identified in humans; 19 of these variants show amino acid changes (41). The null allele of *CYP1B1* has been associated with hereditary glaucoma (91). The role of allelic variants in enzyme activity and their association with different forms of cancers have not yet been fully understood, and literature reports conflicting results. The complexity of haplotype distribution and relatively small functional effects indicate that *CYP1B1* polymorphism alone does not significantly affect cancer risk associated with either lifelong smoking or lifelong exposure to polyaromatic hydrocarbons or oestradiol. New data suggest that combined polymorphisms in the *CYP1B1* and phase II metabolic enzymes (GST, NAT), which are responsible for metabolic activation/detoxification of oestrogen and environmental carcinogens, could be susceptibility factors associated with cancer risk. CYP1B1 and GST polymorphisms in some studies were found significant in the aetiology of breast cancer, especially in women before the age of 60 (92). Stratified analyses demonstrated significant interactions in younger Caucasian women with the *119SS* variant of the *CYP1B1*2* allele, (*A119S* aminoacid change), and in younger African-American women with the *GSTT1* null allele genotype. This trend was also found in Caucasian women with a history of smoking and at least one 114-valine allele at *GSTP1*. In Caucasian women, combined genotype variants *GSTP1- 105IV/VV(Ile105Val)* and *CYP1B1*2, 119AA* resulted in a nearly twofold increase in risk, and the combination of three genotype variants *GSTP1 105IV/VV, CYP1B1 119AS/SS* and *GSTT1* null resulted in an almost fourfold increase in risk. Data also reveal that polymorphisms in phase *I (CYP1B1)* and phase II (*GSTM1, GSTT1, GSTP1*) enzymes may enhance the occurrence of mutations at critical tumour suppressor genes, such as *p53* (93). Since *CYP1B1* belongs to a multitude of genes regulated by the oestrogen receptor alpha (ERalpha) expression, it is of interest to know whether *CYP1B1* polymorphisms have an impact on the ERalpha status of breast cancer. Some authors observed a significant association between the homozygous variant *CYP1B1-1358GG* (increase CYP1B1 enzymatic activity) and negative ERalpha status. They also observed an association between *CYP1B1 1358GG* and progesterone receptor negative status (p=0.015) (94). The association between the cytochrome *CYP1B1*3* allele and breast cancer was assessed (95) through a meta-analysis of all published case-control studies and a pooled analysis of both published and unpublished case-control studies from the Genetic Susceptibility to Environmental Carcinogens (GSEC) database. No association between *CYP1B1*3* and breast cancer was observed in Asians, an inverse association was observed in populations of mixed/African origin, and the pooled analysis suggested a possible association in Caucasians, with effect modification across age categories. Authors suggested that the observed effect of age on the association in Caucasians indicates a

Table 4 *Important drugs which are substrates of enzyme CYP2C9*

Drug groups	Drugs
Angiotensin II receptor blockers	losartan, irbesartan,valsartan
Antidiabetics	tolbutamide, glipizide
Anticoagulants	warfarin
Anticonvulsants	phenytoin
Antimicrobials	metronidazole, sulphamethoxazole
Nonsteroidal antiinflammatory drugs	celecoxib, diclofenac, ibuprofen, indomethacin, naproxen, tenoxicam
Psychotropic drugs	amitriptyline, fluoxetine

need for further investigation of the role of *CYP1B1*3* in oestrogen metabolism according to age, ethnicity, and menopausal status.

Other studies (96) provided some support for polymorphic variation in *CYP1A2* and *CYP1B1* playing a role in colorectal cancer susceptibility. These authors also pointed out the importance of gene-environment interactions to be included in such studies to obtain reliable information about carcinogen exposure and diet. There are reports (97) on significant differences in the distribution of variant alleles *CYP1B1*2* between patients with head and neck squamos cell carcinoma (HNSCC) and controls. Furthermore, data indicated a several-fold increase in the risk of HNSCC in patients with the variant alleles *CYP1B1*2* and *CYP1B1*3* who either smoked or chewed tobacco or drank alcohol. Another recent study (98) has also underlined the relevance of the *CYP1B1* genotypes combined with exposure to tobacco smoke for HNSCC susceptibility. It investigated individual genetic predisposition to HNSCC associated with enzymes of xenobiotic metabolism and repair enzymes affected by tobacco smoke and included 22 sequence variations in *CYP1A1, CYP1B1, CYP2E1, ERCC2/XPD, GSTM1, GSTP1, GSTT1, NAT2, NQO1*, and *XRCC1*. To assess relevant main and interactive effects of polymorphic genes on the susceptibility to HNSCC they used statistical models such as log regression and a Bayesian version of log regression. In subgroup analysis of nonsmokers, the main effects in *ERCC2 (Lys751Gln) C/C* genotype and combined *ERCC2 (Arg156Arg) C/A* and *A/A* genotypes were predominant. When stratifying for smokers, the data revealed main effects on *CYP1B1*3/*3* genotypes, followed by *CYP1B1*1/*3,* and *CYP2E1*7B.* When fitting log regression models including relevant main effects and interactions in smokers, the authors found relevant association beetween genotypes containing *CYP1B1*3* or *CYP2E1*7B* and HNSCC as well as between *CYP1B1*3/*3* or *GSTM1 null/null* genotype and HNSCC.

Another group (99) have similar approach to determine genetic interactions in HNSCC. They used log regression, which is well suited for *SNPs*, and Bayesian generalisation, which allows for incorporating additional expert knowledge. These methods determined several important interactions such as association between *CYP1B1*, tobacco smoke, and *p53* mutations and interactions between *CYP1B1* and glutathione S-transferases in smokers, which included a three-way interaction between *CYP1B1, CYP2E1*, and *GSTP1*. An association study (100) based on 1,023 patients and 1,121 controls, investigated the influence of environmental factors combinated with six *SNPs* located in *CYP1A2, CYP2E1, CYP1B1*, and *CYP2C9* on the risk of sporadic colorectal cancers (CRC). Whereas separate analyses of the *SNP*s showed no effect on CRC risk, three allelic variant combinations were found to be associated with a significant increase in CRC risk in interaction with an excessive red meat consumption. One of these three predisposing combinations was also shown to interact positively with obesity. Some study results (101) suggest that genetic polymorphisms in *CYP1B1* may modify the risk of prostate cancer. Another report (102) on the association between the *CYP1B1*3* allele and survival in patients with prostate cancer receiving docetaxel has provided evidence that *CYP1B1*3* may be an important marker for estimating docetaxel efficacy, explaining this by *CYP1B1*3* genotype-dependent oestrogen metabolism.

It appears that CYP1B1 along with Phase II enzymes play a key role in the activation of carcinogens at several organ targets, with a complex gene-environment interactions.

CYP2C9

CYP2C9 is predominantly expressed in the liver, representing about 20 % of the hepatic CYP content. It metabolises about 15 % of drugs in current use, some of which are of substantial clinical importance such as angiotensin-2 antagonists, nonsteroidal antiinflammatory drugs (NSAIDs), oral antidiabetics, antiepileptics, oral anticoagulants, psychotropic drugs, and alkylating anticancer prodrugs (Table 4) (103, 104). In addition, CYP2C9 metabolises endogenous substrates arachidonic and linolenic acid (105). CYP2C9 also mediates 3-hydroxylation of B[a]P and metabolic activation of several PAH-diols to active metabolites at much slower rates than those by CYP1 enzymes (106). Genetic polymorphisms of *CYP2C9* include more than 34 alleles (41). Alleles *CYP2C9*2, *3, *4, *5,* and **30* have aminoacid replacement, and have been reported to reduce *in vitro* (107,108) and/or *in vivo* catalityc activities (108, 109, 110).

There is a large interindividual variation in CYP2C9 activity resulting in variations in drug response and adverse effects. In Caucasian population, poor metabolisers make 3 % to 5 %. The most frequent variants are the *CYP2C9*2* and *CYP2C9*3* alleles. Of special interest are drug substrates with a narrow

therapeutic index such as S-warfarin, tolbutamide and phenytoin, where impaired CYP2C9 metabolic activity might cause difficulties in dose adjustment as well as toxicity (111, 112). Patients with the *CYP2C9*2* and *CYP2C9*3* alleles have lower mean daily warfarin doses and a greater risk of bleeding (113). CYP2C9 polymorphisms can also be associated with an increased rate of NSAID-induced adverse events (114). NSAIDs have been shown to effectively prevent colorectal neoplasia. Polymorphisms in NSAID targets or metabolising enzymes may affect NSAID efficacy or toxicity (115). Some authors (116) reported enhanced chemopreventive activity of ibuprofen against colorectal cancer by slower-metabolising *CYP2C9* variants (*2/*3). Others (117) investigated the association of elimination rate and clinical outcome of anticancer agent indisulam with *CYP2C9*/*CYP2C19* gene variants. *CYP2C9*3, CYP2C19*2,* and *CYP2C19*3* polymorphisms resulted in a reduced elimination rate of indisulam. These mutant alleles significantly increase the risk of severe neutropenia, and dose reductions of 50 mg m^{-2} to 100 mg m^{-2} per mutated allele may be required to normalise the risk.

Beside genetic polymorphisms, interindividual variability in CYP2C9 enzyme activity can also be changed by environmental factors; it is induced by prototypical CAR, PXR, and GR ligands through different elements in the promoter region or inhibited by oral contraceptives, as shown in a study on healthy women (118). The observed intraethnic variability reinforces the need for proper selection of control subjects and argues against the use of surrogate control groups for studies on the association between CYP2C9 alleles and adverse drug reactions or spontaneous diseases (119).

CYP2C19

When it comes to drug metabolysm catalysed by CYP2C19, two to five percent of Caucasians and about 20 % of Asians are poor metabolisers (PMs) (120). Currently, there are over 25 different alleles of the *CYP2C19* gene (*2C19*1-*25*), of which *CYP2C19*2-*8* code for inactive versions of the enzyme and *CYP2C19*17* for increased enzyme activity (41). In Asians, alleles *CYP2C19*2* and *3* together account for 100 % of the defective alleles. In the Caucasian population 85 % of PMs are homozygous for *CYP2C19*2*. *CYP2C19*3* to *25* alleles are extremely rare in Caucasians. The *CYP2C19* genotype can seriously affect the success of drug therapy. In PMs, proton pump inhibitor omeprazole has a considerably prolonged half-life. Patients heterozygous for a defective *CYP2C19* allele displayed an improved cure rate for *Helicobacter pylori* infections during concomitant omeprazole and amoxicillin treatment. Patients with two defective alleles had a cure rate of 100 % (121). Other important clinically used drugs that are affected by *CYP2C19* polymorphisms are the tricyclic antidepressants amitriptyline and clomipramine, selective serotonin reuptake inhibitors sertraline and citalopram, the monoamine oxidase inhibitor moclobemide, barbiturates, the anxiolytic diazepam and the antimalarial drug proguanil (Table 5) (122). The CYP2C19 phenotype is measured through oral administration of S-mephenytoin. In individuals with the extensive metabolic phenotype, S-mephenytoin is quickly conjugated and excreted in the urine. In contrast, in PMs, virtually no hydroxylation occurs. A recent study found that patients (n=166) on escitalopram therapy, carrying the *CYP2C19*17* allele (UM phenotype) exhibited 42 % lower plasma concentrations than those homozygous for *CYP2C19*1* and underlined the necessity of dose adjustment (123). The rate of nelfinavir (for HIV treatment) biotransformation to M8 was reduced by 50 % in patients with the *CYP2C19*1/*2* or *2/*2* genotype compared to those with the *1/*1* genotype, with consequences of modified short-term efficacy and toxicity and final virological response (124). Some reports documented that the *CYP2C19*2* loss-of-function polymorphism was associated with an increased treatment-related mortality (TRM) in patients undergoing allogenic transplantation (125). Patients genotyped as PMs had a significantly higher rate of hepato- and nephrotoxicities than intermediate or extensive metabolisers. Multivariate analysis including all potential factors that might influence TRM have confirmed that the *CYP2C19* genotype is an independent factor which considerably influences TRM. These results suggest that genotyping for *CYP2C19* can help to identify patients with a higher risk of TRM.

CYP2D6

CYP2D6 constitutes a surprisingly important enzyme for drug metabolism, despite its low hepatic content (about 2 %). Its polymorphisms are of the greatest importance for drug metabolism of all phase I and II metabolising enzymes. There are more than 80 different allelic variants, and about 25 % of all drugs on the market are metabolised by this enzyme (126).

The most important substrates of CYP2D6 (Table 6) are antidepressants, neuroleptics, antiarrhytmics, analgesics, antiemetics, and anticancer drugs (127, 128). The enzyme also appears to be one of the most important polymorphic drug metabolizing enzymes in causing adverse drug reactions (129). In addition, the enzyme utilises amines and steroids as endogenous substrates (5-methoxyindolethylamine and 5-methoxytryptamine) (130). Besides, it may have a major role in the metabolism of food constituents, alkaloids in particular (131). CYP2D6 is the only non-inducible drug metabolizing CYP, and therefore, genetic variation contributes largely to interindividual variation in enzyme activity. Different functional *CYP2D6* gene variants have been described which can be classified in categories according to whether they abolish, decrease, leave normal, increase, or qualitatively alter catalytic activity. The distribution of the most common variant alleles among ethnic groups and all variant alleles are presented at the home page of the human CYP allele nomenclature committee (41). The most important variants are *CYP2D6*2*, *CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*10, CYP2D6*17*, and *CYP2D6*41*. There are four polymorphism-related phenotypes; poor (PM), intermediate (IM), extensive (EM), or ultrarapid metabolisers (UM). It is plausible that the UM genotype (*CYP2D6*2xN-duplications*), with more than one active gene on one allele, is the outcome of selective diet in certain North and East African populations (132). In the Ethiopian and Algerian population the prevalence of UMs is 29 % (133-135). 20 % of the population in Oceania are also UMs. However, the duplication event in the Oceania population appears to be of another origin since the allele found is *CYP2D6*1Xn*, and has most probably evolved independently from the duplication in the African population. The UM phenotype makes 1 % to 10 % of the European population and the PM phenotype 3 % to 10 % (136-139).

New variants of the *CYP2D6* gene are continuously added to the CYP allele Web page (41). Genotyping for 12 *SNPs* representing 20 different haplotypes would predict the real phenotype with about 90 % to 95 % accuracy (140). Phenotyping with a probe drug like dextromethorphan might provide an even more accurate estimate (141).

CYP2D6 polymorphism significantly affects the pharmacokinetics of about 50 % of drugs in clinical use (Table 6). The consequences at normal drug doses can be either adverse drug reactions (142, 143) or no drug response (144). *CYP2D6* polymorphism can affect the efficacy and cost of drug treatment. Predictive *CYP2D6* genotyping is estimated to be beneficial for treatment of about 30 % to 50 % of CYP2D6 drug substrates (145). The *CYP2D6* genotype has been shown to successfully predict the clearance of antidepressants desipramine, fluvoxamine, mexiletine, mianserin, nortryptiline, and paroxetine as well as the clearance of the neuroleptics perphenazine and zuclopenthixol and the competitive muscarinic receptor antagonist tolterodine (146). A lack of CYP2D6 enzyme results in reduced effectiveness of drug therapy in instances where prodrugs requiring activation by CYP2D6 are used. This is seen for the analgesic effect of tramadol and codeine. Tamoxifen is metabolised into its active metabolite endoxifen by N-demethylation and 4-hydroxylation, reactions that are catalysed by CYP2D6. Lower therapeutic effect has been observed in PMs for CYP2D6, and predictive pheno/genotyping is advised before entering the treatment (147). When a prodrug like codeine is administered to UMs they may suffer of adverse effects due to higher-than-expected concentrations of active metabolite morphine (148, 149). Mutations in *CYP2D6* gene can also alter substrate specificity (150).

CYP2E1

In the CYP2E locus only one gene has been described in humans. CYP2E1 is expressed in the liver with the highest concentration in the centrilobular region. This enzyme is reasonably conserved, most likely due to important endogenous roles. The endogenous regulation of CYP2E1 is similar to that of other gluconeogenetic enzymes; the enzyme expression

Table 5 *Important drugs which are substrates of enzyme CYP2C19*

Drug groups	Drugs
Anticonvulsants	barbiturates, phenytoin, valproates
Proton pump inhibitors	omeprazole, lansoprazole, pantoprazole
Psychotropic drugs	diazepam, imipramine, clomipramine, sertraline, citalopram, moclobemide
Other	proguanil, propranolol, ritonavir, tolbutamide

is repressed during normal diet and increased during starvation and diabetes. Its physiological substrates seem to be gluconeogenetic precursors acetone and acetol and fatty acids. A study in rats (151) showed increased CYP2E1 either at transcriptional or post-transcriptional level in chemically induced diabetes and starvation.

The expression of CYP2E1 is also regulated by different cytokines. Similar to CYP1A2, CYP2C, and CYP3A, the level of CYP2E1 is decreased by IL-1, IL-6, and TNF-α in primary culture of human hepatocytes (152). By contrast, IL-4 induces the expression of the enzyme. CYP2E1 has a very broad substrate specificity. More than 70 different chemicals with diverse structures are metabolised by CYP2E1 (Tables 1 and 2). Most of these substrates are small and hydrophobic. They include alcohols/ketones/aldehydes, aromatic compounds, halogenated alkanes or alkenes, anaesthetics, drugs, and premutagens such nitrosamines (found in cigarette smoke) and azo carcinogens (153-156). Many of the CYP2E1 substrates are also inducers of the enzyme. Commonly used inducers in experimental animals are ethanol, acetone, isoniazid, pyridine, and pyrazole. CYP2E1 activity in liver microsomes and *in vivo* is most often measured using the chlorzoxazone 6-hydroxylation method. Although the frequency of variant alleles is high, their functional significance is not clear, most likely due to a high endogenous importance of this enzyme in gluconeogenesis during severe fasting/starvation. Some investigations suggest that the *CYP2E1*5B* variant increases the susceptibility to colorectal cancer (157). In general, gene-environment interactions between *CYP2E1* polymorphism and smoking or alcohol drinking have been associated with the risk of colorectal neoplasia. Vinyl chloride (VC) is a human carcinogen known to be metabolised by CYP2E1 into reactive intermediates that can cause oncogene and tumour suppressor gene mutations, and which are further metabolised by acetaldehyde dehydrogenase (ALDH2) and glutathione-S-transferases to non-mutagenic end-products. Schindler et al. (158) have found that the presence of the *CYP2E1*5B* allele variant was significantly associated with the either or both mutant biomarkers (ras-*p21* and *p53*), even after controlling for potential confounders, including cumulative VC exposure. The effects of **5B* allele and VC exposure were approximately additive. These results also suggest possible gene-environment interactions between polymorphisms in the VC metabolic pathway and VC exposure that could contribute to variable susceptibility to the mutagenic effects of VC in exposed populations. Other data (159) also suggest that genetic polymorphism in *CYP2E1* may be associated for individual differences in susceptibility to liver fibrosis with regard to chronic vinyl chloride monomer (VCM) exposure. Analysis of metabolising enzymes might be useful in the risk assessment of liver damage in workers occupationally exposed to VCM.

Some published data (160) suggest that the genotypes of *CYP2E1* and of DNA repair genes *XRCC1 194* (X-ray repair cross-complementing group) and *XPD 751* (xeroderma pigmentosum complementary group D) are associated with the level of DNA damage, and that they may contribute to variable sensitivity to DNA damage induced by VCM at the workplace. The *CYP2E*5B* and *NAT2* variants (*NAT2*4/*7*, *NAT2*5/*6*, *NAT2*5/*7, NAT2*6/*6* and *NAT2*6/*7* genotypes) were associated with chronic obstructive pulmonary disease (161). A group of Norwegian scientists (162) in their comprehensive study of 105 *SNPs* in 31 xenobiotic-metabolising enzyme genes found strong associations with the risk of NSCLC. Results indicated that several *SNPs* in phase I genes *CYP1B1*, *CYP2D6*, *CYP2E1*, and *CYP3A4* were associated with the risk of NSCLC. Moreover, significant associations were also found

Table 6 *Important drugs which are substrates of enzyme CYP2D6*

Drug groups	Drugs
Analgesics	codeine, dextromethorphan, fentanyl, hydrocodon, meperidine, methadone, morphine, oxycodone, tramadol
Antiarrhythmics	amiodarone, aimaline, flecainide, lidocaine, mexiletin, propafenone
β-Adrenoceptor antagonists	alprenolol, bisoprolol, bufuralol, carvedilol, labetalol, metoprolol, pindolol, propranolol, timolol
Psychotropic drugs	amphetamine, amitriptyline, fluoxetine, fluvoxamine, haloperidol, imipramine, clomipramine, chlorpromazine, clozapine, maprotiline, paroxetine, risperidone, thioridazin, trazodone, venlafaxin, zuclopenthixol
Other	guanoxane, captopril, tamoxifen, trimetoprim

with multiple *SNP*s in phase II genes *ALDH2, COMT, EPHX1, SOD2, NAT1, NAT2, GSTM3, GSTP1, GSTT2,* and *MPO*.

CYP3A4/5

CYP3A4 is the most abundant P450 enzyme in the human liver (about 30 % of total P450). CYP3A enzymes facilitate the metabolism of a wide range of structurally different xenobiotics and of 50 % of all clinically used drugs (Table 7) (163, 164). In addition, they have a key role in the metabolism of endogenous substrates such as retinoic and bile acids and steroid hormones such as testosterone and oestrogen (127, 165). CYP3A4 is also very important for the metabolism/activation of dietary and environmental chemicals such as PAH-diols, mycotoxins, aflatoxins B1, G1, and sterigmatocystin, pesticides, flavonoids, and a number of food additives (166-168). Catalytic activity of CYP3A4 in PAH activation is lower than of the CYP1 family enzymes. There are four CYP3A human genes, *CYP3A4, CYP3A5, CYP3A7, and CYP3A43,* located at chromosome 7q21-q22.1 (169).

Clinically relevant CYP3A enzymes, CYP3A4, CYP3A5 and CYP3A7, have similar substrate specificities and are mostly expressed in the liver. CYP3A4 and CYP3A7 show an opposite expression pattern during development (170). CYP3A7 is predominantly expressed in the foetal liver and is present up to 6 months of postnatal age, although this enzyme can be found in some adult livers and in other organs (171). CYP3A4 is the major cytochrome P450 isoform present in adult liver. CYP3A5 content is constant at all developmental stages, regardless of polymorphism. In the foetus, CYP3A7 plays an important role in the metabolism of endogenous substrates, such as key steroids and retinoic acid, and also in the metabolism of xenobiotics reaching the foetus from maternal circulation. Interindividual variation in CYP3A7 expression could therefore result in interindividual differences in embryotoxicity and teratogenicity of different substances (172, 173).

CYP3A4 can be inhibited by a number of drugs and chemicals. These include azole antifungal agents such as ketoconazole, macrolide antibiotics such as troleandomycin, HIV protease inhibitors such as saquinavir, antidepressants such as fluoxetine, and furanocoumarin, 6',7'-dihydroxybergamottin found in grapefruit juice (174-176). CYP3A4 enzyme is also highly inducible by many drugs and dietary chemicals. Drug inducers include the macrolide antibiotic rifampicin, anticonvulsants such as carbamazepine, and glucocorticoids. Components of St John's wort (*Hypericum perforatum*), hyperforin in particular, are potent inducers of CYP3A4 (177). All of them are importan for interactions during pharmacotherapy. Statins (antilipemic drugs) are mainly metabolised by CYP3A4, except fluvastatin, which is metabolised by CYP2C9 and pravastatin, which is largely excreted unchanged. Myopathy is a serious adverse effect of statins. Concurrent use of statins and fibrates, seems to particularly increase the risk of muscular toxicity (178).

Coadministration with rifampicin, phenytoin, or carbamazepine may reduce plasma AUCs to less than half for a broad range of CYP3A4 drug substrates (179). A combination of a powerful inhibitor of CYP3A4 and a drug dependent on CYP3A4 for its metabolism may increase plasma levels of the substrate as much as 10 to 20 times and lead to adverse drug reactions and toxic effects. Correspondingly, a combination with an inducer may decrease plasma levels of the substrate to only 5 % to 10 % of its original concentration, leading to therapeutic failure (180). There is large interindividual variability in hepatic CYP3A4 expression (181). CYP3A4 is also highly expressed in the intestine (182). The enzyme has a substrate specificity and inducibility that is similar to the drug transporter P-glikoprotein (P-gp) encoded by the multi-drug resistant/ATP binding cassette (*MDR1/ABCB1*) gene (183, 184). Both genes are on the same position on chromosome 7q21.1 and apparently use similar DR4 regulatory elements binding PXR (185, 186). The broad substrate specificity, the capacity of CYP3A4 to metabolise xenobiotics, and co-regulation with P-gp makes these two components perhaps the most important complex for the elimination of xenobiotics from the body (187-190). Probe substrates for CYP3A4 include midazolam (1' hydroxylation), erythromycin (N-demethylation), cortisol (6β-hydroxylation *in vivo*) and testosterone (6β-hydroxylation *in vitro*). Although there is a considerable interindividual variation in the expression and activity of CYP3A4, genetic polymorphisms alone do not provide a satisfactory explaination (191). More than 20 mutations in the *CYP3A4* gene have been identified, but were of unclear importance (41). Different CYP3A4 variant proteins have been described, with decreased *(*8,*11,*13*17),* none (**20*), or increased activity *(*18A*) allele *in vitro*. However, their low frequency cannot explain common interindividual differences in CYP3A4 activity. This

suggests that the enzyme is rather well preserved as a result of selection pressure in the past to preserve its function in the metabolism of dietary and other environmental factors. Reasons for variations in CYP3A4 expression and inducibility could be in variations in genes encoding proteins participating in the regulation of *CYP3A4* transcription of *PXR, CAR* and *GR* ligands and in the genes controlling posttranslational regulation of the protein (192-194).

Similar to *CYP3A4, CYP3A7* is a well-conserved gene, and up to now one frameshift mutation (*CYP3A7*3*) and one coding polymorphism have been identified *(CYP3A7*2)* (195, 196). *CYP3A7*2* allele has a frequency of 8 %, 28 %, and 62 % in Caucasians, Asians, and Africans, respectively, but the impact of this polymorphism on foetal drug clearance and endogenous substrate metabolism is still unclear. CYP3A7-specific antibodies show that about 10 % of adult livers express significant CYP3A7 protein levels that contribute to 24 % of total CYP3A protein in these livers.

CYP3A5 has a wide tissue distribution, but is expressed at a much lower level than CYP3A4. Only about 20 % of people express CYP3A5 in the liver. Its expression is generally higher among African-Americans than Caucasians (197, 198). The most common reason for non-expression is a splice site mutation. The frequency of variant alleles shows interethnic differences with the wild-type *CYP3A5*1* allele more common in Africans than Caucasians and Asians (199).

Variability in CYP3A5 expression is a result of several *SNPs* (200), which severely diminish the synthesis of functional CYP3A5 like *CYP3A5*3,*6* (41). Substrate specificity of CYP3A5 is similar to that of CYP3A4, but it is less active. *CYP3A4* and *CYP3A5* genes share a common regulatory pathway for constitutive expression (201). Important substrates of *CYP3A5* are immunosuppressive drugs cyclosporine, tacrolimus, sirolimus, and everolimus, which show a large interindividual variability in pharmacokinetic properties and a narrow therapeutic index (202). Eight independent studies have demonstrated faster clearance of drug substrates by variants carrying one or two *CYP3A5*1* alleles. Some published data suggest that *CYP3A4, CYP3A5*, and *CYP3A7* polymorphisms affect cyclosporine metabolism, and therefore their genotyping could be useful to prospectively optimise cyclosporine prescription in transplant recipients (203). Recent reports also indicate that dose levels of tacrolimus need to be adjusted in transplant patients according to *CYP3A5* polymorphism (204). *CYP3A5*1* homozygotes may have higher systolic blood pressure due to hormone status (199). Some studies explored if individual variations in CYP3A may play a role in breast and prostate carcinogenesis through modulation of sex hormone metabolite levels, or through metabolic activation of exogenous carcinogens (205). Certain combined *CYP3A4/ CYP3A5* haplotypes showed differential susceptibility to prostate cancer. Results obtained suggest that the interaction between *CYP3A5*3* polymorphisms and

Table 7 *Important drugs which are substrates of enzyme CYP3A4*

Drug groups	Drugs
Analgesics	acetaminophen, alfentanil, codeine, dextromethorphan
Antiarrhythmics	dysopiramide, lidocaine, quinidine
Antimicrobials	doxycycline, erytromycin, clarithromycin, clindamycin, ketoconazole, miconazole, troleandomycin, HIV-protease inhibitors
Antihistamines	astemizole, loratadine, terfenadine
Anticonvulsant	carbamazepine, etosuximide
Antilipemics	atorvastatin, fluvastatin, lovastatin, simvastatin
Antitumour drugs	busulphan, cyclophosphamide, doxorubicin, paclitaxel, tamoxifen, vinblastine, vincristine
Ca channel blockers	amlodipine, felodipine, nifedipine, nimodipine, verapamil
Steroids	estradiol, cortisol, progesterone, prednisone, testosterone
Immunosuppressants	cyclosporin, sirolimus, tacrolimus
Cardiotonic glycoside	digitoxin
Narcotics	methadone, cannabinoids, cocaine, fentanyl
Psychotropic drugs	amphetamines, fluoxetine, haloperidol, clomipramine, clonazepam, chlorpromazine, midazolam, risperidone, triazolam

androgen metabolism pathway seems to be significant in prostate cancer (206). In a study by Plummer et al. (207) *CYP3A4*1B/CYP3A5*3* haplotype was positively associated with prostate cancer risk and aggressiveness.

In a multiethnic population study, *CYP3A4 -G* variant *(*1B*) was more common among African-Americans than among white men. Race-stratified analyses revealed little association between the *CYP3A4* variant and prostate cancer risk among white men, but were limited by the small number of white men with the *CYP3A4*1B* variant. However, **1B/*1B* genotype was significantly associated with aggressive prostate cancer in African-American men (208). Females carriers of *CYP3A5*1* (high activity enzyme) appear to reach puberty earlier, which may affect breast cancer risk. Postmortem and *in vivo* studies have provided the first scientific evidence that CYP3A5 is involved in fentanyl metabolism, and homozygous *CYP3A5*3* causes impaired metabolism of fentanyl. The authors have suggested that genotyping for *CYP3A4*1B* and *3A5*3* variants may help to confirm fentanyl toxicity (209).

CONCLUSION

In everyday life, human body is exposed to a number of xenobiotics including drugs, dietary compounds, or environmental carcinogens, which are metabolised by a variety of enzymes through phase I and phase II reactions. These enzymes mainly participate in the conversion of xenobiotics to more polar and water-soluble metabolites which are readily excreted from the body. During metabolism of certain xenobiotics, a variety of unstable and reactive intermediates can be formed, which attack DNA, causing cell toxicity and transformation. Individuals differ in the levels of expression and catalytic activities of metabolic enzymes that activate and/or detoxify xenobiotics in various organs, and these phenomena are thought to be critical in understanding the background of interindividual differences in response to xenobiotics. Factors affecting these variations include induction and inhibition of enzymes by diverse chemicals and by genetic polymorphisms. Inherited DNA sequence variations in genes coding for metabolic enzymes may have major effects on the efficacy/toxicity and carcinogenic potency of xenobiotics. New methods in molecular biology and improved genotyping procedures have become available and have been applied extensively in association studies between metabolic enzyme gene variants and cancer risk. For some CYPs (primarily CYP1A1, CYP1A2, CYP1B1, and CYP2E1) consistent evidence has been reported for the association between polymorphisms and cancer susceptibility. The pathways of carcinogen metabolism are complex, mediated by the activities of multiple genes, as single genes may have a limited impact on cancer risk. The knowledge of environmental determinants and large studies with detailed exposure information are crucial to evaluate reliably any moderate genetic effects. Many controversial data are present in literature. Positive associations were found in certain populations and not confirmed in others. In addition to an expected interethnic variability in allele frequencies, variability has also been found within an ethnic group, resulting in heterogeneity in association studies. Gene-environment interactions could be a confounding factor in these studies, with controversial findings on cancer risk. Furthermore, gene-environment interaction assessment requires a large number of samples in order to achieve significance. Detection of small genetic effects also requires a very large and homogenous sample. Small sample size has limitations, particularly after stratification with respect to risk factors. Due to small samples, estimates may be imprecise, erratic, and biased. Therefore certain findings should be taken with caution. Replication studies are warranted for further conclusions, with careful characterisation of the most confounding factors such as diet, including alcohol and coffee consumption, smoking or tobacco chewing, age, sex, hormonal status, lifestyle, and related diseases. Technological advances in molecular biology which enable genotyping of a large number of SNPs (DNA microarray) and reliable information regarding toxic/carcinogenic exposure could contribute to obtain more conclusive findings in further studies.

Genetic variability of *CYP2C9*, *CYP2C19*, and *CYP2D6* is clinically the most important of all CYPs. Predicting therapeutic failure or severe adverse drug reactions by genotyping for important polymorphisms in key drug-metabolising enzymes has a potential to optimize drug choice and/or dose at the beginning of therapy, avoiding most adverse effects, and decreasing medical costs. Among the particularly important treatment regimens affected by genetic polymorphisms of CYPs are therapies with drugs with a narrow therapeutic index such as some antidepressants, anticoagulants, anticonvulsants, antidiabetics, antipsychotics, and anticancer drugs. In

2007, the United States Food and Drug Administration (FDA) announced for the first time that warfarin's (anticoagulant) label would carry new information describing the role of genetics in drug dosing. The label states that a lower initial warfarin dose "should be considered for patients with certain genetic variations" (210). Genotyping of *CYP2C9* and vitamin K-epoxid reductase complex C1 (*VKORC1*), which is warfarins' target, is recommended before dosing. The FDA also approved the microarray-based AmpliChip CYP450 test, which analyzes genotypes for CYP2D6 and CYP2C19, and is another step toward predicting the safety and efficacy of a drug in individual patients (211). The FDA has been proactive in a number of other ways, including the publication of the "Pharmacogenomics Guidance Document" (212).

While pharmacogenomics is a promising approach to reduce ADRs and increase therapeutic efficacy, the clinical relevance of genetic variability for drug action and metabolism remains to be assessed in many cases. It is generally believed that clinicians tend to ignore a large amount of new information pertaining to pharmacogenetic testing. The main steps for successful implementation of pharmacogenetic testing should include education of clinicians and all others involved in the use and benefits of testing, large prospective association studies showing the benefits of pharmacogenomic genotyping, development of specific clinical guidelines, and creation of a regulatory and ethical framework for testing.

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Sažetak

ULOGA GENSKOG POLIMORFIZMA METABOLIČKIH ENZIMA P450(CYP) KAO ČIMBENIKA OSJETLJIVOSTI NA UČINKOVITOST I TOKSIČNOST LIJEKA TE NASTANAK KARCINOMA

Među enzimima I. faze biotransformacije sustav citokroma P450 (CYP) prednjači po katalitičkoj svestranosti i pokazuje vrlo visok stupanj polimorfnosti. Istraživanja polimorfizama gena *CYP* rezultirala su brojnim genetičkim informacijama koje nam pomažu u razumijevanju učinaka ksenobiotika na ljudski organizam. Ova superporodica enzima najvažniji je enzimski sustav uključen u biotransformaciju mnogih endogenih i egzogenih spojeva uključujući lijekove. Za metabolizam lijekova važan je polimorfizam CYP2C9, CYP2C19, CYP2D6 i CYP3A4/5 enzima. Među najvažnije izoforme odgovorne za biotransformaciju različitih kemijskih spojeva a posebno metaboličku aktivaciju prokarcinogena pripadaju CYP1A1, CYP1A2, CYP1B1, CYP2E1. Genska analiza ključnih enzima metabolizma lijekova pomaže u predviđanju terapijskog učinka ili razvoja štetnih nuspojava lijekova. Stoga primjena genotipizacije u kliničkoj praksi pomaže u optimizaciji i individualizaciji terapije i smanjenju medicinskih troškova. Polimorfizam metaboličkih enzima može imati važan učinak na terapiju antidepresivima, antipsihoticima, antikoagulantima, antidijabeticima, antitumorskim lijekovima te lijekovima za liječenje ulkusa i HIV-a. Podaci koje donosi toksikogenomika istražujući individualne predispozicije za karcinogene, teratogene i druge toksičke učinke ksenobiotika, pridonose rasvjetljavanju molekularnih mehanizama kojima kemijski spojevi iz okoliša ili na radnome mjestu utječu na nastanak bolesti u ljudi. Postoje značajni dokazi o povezanosti genskih polimorfizama i osjetljivosti za razvoj karcinoma. Metabolički putovi karcinogenih supstancija su kompleksni, posredovani aktivnošću različitih gena, dok pojedinačni geni najčešće imaju ograničen učinak. Stoga je multigenski pristup, uz uključivanje važnih čimbenika iz okoliša u studijama s velikim brojem ispitanika bitan za pouzdanu procjenu rizika od razvoja karcinoma.

KLJUČNE RIJEČI: *citokromi P450, farmakogenomika, genotipizacija, individualizacija terapije, karcinogeneza, nuspojaveFirtin telabem diurnihiliam obsed se, C. Sp. Tum tatilnem nosultimis et auconcem audam sunum or la noximuloctus tudam ment.*

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