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REVIEW

Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation

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Abstract We investigated the elimination routes for the 200 drugs that are sold most often by prescription count in the United States. The majority (78%) of the hepatically cleared drugs were found to be subject to oxidative metabolism via cytochromes P450 of the families 1, 2 and 3, with major contributions from CYP3A4/5 (37% of drugs) followed by CYP2C9 (17%), CYP2D6 (15%), CYP2C19 (10%), CYP1A2 (9%), CYP2C8 (6%), and CYP2B6 (4%). Clinically well-established polymorphic CYPs (i.e., CYP2C9, CYP2C19, and CYP2D6) were involved in the metabolism of approximately half of those drugs, including (in particular) NSAIDs metabolized mainly by CYP2C9, proton-pump inhibitors metabolized by CYP2C19, and beta blockers and several antipsychotics and antidepressants metabolized by CYP2D6. In this review, we provide an up-to-date summary of the functional polymorphisms and aspects of the functional genomics of the major human drug-metabolizing cytochrome P450s, as well as their clinical significance.

Keywords Drug metabolism · Functional genomics · Genotype · Mutation · Pharmacogenetics · Phenotype · Single-nucleotide polymorphism

Abbreviations

ADME	Absorption, distribution, metabolism, excretion
CAR	Constitutive androstane receptor
CYP	Cytochrome P450
MALDI-TOF	Matrix-assisted laser desorption ionisation-time of flight
NNRTI	Non-nucleosidic reverse transcriptase inhibitor
NSAID	Nonsteroidal antiinflammatory drug
PD	Pharmacodynamics
PK	Pharmacokinetics
PPI	Proton pump inhibitor
PXR	Pregnane X receptor
XREM	Xenobiotic-responsive enhancer module

Introduction

The human genome comprises 57 cytochrome P450 (CYP) genes and about the same number of pseudogenes, which are grouped according to their sequence similarity into 18 families and 44 subfamilies (http://drnelson.utmem.edu/human.P450.table.html). Isozymes of families CYP1, CYP2 and CYP3 are collectively responsible for most phase I biotransformations of drugs and other xenobiotics in human liver [1, 2]. In contrast to CYPs of families CYP4 to CYP51, which are involved in endogenous metabolic pathways of steroids, fatty acids, prostaglandins, etc., the CYP1, 2 and 3 isozymes have broad and overlapping substrate specificities

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which usually provide for a robust elimination of lipophilic xenobiotics. Nevertheless, extremely variable expressions and functions of these isozymes, typically exceeding 100-fold in a large population sample, lead to unforeseen drug responses, including over-reaction, toxicity, or lack of response in a considerable fraction of treated patients [3–5].

The major sources of interindividual and intraindividual variability in CYP activity are environmental influences, including inhibition or induction by concomitant medications (drug–drug interactions), biological factors including sex and physiological determinants, such as hormonal status, disease, and circadian rhythms, and genetic polymorphisms in cytochrome P450 genes and their regulators. There are large differences between the individual CYP isoforms regarding their susceptibility to these mechanisms. CYP1 family enzymes are commonly inducible by polycyclic aromatic hydrocarbons through the Ah-receptor/ARNT pathway, and those of families 2 and 3 are generally inducible, but to various extents, by a diverse class of structurally unrelated xenobiotics which are usually ligands of the orphan nuclear receptors pregnane X receptor (PXR) and constitutively active receptor (CAR) [6]. Sex differences in CYP expression are a controversial but intensely debated topic, and some CYPs, in particular CYP3A4, show significant differences in humans [7]. Circadian rhythms can have a strong influence on the cytochrome P450 systems of laboratory animals, but their relevance to humans is not well known [8]. The impact of disease has been particularly well investigated in the context of inflammation, which generally leads to transcriptional repression that affects some isoforms more than others [9].

Genetic polymorphisms, although present in practically all human genes, only affect some CYP isoforms to a functionally relevant extent. Genetic variability particularly affects *CYP2D6*, which is barely influenced by inducing agents and other factors. On the other side of the spectrum are *CYP1A2* and *CYP3A4*, with polymorphisms that do not generally penetrate to the phenotype level. CYP isoforms that are both inducible and significantly polymorphic include CYPs of the CYP2C and 2B subfamily. However, of the many hundreds of SNPs and other sequence variations reported to date, most are not functionally relevant, i.e., they do not cause marked changes in expression, substrate selectivity or enzymatic activity (CYP allele nomenclature homepage at http://www.cypalleles.ki.se). The focus of this article is on providing an update on the functionally relevant polymorphisms of the human drug-metabolizing P450 forms and their role in the metabolism of the most often prescribed drugs.

Biotransformation of the 200 most widely used drugs

The routes of elimination for the 200 drugs most often prescribed ("top 200") in the United States according to the RxList data listed in April 2008 (http://www.rxlist.com) were investigated. Among the top 200 drugs, the vast majority were found to be subject to hepatic elimination by either metabolism or excretion into bile, the latter contributing to a minor proportion of hepatic processes. Approximately 25% of the drugs are excreted unchanged into the urine via the kidneys, and no detailed information about the exact elimination pathway was available in the literature for 5% of them. Metabolism via CYP-mediated reactions represented the absolute majority of hepatic biotransformation processes (Table 1). Members of the CYP3A family contributed to the metabolism of 37% of the drugs, followed by CYP2C9 (17%), CYP2D6 (15%), CYP2C19 (10%), CYP1A2 (9%), and CYP2C8 (6%). CYP2B6 and other CYP isoforms (CYP2A6 and CYP2E1) participated in the metabolism of 4% and 2% of the drugs, respectively. An overview of these findings is given in Fig. 1. Table 2 summarizes the general features of these CYP enzymes. The clinically well-established polymorphisms of CYP2C9, CYP2C19, and CYP2D6 are involved in approximately half of these top 200 drugs, since many of the drugs used in high-prevalence diseases and conditions in the Western world are known to be metabolized by these CYPs. In particular, these include NSAIDs metabolized mainly by CYP2C9, proton-pump inhibitors metabolized by CYP2C19, and beta blockers and several antipsychotics and antidepressants metabolized by CYP2D6.

Functional genomics of human drug metabolizing cytochromes P450

We limited this part to the P450s that are reported as the major forms involved in the metabolism of at least one of the top 200 drugs. These are CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. We furthermore aimed to focus our attention on the more common polymorphisms, i.e., those that occur with frequencies of >5% in at least one population. Nevertheless, rare alleles with functional impacts and other important drug substrates are mentioned when appropriate. We generally favored newer literature. For older studies, the reader is referred to specialized reviews or to the references given in the newer papers. Although genetic polymorphisms exist for CYP2A6, this isozyme was not included, because no major clinical drug substrate has been identified. However, it is known to play a major role in the C-oxidation of nicotine, and its expression and function are influenced by numerous genetic polymorphisms. Readers interested in CYP2A6 are referred to a recent review article [2, 110]. Similarly, CYP2E1 is significantly expressed in human liver and plays a major role in hepatotoxicity by metabolically activating a large number of toxicants and carcinogens [111], but due to the absence of clinically used drug substrates and the lack of predictive polymorphisms it was also omitted from this review.

Table 1 Drugs from the top 200 list (http://www.rxlist.com) that are eliminated by cytochrome P450s

Drug	P450	Reference
Analgesics		
Acetaminophen	Phase II (+3A4/5, 2E1)	[10]
Buprenorphine	3A4/5	[11]
Celecoxib	2C9, 3A4/5	[12]
Codeine	2D6	[13]
Diclofenac	2C9	[14]
Etodolac	2C9	[15]
Fentanyl	3A4/5	[16]
Hydrocodone	2D6, 3A4/5	[17]
Hydromorphone	2C9, 3A4/5	[18]
Ibuprofen	2C9, 2C8	[19]
Indomethacin	2C9	[20]
Meloxicam	2C9, 3A4/5	[21]
Meperidine	2B6, 3A4/5, 2C19	[22]
Methadone	2B6, 2C19, (3A4/5?)	[23, 24]
Naproxen	2C9, 1A2, 2C8	[25]
Oxycodone	2D6, 3A4/5	[26]
Piroxicam	2C9	[27]
Propoxyphene	3A4/5	[28]
Tramadol	2D6, 2B6, 3A4/5	[29]
Antidepressants and antipsychotics		
Amitriptyline	2D6, 2C19, (2C9, 3A4/5)	[30, 31]
Aripiprazole	2D6	[32]
Bupropion	2B6	[33, 34]
Citalopram	2C19, 3A4/5	[35]
Duloxetine	1A2	[36]
Escitalopram	2C19, (2D6, 3A4/5)	[37]
Fluoxetine	2C9, 2D6, 2C19, 3A4/5	[35]
Haloperidol	3A4/5 (2D6)	[38]
Mirtazapine	2D6, 1A2, 3A4/5	[39, 40]
Olanzapine	1A2, 2D6	[41]
Paroxetine	2D6	[35]
Quetiapine	3A4/5	[42]
Risperidone	2D6 (3A4/5)	[43]
Sertraline	3A4/5	[35]
Trazodone	3A4/5	[44]
Venlafaxine	2D6, 3A4/5	[45]
Ziprasidone	3A4/5	[46]
Antidiabetics and cholesterol-lowering drugs		
Atorvastatin	3A4/5	[47]
Fenofibrate	3A4/5	[48]
Glipizide	2C9	[49]
Lovastatin	3A4/5	[47]
Pioglitazone	2C8, 3A4/5	[50]
Rosiglitazone	2C8, (2C9)	[51]
Rosuvastatin	2C9*	[47]
Simvastatin	3A4/5, 2C8	[47]
Antimicrobials		
Clarithromycin	3A4/5	[52]
Clindamycin	3A4/5	[53]
Erythromycin	3A4/5	[54]
Sulfamethoxazole	2C9	[55]
Cardiovascular drugs		
Amiodarone	2C8, 3A4/5	[56]
Carvedilol	2D6**	[57]
Clopidogrel	3A4/5, 2B6 (1A2, 2C19)	[58, 59]
Irbesartan	2C9	[60]
Losartan	2C9, 3A4/5	[61]
Metoprolol	2D6	[62]
Propranolol	1A2, 2D6	[63]
Terazosin	3A4/5	[64]
Triamterene	1A2	[65]
Valsartan	2C9	[66]
Verapamil	3A4/5, 1A2, 2C8, 2C9	[67, 68]
Warfarin	2C9/1A2, 3A4/5***	[69]
Female sex steroids		
Ethinyl estradiol	2C9, 3A4/5, (1A2, 2C19)	[70]
Medroxyprogesterone	3A4/5	[71]
Progesterone	2C9, 2C19, 3A4/5	[72]
Gastroenterology and urology		
Esomeprazole	2C19, 3A4/5	[73]
Lansoprazole	2C19, 3A4/5	[74]
Metoclopramide	2D6, 1A2	[75]
Omeprazole	2C19, 3A4/5	[73]
Pantoprazole	2C19, 3A4/5	[76]
Rabeprazole	2C19	[77]
Sildenafil	3A4/5, 2C9	[78]
Tadalafil	3A4/5	[79]
Tamsulosin	3A4/5, 2D6	[80]
Neurological drugs		
Benztropine	2C, 2D6	[81]
Carbamazepine	3A4/5, 2C8	[82]
Donepezil	2D6, 3A4/5	[83]
Phenytoin	2C9, 2C19	[84]
Sodium valproate and valproic acid	2C9, 2A6, 2B6	[85]
Respiratory diseases and allergy		
Chlorpheniramine	2D6, 3A4/5	[86]
Diphenhydramine	2D6 (1A2, 2C9, 2C19)	[87]
Fluticasone	3A4/5	[88]
Hydroxyzine	3A4/5**	[89]
Loratadine	2D6, 3A4/5	[90]
Montelukast	2C9, 3A4/5	[91]
Salmeterol	3A4/5	[92]
Sedatives, hypnotics and muscle relaxants		
Alprazolam	3A4/5	[93]
Carisoprodol	2C19	[94]
Cyclobenzaprine	3A4/5, 1A2, 2D6	[95]
Diazepam	3A4/5, 2C19	[96]
Eszopiclone	3A4/5, 2E1	[97]
Tizanidine	1A2	[98]
Zolpidem	3A4/5 (1A2)	[99]

Table 1 (continued)

Drug	P450	Reference
Others		
Amphetamine	2D6	[100]
Atomoxetine	2D6	[101]
Buspirone	3A4/5	[102]
Caffeine	1A2	[103]
Dexamethasone	3A4/5	[104]
Isotretinoin	2C8, 2C9, 3A4/5	[105]
Modafinil	3A4/5	[106]
Promethazine	2D6	[107]
Sibutramine	3A4/5	[108]
Tretinoin	2C8, 2C9, 3A4/5	[109]

* Eliminated largely unchanged into urine and feces
** P450 route is not the main metabolic pathway
*** *S*-Enantiomer via 2C9, *R*-enantiomer via 1A2 and 3A4/5
Drugs in combination preparations are listed separately
CYPs are presented in order of importance, and minor CYPs participating in the metabolism are listed in parentheses

CYP1A2

The *CYP1* family genes are located on chromosome 15 and they encode the three P450 functional enzymes CYP1A1, CYP1A2, and CYP1B1. Their expression is coordinately regulated at the transcriptional level involving the aryl hydrocarbon receptor (AhR) pathway. Only CYP1A2 is expressed predominantly in liver, where it contributes on average ~10% of the total microsomal P450 pool. The substrate specificities of the CYP1 enzymes include many polycyclic aromatic hydrocarbons, with CYP1A2 showing a preference for N-hydroxylation of aromatic amines and heterocyclic compounds. Endogenous substrates are also known, e.g., prostaglandins, estrogens and retinoic acid. Only CYP1A2 metabolizes a significant number of the top 200 and other important drugs, including caffeine and theophylline, antipsychotics (olanzapine, clozapine), antidepressants (duloxetine), and others (Tables 1 and 2).

Genetic polymorphisms have been found in all human *CYP1* genes, and earlier work mainly concentrated on their associations with various forms of cancer, because many of their substrates occur in industrial combustion products, cigarette smoke and charred food, and are carcinogenic or are at least converted into carcinogens. There is a long history of investigations into genetic influences on CYP1A2 variability [112]. By studying a large sample of mono- and dizygotic twins selected to exclude the influence of smoking, oral contraceptives and gender, a strong overall heritability of 0.72 was found for the CYP1A2-related caffeine metabolic ratio, supporting the expectation of a strong genetic contribution [113]. Indeed, numerous SNPs in coding and noncoding regions exist in the *CYP1A2* gene in various haplotypes, but only two common SNPs are currently considered to be of potential predictive value. These are a 5′-upstream variant -3860G>A (*CYP1A2*1C*) and an intron 1 polymorphism -163C>A (*CYP1A2*1F*) located downstream of the untranslated first exon. The *CYP1A2*1C* allele has been associated with decreased caffeine 3-demethylation in Japanese smokers [114], and the *CYP1A2*1F* allele was correlated to increased activity in German [115] and Swedish [116] smokers, indicating an opposite influence of these SNPs on CYP1A2 inducibility. Consistent with these findings, the combined genotype *CYP1A2*1C/*1F* was shown to be uninduced by omeprazole [117]. Contradictory findings were, however, reported for caffeine metabolism in nonsmoking breast cancer patients [118], and studies with other substrates have not been able to reproduce these findings for clozapine [119], haloperidol [120], and trazodone [121]. As promoter variations are unlikely to contribute substrate-dependent effects, it may be more likely that ethnically diverse haplotype patterns contribute to these discrepancies.

For some rare variants, a proven impact on activity has also been shown. For example, one lack of function mutation is the R431W substitution (*CYP1A2*6*), which is located in the "meander" peptide region critical to the maintenance of protein tertiary structure [122]. However, they are of limited practical use for genetic testing due to their rare occurrence. Newly discovered SNPs of *CYP1A2* have not, so far, changed the overall picture. In Chinese subjects phenotyped with caffeine, a common haplotype containing the novel SNP -3113G>A had significantly lower metabolic activity, but it remained unclear as to whether this SNP, which is located in a proposed regulatory element, or other SNPs found on the same haplotype are responsible for the observed functional

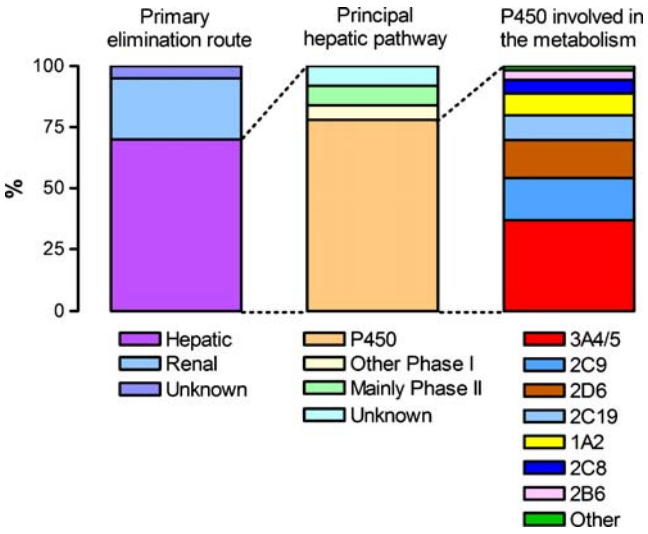

Fig. 1 The routes of elimination for the top 200 drugs by prescription in the United States according to the RxList data listed in April 2008 (http://www.rxlist.com). Adapted from [247]

Table 2 Properties of important human hepatic drug-metabolizing cytochromes P450

P450 and general structural characteristics of substrates	Substrates (in vivo probe drugs are shown in bold type)	Inhibitors	Inducers
CYP1A2	Acetaminophen	Cimetidine	Broccoli
Planar polyaromatic amides and amines	**Caffeine**	Ciprofloxacin	Cigarette smoke
	Clozapine	Enoxacin	Omeprazole
	Estradiol	Fluvoxamine	PAHs
	Olanzapine	Mexiletine	TCDD
	Phenacetin	Oral contraceptives	
	Propranolol		
	Theophylline		
	Tizanidine		
CYP2B6	Artemisinine	Clopidogrel	Artemisinine
Neutral or weakly basic nonplanar molecules with 1–2 hydrogen bond acceptors	**Bupropion**	ThioTEPA	Cyclophosphamide
	Cyclophosphamide	Ticlopidine	Efavirenz
	Efavirenz		Metamizole
	Ketamine		Phenobarbital
	Meperidine		Rifampicin
	Propofol		Statins
	Selegiline		Vitamin D
	***S*-Mephenytoin**		
CYP2C8	Amiodarone	Gemfibrozil	Rifampicin
Relatively large and weakly acidic molecules	Amodiaquine	Montelukast	
	Oral antidiabetics	Trimethoprim	
	Paclitaxel		
	Retinoic acid		
CYP2C9	**Warfarin**	Amiodarone	Norethindrone
Weakly acidic molecules with a hydrogen bond acceptor	**Diclofenac**	Fluconazole	Prednisone
	NSAIDs	Sulphaphenazole	Rifampicin
	Losartan		
	Tolbutamide		
CYP2C19	(*S*)-Mephenytoin	Clopidogrel	Carbamazepine
Weakly basic molecules or amides with two hydrogen bond acceptors	**(Es)omeprazole**	Fluvoxamine	Rifampicin
	Pantoprazole	Ticlopidine	
	Rabeprazole		
	Diazepam		
CYP2D6	Bufuralol	Fluoxetine	None
Basic molecules with a protonatable nitrogen atom 4–7 Å from the metabolism site	**Dextromethorphan**	Quinidine	
	Haloperidol	Paroxetine	
	Metoprolol	Celecoxib	
	Propafenone		
	Risperidone		
	Imipramine		
CYP3A4	Atorvastatin	Ethinylestradiol	Carbamazepine
Large molecules, preferentially lipophilic, with very diverse structures	**Erythromycin**	Azole antimycotics	Efavirenz
	Modazolam	Claritromycin	Glucocorticoids
	Quinidine		Hyperforin
	Testosterone		Nevirapine
	Verapamil		Phenobarbital
	Nifedipine		Rifampicin
			Statins
CYP3A5 (same as CYP3A4)	Same as CYP3A4	Probablythe same as CYP3A4	Rifampicin

difference [123]. In a recent study, the human *CYP1A1-CYP1A2* locus was resequenced in five major phenotyped ethnicities, revealing a total of 85 SNPs, 57 of which occurred more than once [124]. Attempts to relate the most common of these SNPs to phenotype in genotyped volunteers were disappointing, and it was concluded that an SNP or haplotype in the *CYP1A2* gene that has a clear predictive value is yet to be identified. In conclusion, it is still possible that undiscovered common SNPs (probably in introns or in the 5′- or 3′-parts of the gene) and/or unrecognized haplotypes exist which strongly affect the CYP1A2 phenotype. The strong genetic component may, however, also be explained by genetic variations in other genes that contribute to the regulation of CYP1A2 expression, in particular the Ah receptor pathway. Although AhR polymorphisms have been reported [125], systematic investigations are lacking.

CYP2B6

The *CYP2B6* gene together with the expressed pseudogene *CYP2B7* is located within a 350-kb *CYP2ABFGST* gene cluster on chromosome 19 that contains genes and pseudogenes of the *CYP2A, 2B, 2F, 2G, 2S* and *2T* subfamilies [126]. Studies in human liver microsomes suggest that the average CYP2B6 content in human liver is about 3–6% of the total microsomal P450 pool, and the between-individual variability in protein levels is approximately 100-fold [127]. Like the rodent phenobarbital-inducible *CYP2B* genes, human CYP2B6 is strongly inducible by numerous drugs and chemicals, including rifampin, barbiturates, cyclophosphamide, artemisinin, carbamazepine, efavirenz and nevirapine, and metamizole [128]. Clinically important drug substrates include the antidepressant and smoking cessation agent bupropion, the synthetic opioid methadone, as well as the cytostatic cyclophosphamide, the HIV drugs efavirenz and nevirapine, the antimalarial artemisinin, and the anesthetics propofol and ketamine [129].

Recent work from our group and from others has shown that *CYP2B6* belongs to the most polymorphic *CYP* genes in humans, with over 100 documented DNA variations, including numerous nonsynonymous mutations as well as silent, promoter and intronic changes, with many of them showing extensive linkage disequilibrium, giving rise to distinct haplotypes [130]. The most common variant allele, *CYP2B6*6*, occurs with frequencies of between 15 and 60% across different populations and changes two amino acids (Q172H, K262R, Table 3) which are associated with an up to 75% decrease in hepatic protein expression [131, 132]. The mechanism of deficient expression of this variant has been shown to be caused by the c.516G>T [Q172H] polymorphism [127]. Although this amino acid change in exon 4 may also affect substrate specificity or turnover, it primarily prevents the correct splicing of the CYP2B6 pre-mRNA, thus leading to a shorter mature mRNA that lacks exons 4–6 and codes for a deficient enzyme. Whereas this SNP rarely occurs by itself (allele **9*), the K262R variant also occurs as an own allele **4* (Table 3). Another functionally deficient allele that should be included if black subjects are investigated is *CYP2B6*18*, a nonsynonymous allele that did not form a functional protein in transfected mammalian cells and may thus be a *null* allele [133]. It is absent in Caucasian populations, but consistently found among black subjects [134].

HIV-infected patients homozygous for *CYP2B6*6* have strongly elevated plasma levels of efavirenz, and in some studies presented with increased risk for neurotoxicity (summarized in [135]). Determinations of less frequent loss of function alleles, including **11* and **18* and the newly identified **27, *28,* and **29*, improved the prediction of high efavirenz plasma levels [136, 137]). In a recent study with Japanese HIV patients, it was shown for the first time that prospective, genotype-based dose adjustment successfully reduced the therapeutic dose of efavirenz and succeeded in improving CNS-related side effects [138]. The CYP2B6 genotype also affects plasma levels of nevirapine, another NNRTI drug [139]. However, some other substrates of CYP2B6 behave differently. A single-dose pharmacokinetic study in 121 healthy male volunteers revealed that the total bupropion clearance via alleles **1, *2, *5* and **6* did not differ, although C_{max}, AUC and metabolic ratio for hydroxybupropion were considerably lower in **6/*6* and **1/*6* compared to **1/*1* [140]. A 1.66-fold higher clearance was, however, found for allele **4*, consistent with the higher activity of the K262R variant. Interestingly, the **4* allele was also found to have a dominant enhancing effect on the nicotine metabolism rate, while **5* and **6* alleles had no influence [141]. Whether the *CYP2B6* genotype affects bupropione smoking cessation outcome is a complex question, because hydroxybupropione is an active metabolite. An influence of the **5* allele was recently reported [142].

Cyclophosphamide, one of the most widely used anticancer and immunosuppressant drugs, requires biotransformation as a prodrug by P450 enzymes, mainly CYP2B6 and CYP2C19, to yield the active 4-hydroxy metabolite, which is further decomposed chemically to the ultimate cytotoxic metabolite phosphoramide mustard. Limited studies reported that cyclophosphamide bioactivation may be enhanced by the c.516G>T allele in white subjects [143], whereas a certain promoter haplotype appears to affect Japanese subjects [144].

The metabolism of the synthetic μ-opioid receptor agonist methadone, which is used as a maintenance treatment for opioid addiction, depends on CYP2B6 [23, 24]. (*S*)-Methadone metabolism and to a lesser extent (*R*)-methadone metabolism are influenced by *CYP2B6* genotype, and (*S*)-methadone plasma levels were about twice as high in **6/*6* carriers compared to the unmutated genotype. The authors

Table 3 Clinically important genetic polymorphisms of human cytochromes P450

CYP allele designation[a]	Key mutation(s)[b], rs number	Location, protein effect	Allele frequencies[c]	Functional effect
*CYP1A2*1C*	-3860G>A rs2069514	Promoter	0.40 AA, Af 0.081 Ca 0.20 Hs 0.24 Pc	↓ inducibility (smokers)
*CYP1A2*1F*	-163C>A rs762551	Intron 1	0.6–0.8 for all ethnicities	↑ inducibility (smokers, omeprazole)
*CYP2B6*4*	18053A>G rs2279343	K262R (isolated)	0.00 AA, Af 0.04 Ca 0.07 As	↑ expression & activity
*CYP2B6*6*	15631G>T rs3745274 18053A>G rs2279343	Q172H K262R	0.33–0.5 AA, Af 0.17 As 0.25 Ca 0.37 Hs	↓ expression & activity
*CYP2B6*18*	21011 T>C rs28399499	I328T	0.04–0.07 AA, Af 0.00 As, Ca, Hs	↓ expression & activity
*CYP2C8*2*	11054A>T rs11572103	I269F	0.10–0.21 AA, Af 0.00 As, Ca	↓activity
*CYP2C8*3*	2130G>A rs11572080 30411A>G rs10509681	R139K K399R	0.13 Ca 0.00 AA, Af, As	↓activity (paclitaxel) ↑activity (antidiabetics)
*CYP2C9*2*	3608C>T rs1799853	R144C	0.07 AA, Hs 0.00 Af 0.13–0.17 Ca 0.02 Pc	↓activity
*CYP2C9*3*	42614A>C rs1057910	I359L	0.00–0.01 Af, AA 0.04 As 0.06 Ca	↓↓ activity
*CYP2C19*2*	19154G>A rs4244285	Splicing defect	0.10–0.16 AA, Af 0.22–0.32 As 0.15 Ca	Null allele
*CYP2C19*3*	17948G>A rs4986893	W212X	0.00–0.01 Af, Ca 0.03–0.07 As, Pc	Null allele
*CYP2C19*17*	-806C>T rs12248560	Promoter	0.15–0.25 AA, Af, Ca 0.04 As	↑ expression & activity
*CYP2D6*3*	2549delA rs35742686	Frameshift	0.00–0.01 for all ethnicities	Null allele
*CYP2D6*4*	1846G>A rs3892097	Splicing defect	0.15–0.25 Ca <0.01 for most of the others	Null allele
*CYP2D6*5*	Recombination	Deletion	0.03–0.06 for all ethnicities	Null allele
*CYP2D6*6*	1707delT rs5030655	Frameshift	0.00–0.01 for all ethnicities	Null allele
*CYP2D6*10*	100C>T rs1065852	P34S	0.02 Ca 0.40–0.50 As	↓ expression & activity
*CYP2D6*17*	1023C>T rs28371706 2850C>T rs16947	T107I R296C	0.34 Af 0.00 As, Ca	↓ expression & activity
*CYP2D6*41*	2988G>A rs28371725	Splicing defect	0.085 Ca <0.01 for all others	↓ expression & activity
*CYP2D6*Nxn*	Recombination	Copy number variations	0.01–0.09 Ca up to 0.30 Af, Ar	↑ expression & activity
*CYP3A4*1B*	-392A>G rs2740574	Promoter	0.68–0.82 AA, Af 0.00 As 0.03–0.05 Ca, Hs	Probably effect on transcription
*CYP3A5*3*	6986A>G rs776746	Splicing defect	0.37 AA 0.12–0.15 Af 0.66–0.75 As, Hs 0.94 Ca	↓ expression & activity

[a] According to the CYP allele nomenclature homepage (http://www.cypalleles.ki.se)

[b] Genomic positions are given

[c] Frequencies of the indicated variant alleles were obtained for different ethnicities (*AA*, African American; *Af* African; *As* Asian; *Ar*, Arab; *Ca*, Caucasian; *Hs*, Hispanic; *Pc*, Pacific) from dbSNP at http://www.ncbi.nlm.nih.gov/SNP or from the references indicated in the text.

argued that this is unlikely to have a major impact on μ-opioid receptor activation, which is mainly due to (*R*)-methadone [145]. However, in a recent follow-up study, it was shown that (*S*)-methadone is more potent than the (*R*)-enantiomer at blocking the voltage-gated hERG potassium channel, which plays a crucial role in the repolarization and duration of the cardiac action potential [146]. As discussed in this study, the blockage of hERG by methadone and other structurally diverse drugs can cause a prolonged QT interval, and this was indeed found in carriers of the **6/*6* genotype as compared to all other genotypes, indicating a higher risk of severe cardiac arrhythmias and sudden death for individuals carrying this genotype. Great inter-patient variability also exists in the dose of propofol required for efficient anesthetization. Common haplotypic differences in *CYP2B6* and *GABRE* genes did not, however, account for a large part of the inter-patient variability [147].

In conclusion, *CYP2B6* pharmacogenetics has only recently been considered. *CYP2B6* genotyping predicts elevated plasma concentrations of efavirenz and nevirapine in HIV-infected individuals. This is in agreement with the lower activities of a number of alleles. However, as amino acid variants are common, substrate-dependent effects have to be expected. There is a lack of in vitro data for several important substrates which would provide a useful basis for further pharmacogenetic studies.

CYP2C subfamily

The human *CYP2C* subfamily consists of the four genes *CYP2C18*, *2C19*, *2C9* and *2C8*, which are localized in this order in a gene cluster on chromosome 10q24 [148]. Of these, CYP2C18 is highly expressed in liver as mRNA, but for as-yet unknown reasons the mRNA does not get efficiently translated into protein [149]. Its contribution to drug metabolism is therefore limited. The other three members are expressed in the order CYP2C9>CYP2C8» CYP2C19, together constituting on average between 30 and 40% of the microsomal hepatic P450 pool. They are also expressed at lower levels but as functional enzymes in the human small intestine, where they are independently regulated [150]. All three expressed CYP2C enzymes are inducible by ligands of the PXR/CAR and glucocorticoid (GR) nuclear receptor pathways through different *cis*-acting elements in their upstream regulatory regions [151–153]. Given their strong relatedness with respect to DNA and protein sequence (>82%) and their common mechanisms of transcriptional regulation, it is quite surprising just how unique each enzyme is in terms of substrate specificity and clinical significance. All four *CYP2C* genes are genetically polymorphic, but only the CYP2C19 polymorphism comprises null alleles of sufficiently high frequency to produce a *poor metabolizer* phenotype, whereas the more common CYP2C8 and CYP2C9 polymorphisms result in functional amino acid variants. The CYP2C subfamily enzymes also metabolize arachidonic acid and some steroids, and they are expressed in endothelial cells, where they are implicated in the regulation of vascular tone [154].

CYP2C8

Among the top 200 drugs, CYP2C8 is mainly responsible for the metabolism of the antidiabetics rosiglitazone and pioglitazone, the antiarrhythmic amiodarone, and retinoic acid drugs used in acne and cancer treatment; it also participates in the metabolism of some drugs also metabolized by CYP2C9, e.g., ibuprofen (Table 1). Additional important drug oxidations catalyzed primarily by CYP2C8 are the 6-alpha hydroxylation of the natural anticancer drug paclitaxel and the deethylation of the antimalarial amodiaquine, both of which are useful probe drugs for CYP2C8 phenotyping. CYP2C8 plays a major role in metabolizing antimalarials, as chloroquine and dapsone are also substrates [155]. The clinical significance of CYP2C8 became clear after cerivastatin had to be removed from the market following fatal drug interactions which were in part due to its potent inhibition by gemfibrozil acyl-glucuronide, ultimately leading to rhabdomyolysis [156, 157]. Other potent inhibitors at clinically relevant concentrations include antiretroviral drugs, such as efavirenz, saquinavir, lopinavir, and tipranavir.

Apart from rare variants with no (**5, *7*), reduced (**8*) or unknown activity, there are three more common alleles *CYP2C8*2, *3, and *4,* which code for functional amino acid variants of the protein (Table 3). The frequency of the **2* allele is highest in black subjects, with reported frequencies of 15–20%, but much lower and absent, respectively, in Caucasians and Asians [158–161]. The variant had twofold increased intrinsic clearance for paclitaxel due to increased K_m, but no significant in vivo associations were reported. The *3 allele occurs more frequently in white subjects (13–23%) and is virtually absent in Africans and Asians [158–162], whereas the **4* allele, which is not well investigated from a functional point of view, also occurs in Caucasians (~8%) and is practically absent in the other major races. The CYP2C8.3 variant was initially shown to reduce the metabolism of arachidonic acid and paclitaxel hydroxylation in vitro by ~40% and ~80%, respectively [158]. Recent clinical studies involving patients treated with paclitaxel [163] as well as amodiaquine [161] did not, however, find any evidence for altered pharmacokinetics, toxicity, or efficacy of these drugs in carriers of any of these alleles. It should be noted that the *CYP2C8*3* variant is in partial linkage disequilibrium with the *CYP2C9*2* allele, which should be of particular importance for substrates metabolized by both enzymes such as ibuprofen. Indeed, *CYP2C8*3* genotypes were associated, together with *CYP2C9*2* and **3*

alleles, with reduced clearance of ibuprofen [164]. Functional effects of *CYP2C8*3* appear to be substrate-dependent, because a higher metabolic capacity was observed for repaglinide [165] and rosiglitazone [166]. In conclusion, the CYP2C8 polymorphisms show high interethnic variation, with three nonsynonymous alleles **2, *3,* and **4* having frequencies of between 7.5 and 20%. Their functional effects appear to be substrate-dependent.

CYP2C9

This P450, which is very abundantly expressed hepatically, accepts many weakly acidic substances like the anticoagulant warfarin, the anticonvulsants phenytoin and valproic acid, cardiovascular drugs like rosuvastatin and losartan, and several nonsteroidal anti-inflammatory drugs (NSAIDs, Table 1). Many of these drugs have a narrow therapeutic index, and variations in CYP2C9 activity are thus among the recognized factors for adverse drug reactions.

The **2* and **3* alleles were discovered first and have been investigated more thoroughly than the more recently identified alleles. These two alleles are present in approximately 35% of Caucasian individuals, but are much less prevalent in black and Asian populations [167]. In vitro data have consistently demonstrated that the *CYP2C9*2* and **3* alleles are associated with significant but highly variable reductions in intrinsic clearance, depending on the particular substrate [168]. The **3* allele is more strongly affected than **2*, and the reduction in activity can be up to 90% for some substrates. Other alleles with decreased function but rare occurrence are **5*, **6*, **8*, **11* and several promoter variants with as-yet unclear significances [169]. Numerous clinical studies have demonstrated the clinical significance of the *CYP2C9*2* and **3* polymorphisms for most of the drug substrates mentioned above. For example, carriers of **2* and **3* alleles were reported to experience higher incidences of adverse drug reactions like hypoglycemia from hypoglycemic drugs [170], gastrointestinal bleeding from NSAIDs [171], and serious bleeding from warfarin treatment, where anticoagulant response also depends on variants of vitamin K epoxide reductase [172].

CYP2C19

This CYP2C isozyme, the least expressed, was the first to be discovered due to its marked genetic polymorphism, resulting in (*S*)-mephenytoin-poor (PM) and extensive metabolizer (EM) phenotypes. Although not initially of any particular clinical interest, the CYP2C19 isozyme was later found to show a marked preference for proton-pump inhibitors (PPI) like omeprazole and pantoprazole, and numerous additional important drugs have been identified as major CYP2C19 substrates in recent years (Table 1). The PM phenotype results from two null alleles, leading to the absence of functional CYP2C19 protein, whereas extensive metabolizers carry at least one functional allele. About 3–5% of white and black populations but up to 20% of Asians are carriers of two null alleles. The two most common null alleles are *CYP2C19*2*, which occurs almost exclusively in Caucasians, and *CYP2C19*3*, which occurs primarily in Asians [173]. A promoter variant has recently been identified which appears to be related to increased substrate turnover by an as-yet unexplained mechanism [174]. CYP2C19 plays a prominent role in the metabolism of several first- and second-generation antidepressants [175, 176]. Pharmacokinetic effects of the CYP2C19 genotype have been observed, for example for clomipramine [177], citalopram [178], and amitriptyline [179]. These were sometimes related to adverse side effects, but an influence on pharmacodynamic outcome has not been apparent in the studies performed so far.

The effect of the *CYP2C19* polymorphism on *H. pylori* eradication therapy is a particularly intriguing example of the clinical application of pharmacogenetics. The common eradication strategy involves the application of two antibiotics, e.g., amoxicillin and clarithromycin, together with the proton-pump inhibitor. The rationale for this combination is that acid suppression not only contributes to accelerated ulcer healing and improvement in symptoms, but it also increases the effectiveness of the antibiotics. The PPI-induced increase in the intragastric pH value depends on the plasma concentrations achieved over time, which are strongly influenced by CYP2C19 polymorphism. In several studies in Asia and Europe, it was shown that, in this case, PM subjects benefit from their lower metabolism rate because their drug levels stay higher for longer periods [180–182]. Other studies also confirmed the beneficial influence of CYP2C19-deficient alleles in the treatment of gastroesophageal reflux disease (GERD) with PPIs [183]. Esomeprazole-induced healing of GERD, however, appears to be unrelated to the *CYP2C19* genotype, which can be explained by the metabolic shift toward the CYP3A4-mediated pathway [184]. Therefore, these data suggest that subjects with the **1/*1* genotype should receive higher doses of these PPIs in order to achieve stronger acid suppression compared to **1/*2* and **2/*2* subjects.

In contrast to the increased response to PPIs, CYP2C19 PMs were shown to have a significantly lower antiplatelet effect due to clopidogrel. Several studies found that *CYPC19*2* is a major determinant of clopidogrel plasma levels and inter-individual variability in response [185–188]. The activation of clopidogrel by P450-dependent oxidation has been investigated, but CYP3A and not CYP2C19 have been identified as the major contributor [58]. Moreover, as clopidogrel is a potent inhibitor of both CYP2C19 and CYP2B6 [189], the basis for the influence of CYP2C19

genotype on the clopidogrel treatment effect awaits further investigation.

CYP2D6

This was the first P450 for which a classical pharmacogenetic polymorphism became known, and is the most intensely studied polymorphic P450. CYP2D6 is primarily expressed in the liver, but it is also localized in brain neurons, where it may participate in local drug metabolism and/or in certain endogenous biotransformations. Among all of the P450s discussed here, CYP2D6 is undoubtedly the one with the biggest genetic influence and, as environmental factors are of minor importance, the CYP2D6 drug oxidation phenotype, usually determined from the urinary metabolic ratio of a test drug, represents a stable and reproducible personal parameter. Debrisoquine, dextromethorphan, metoprolol, sparteine, and tramadol have been used for this purpose. For historical and basic facts about CYP2D6 polymorphism and allele frequencies, the reader is referred to recent specific review articles [190, 191].

About 5–10% of Caucasians carry two null alleles and are thus PMs, whereas this phenotype has a frequency of only 0–1% in Africans and Asians. The most frequent null allele is **4*, with an allele frequency of about 20–25% in Caucasians, where it is responsible for 70–90% of all PMs. The absence of a PM phenotype in Oriental populations is due to the virtual absence of the **4* allele. In African and in African-American populations it is present with frequencies that are intermediate between those for Asians and Caucasians. The *CYP2D6* gene deletion allele **5* is present at a similar frequency of 3–5% in most populations. The null alleles **3* and **6* are present at frequencies of slightly above 1% in Caucasians, but all other null alleles appear to be very rare (see the CYP allele nomenclature homepage). Recent studies in our lab have concentrated on the so-called intermediate metabolizer phenotype, which occurs in about 10–15% of white individuals. We found that most Caucasian IMs carry the partially defective allele **41* in combination with either a null allele or the same or another partially defective allele [192]. The mechanism by which the **41* allele reduces function is through a mutation 2988G>A in intron 6 of **41*, which leads to erroneous splicing, resulting in only a fraction of the correctly spliced mRNA [193]. In Africans and Asians, there are other partially defective alleles, termed **17* and **10*, respectively. In black populations the **17* allele is present at frequencies of up to 30%, whereas the **10* variant occurs at levels of up to 50% in Asians.

The CYP2D locus on chromosome 22 also includes two pseudogenes, CYP2D7 and CYP2D8P. Unequal crossover between these genes, involving a certain repetitive sequence also present in the *c-myc* gene, leads to recombination events that result in gross structural variants where the functional gene can be either deleted (**5*) or duplicated, leading to the UM phenotype due to overexpression in liver [194–196]. *CYP2D6* gene duplications are now known to have occured with various alleles, including **1,*2, *4, *6, *10, *17, *29, *35,*41, *43* and **45*. The frequency of the gene duplications varies between 10 and over 50% in some ethnic populations, including certain Arabian, Eastern African and Pacific populations, whereas in Europe it is usually between 1 and 5%. It has been speculated that the remarkable preference of CYP2D6 for plant alkaloids may have been the result of natural selection in some East African populations that depended on food with toxic alkaloids, thereby leading to the accumulation of alleles with increased copy number and higher activity, and probably also because an efficient induction mechanism was not available for this enzyme [195]. An assay based on TaqMan real-time quantification of *CYP2D6* in relation to albumin as an internal reference gene was shown to correctly measure the overall number of *CYP2D6* gene copies in a variety of genetic constellations [197]. It was also demonstrated that the strategy of copy number determination in combination with SNP analysis is sufficient for correct phenotype prediction. The *CYP2D6* variants that we recommend for inclusion in regular genotyping are summarized in Table 3.

Recent studies on the impact of the *CYP2D6* genotype on treatment outcome and/or adverse drug reactions included metoprolol [198], propafenone [199], amitriptyline [179], and other antidepressants [176, 200]. In the case of prodrugs, metabolism leads to the pharmacologically active substance, as is the case for codeine, which is O-demethylated by CYP2D6 to morphine. An increased effectiveness of codeine with sometimes life-threatening opioid intoxication was observed in patients with multiple *CYP2D6* gene copies, consistent with the UM phenotype [201–203].

An important example of cancer therapy where CYP2D6 pharmacogenetics appears to have a major impact is the adjuvant treatment of breast cancer with tamoxifen, an antiestrogen that is extensively metabolized in the liver to several primary and secondary metabolites. Two of these, 4-hydroxytamoxifen and the secondary metabolite endoxifen, are mainly formed by CYP2D6, and they show high affinity to the estrogen receptor and are thought to be mainly responsible for the antiestrogenic effect [204, 205]. Several recent retrospective and prospective studies demonstrated a significant impact of the CYP2D6 genotype on the plasma concentrations of the active tamoxifen metabolites, treatment outcome and adverse effects (reviewed by [206]). According to these studies, patients with PM (**null/*null*) and IM (e.g., **41/**null) genotypes (i.e., those with low metabolic activation rates) have extremely low levels of the active metabolites and thus profit less from the treatment. They have a shorter time to recurrence and worse

relapse-free survival relative to patients with the EM genotype [207, 208]. These recent findings do not yet allow us to design new treatment strategies. However, with appropriately conducted prospective studies, they may open up new paths to more and better treatment alternatives for woman with breast cancer.

CYP3A subfamily

CYP3A enzymes are responsible for the metabolism of approximately 37% of the top 200 and many other important drugs, including drugs from all therapeutic categories, like the immunosuppressants cyclosporin A and tacrolimus, macrolide antibiotics like erythromycin, anticancer drugs like taxol, benzodiazepines, HMG-CoA reductase inhibitors like simvastatin and atorvastatin, anesthetics, and many more [209]. Besides drugs, CYP3A4 also plays an important role in the metabolism of several endogenous substances, including testosterone, progesterone, androstenedione and bile acids [210, 211].

The CYP3A subfamily consists of the four genes 3A4, 3A5, 3A7, and 3A43, which are located on chromosome 7. This subfamily contributes to the metabolism of the most diverse group of substrates of all human P450s, as their active sites are large and flexible enough to bind and metabolize many preferentially lipophilic compounds with comparatively large structures [212]. The expressions of the three isoforms CYP3A5, CYP3A7 and CYP3A43 are generally much lower than that for CYP3A4, and CYP3A7 is more abundantly expressed in fetal liver than in adult liver, whereas CYP3A43 is practically undetectable. Several pathways contribute to the complex regulation of CYP3A enzymes, primarily at the transcriptional level. Following exposure to a number of structurally diverse drugs that bind as ligands to the nuclear receptor PXR (pregnane X receptor), the gene transcription rate is enhanced as PXR/RXR heterodimers interact with PXR responsive elements (PXRE) located in the proximal promoter and in the XREM region located −8 kb upstream [213]. Another recognized pathway for the transcriptional regulation of CYP3A4 expression is via inflammatory signaling pathways [214]. Furthermore, CYP3A4 is the only human drug-metabolizing P450 that shows a significant sex difference, in that women express approximately 1.5- to 2-fold more CYP3A4 than men do [215]. This contributes to a higher in vivo clearance of several typical CYP3A4 drug substrates [7]. The mechanism (s) behind the sex differences in expression are presumably transcriptional in nature and they may be related to the sex differences in plasma growth hormone profiles [216]. One study also indicated gene–sex interactions for some polymorphisms at the CYP3A locus [217].

It has been proposed that genetic factors play a major role in CYP3A4 phenotype determination [218]. However, there is currently little evidence for a significant contribution of *CYP3A4* gene polymorphisms in determining CYP3A4 activity. Besides a number of rare amino acid variants [219], no polymorphisms with a clear genotype–phenotype relationship have so far been described for the *CYP3A4* gene, although a number of large-scale sequencing and phenotype–genotype correlation studies have been carried out [217, 220, 221]. The most extensively studied polymorphism is the -392A>G proximal promoter variant (*CYP3A4*1B*), which has a frequency in white populations of about 4%, but a much higher frequency in black subjects (Table 3). Its functional effect remains controversial [222, 223]. A few common defective alleles of *CYP3A5* and *CYP3A7* restrict their expression to the fraction of the population who carry the respective functional **1* allele [220, 224–226]. The *CYP3A5*1* frequency is rather low in Caucasians, but in Africans it is the more frequent variant, leading to a higher average proportion of CYP3A5 in the total liver CYP3A pool in subjects of black origin (Table 3). The mechanism leading to lower expression from the **3* and **6* alleles involves aberrant splicing [220, 224].

*CYP3A4*1B* was initially discovered through its association with high-grade prostate cancer [227], and with a reduced risk for treatment-related leukemia [228]. Because CYP3A5 is the major form expressed in the prostate, where it may contribute to andogen metabolism, and because the *CYP3A4*1B* allele and the functional *CYP3A5*1* allele are in partial linkage disequilibrium, it has been suggested that the reported association between the *CYP3A4*1B* allele and high-grade prostate cancer could also be explained by increased CYP3A5 expression rather than by altered expression or activity of CYP3A4 [229, 230]. Although the impact of polymorphic CYP3A5 is generally low due to the absence of specific substrates, and because of the large contribution of nongenetic mechanisms to variability, effects of CYP3A5 expression status have recently been found for therapy with the immunosuppressant tacrolimus [231, 232] the antihypertensive verapamil [233], and the HIV protease inhibitor saquinavir [234].

In the absence of clearly predictive polymorphisms in the CYP3A4 gene, recent studies have pointed out that other genes may effectively influence CYP3A4 basal and inducible expression phenotype. The MDR1 2677T (Ser893) allele resulted in higher basal CYP3A4 expression and activity, whereas the 2677G allele showed a higher rifampin induction ratio in primary hepatocytes [235]. Moreover, polymorphisms mostly located in promoter or intron 1 regions of PXR were found to be associated with CYP3A4 basal expression levels and to influence inducibility, depending to some extent on sex [236]. Candidate gene approaches with a broad coverage of genes that potentially influence constitutive and inducible CYP3A4 gene expression in phenotypically well-defined tissues or volunteers

may thus help to advance the functional genomics of CYP3A4.

Conclusions and future perspectives

Eight human cytochrome P450 enzymes from five subfamilies (*1A, 2B, 2C, 2D, 3A*) are responsible for the vast majority of oxidative drug metabolisms of the most important clinical drugs. Among the 200 drugs sold in the greatest quantities in the US, about 80% are cleared primarily by these CYPs. Cytochromes P450 CYP1A2, CYP2C8 and CYP3A4, which lack major functional polymorphisms, are responsible for about half of these (52%), whereas the rest take metabolic routes that are significantly influenced by gene polymorphisms in the *CYP2B6, CYP2C9, CYP2C19* and *CYP2D6* genes. For these polymorphic enzymes, probably most of the functional polymorphisms that are common (>5%) in Caucasians may have been identified, although in other races there may still be important undiscovered alleles. From an analytical point of view, there are numerous reliable genotyping methods, from low to high throughput, including real-time PCR for individual SNPs or determination of gene copy number [197], pyrosequencing [237], MALDI-TOF mass spectrometry [238], as well as dedicated microarrays [239] that are now available. Impressive examples of genotype–phenotype or genotype–clinical outcome relationships have been elucidated for these polymorphic CYPs over the past few years which warrant clinical application. Nevertheless, these studies emphasize the complexities that arise at the level of basic mechanisms (*null* alleles, partially functional alleles, substrate-dependent effects, linkage disequilibrium, etc.), as well as the pharmacological and clinical levels (PD versus PK, adverse reactions, prodrugs, etc.). Drug toxicity and treatment outcome depend on many additional genetic and nongenetic factors, not just on a single genotype. Only in a few instances, with particular drugs and treatment schemes, will the patient have a clearly predictable benefit from simple genotyping. In the majority of clinical situations, multigene or multifactorial approaches will be needed to achieve an overall improvement in drug therapy, which implies minimizing the risk of adverse reactions while increasing the chances of effective treatment. To progress, well-designed studies are required that take an integrated approach in order to consider not only validated gene polymorphisms but also other recognized factors, depending on the particular drug or disease studied, as exemplified by our recent study on fluorouracil toxicity [240]. Regarding the less predictable genes, especially *CYP1A2* and *CYP3A4*, the inclusion of multiple external candidate genes which influence their expression along different pathways may lead to the discovery of novel polymorphisms within those genes, although it is expected that these will be genes/polymorphisms that have only minor impacts, comparable to the situation in multifactorial diseases. Similarly, full-genome scans with high-density SNP microarrays have also not been applied so far in order to identify further genes of interest for functional prediction, neither in cytochrome P450 research in the narrow sense nor in the general sense of phamacogenetics/genomics. Other largely unexplored areas of future research with particular relevance to unexplained variability in drug-metabolizing enzyme function include epigenetics [241] and RNA silencing mechanisms [2, 242], but also protein phosphorylation, which was shown to affect, for example, the activity of rat CYP2B1 [243]. The integrations of such diverse data into comprehensive models of metabolic and gene regulatory networks, not only within ADME genes but especially with respect to their connections to central cellular metabolism, cholesterol homeostasis [244] and other cellular processes, is a further challenge that may be accomplished by systems biology approaches [245, 246].

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