Pharmacology & Therapeutics 138 (2013) 103–141

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: H. Bönisch

Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation

Ulrich M. Zanger *, Matthias Schwab

Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Auerbachstr. 112 D, 70376 Stuttgart, Germany
Department of Clinical Pharmacology, The University of Tuebingen Medical Faculty, Tuebingen, Germany

ARTICLE INFO

Keywords:
Biotransformation
Cytochrome P450 monooxygenase
NADPH:cytochrome P450 reductase
Pharmacogenetics
Polymorphism
Xenobiotic

ABSTRACT

Cytochromes P450 (CYP) are a major source of variability in drug pharmacokinetics and response. Of 57 putatively functional human CYPs only about a dozen enzymes, belonging to the CYP1, 2, and 3 families, are responsible for the biotransformation of most foreign substances including 70–80% of all drugs in clinical use. The highest expressed forms in liver are CYPs 3A4, 2C9, 2C8, 2E1, and 1A2, while 2A6, 2D6, 2B6, 2C19 and 3A5 are less abundant and CYPs 2J2, 1A1, and 1B1 are mainly expressed extrahepatically. Expression of each CYP is influenced by a unique combination of mechanisms and factors including genetic polymorphisms, induction by xenobiotics, regulation by cytokines, hormones and during disease states, as well as sex, age, and others. Multiallelic genetic polymorphisms, which strongly depend on ethnicity, play a major role for the function of CYPs 2D6, 2C19, 2C9, 2B6, 3A5 and 2A6, and lead to distinct pharmacogenetic phenotypes termed as poor, intermediate, extensive, and ultrarapid metabolizers. For these CYPs, the evidence for clinical significance regarding adverse drug reactions (ADRs), drug efficacy and dose requirement is rapidly growing. Polymorphisms in CYPs 1A1, 1A2, 2C8, 2E1, 2J2, and 3A4 are generally less predictive, but new data on CYP3A4 show that predictive variants exist and that additional variants in regulatory genes or in NADPH: cytochrome P450 oxidoreductase (POR) can have an influence. Here we review the recent progress on drug metabolism activity profiles, interindividual variability and regulation of expression, and the functional and clinical impact of genetic variation in drug metabolizing P450s.

© 2013 Elsevier Inc. Open access under CC BY-NC-ND license.

Contents

1. Introduction . . . 104
2. Factors that influence cytochromes P450 expression and function . . . 104
3. Family *CYP1*: *CYP1A1*, *CYP1A2*, *CYP1B1* . . . 104
4. Family *CYP2* . . . 105
5. Family CYP3: CYP3A4, CYP3A5, CYP3A7, CYP3A43 . . . 105
6. NADPH:cytochrome P450 oxidoreductase (*POR*) . . . 109
7. Conclusions and future perspectives . . . 109
Conflict of interest statement . . . 110
Acknowledgments . . . 110
References . . . 111

Abbreviations: ADME, absorption, distribution, metabolism, excretion; ADR, adverse drug reaction; AhR, aromatic hydrocarbon receptor; CNV, copy number variant; CYP, cytochrome P450; DDI, drug-drug interaction; EM, extensive metabolizer; ERα, estrogen receptor alpha; FXR, farnesoid X receptor; GR, glucocorticoid receptor; GWAS, genome-wide association study; IM, intermediate metabolizer; LD, linkage disequilibrium; LXR, liver X receptor; MAF, minor allele frequency; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBREM, phenobarbital-responsive enhancer module; PCR, polymerase chain reaction; PM, poor metabolizer; POR, NADPH:cytochrome P450 oxidoreductase; PPAR, peroxisome proliferator-activated receptor; SERM, selective estrogen receptor modulator; SLCO1B1, organic anion transporting polypeptide 1B1; UM, ultrarapid metabolizer; VDR, vitamin D receptor; XREM, xenobiotics-responsive enhancer module.

* Corresponding author at: Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Auerbachstr. 112 D, 70376 Stuttgart, Germany. Tel.: +49 711 81 01 37 04; fax: +49 711 85 92 95.
E-mail address: uli.zanger@ikp-stuttgart.de (U.M. Zanger).

0163-7258 © 2013 Elsevier Inc. Open access under CC BY-NC-ND license.
http://dx.doi.org/10.1016/j.pharmthera.2012.12.007

1. Introduction

Predicting the fate of a drug in a particular patient and his or her subsequent response is still a vision and far away from application in routine clinical practice. Recognizing the sources and understanding the factors that contribute to the extraordinary pharmacokinetic and pharmacodynamic variability within and between individuals remains a challenge of particular importance for drugs with narrow therapeutic index (Lin, 2007). The cytochromes P450 (CYPs) constitute the major enzyme family capable of catalyzing the oxidative biotransformation of most drugs and other lipophilic xenobiotics and are therefore of particular relevance for clinical pharmacology (Nelson, 2004; Guengerich, 2008; Zanger et al., 2008). In humans 57 putatively functional genes and 58 pseudogenes are encoded by various gene clusters distributed over most autosomal chromosomes, in comparison to 108 functional and 88 pseudogenes in the mouse (Nelson et al., 2004). Most of the human genes, which are grouped according to their sequence similarity into 18 families and 44 subfamilies (http://drnelson.uthsc.edu/human.P450.table.html), have specific endogenous functions including the biosynthesis of steroid hormones, prostaglandins, bile acids, and others (Nebert & Russell, 2002). Only about a dozen enzymes belonging to the 1, 2, and 3 CYP-families are responsible for the metabolism of the majority of drugs and other xenobiotics. Despite the broad and overlapping substrate specificities of these enzymes, many drugs are metabolized at clinically relevant concentrations by one or few enzymes only, which limits the important redundancy of the phase I drug oxidation system. Knowledge of the intrinsic and extrinsic factors that influence expression and function of the responsible enzymes is thus a prerequisite for predicting variable pharmacokinetics and drug response. While monogenic polymorphisms explain a major part of the variability for only few enzymes (in particular CYP2D6), most enzymes are multifactorially controlled including additional polymorphisms in regulatory trans-genes and nongenetic host factors including sex, age, disease, hormonal and diurnal influences and other factors (Fig. 1). In this review we cover the CYPs of families 1 to 3 which have been shown to be of major importance for the biotransformation of drugs. We review the recent progress on drug metabolism activity profiles, interindividual variability and regulation of expression, and the functional and clinical impact of genetic variation in drug metabolizing P450s, whereas epidemiological studies were only mentioned occasionally. Our intention was to provide basic knowledge for each CYP on all these aspects but to focus for the literature survey on the past ten years. In view of the enormous body of literature we could not cite all studies and we are aware that it is difficult to provide an entirely objective overview. In this sense, we would like to apologize to all authors of studies not mentioned in this review.

2. Factors that influence cytochromes P450 expression and function

2.1. Genetic polymorphism

Heritable genetic variation in drug metabolizing enzyme genes has been studied for over 60 years and many intriguing examples of the genetic influence on drug biotransformation have been investigated at great detail and for some of them clinical relevance has been studied (Meyer, 2004). Interestingly, loss-of-function polymorphisms in *CYP* genes surprisingly often affect splicing and expression, rather than transcription or protein structure (Sadee et al., 2011). Gain-of-function variants include copy number variants (CNV) with an increased number of functional gene copies in *CYP2D6* and *CYP2A6* (Johansson & Ingelman-Sundberg, 2008), as well as promoter variants (e.g. in *CYP2B6*, *CYP2C19*) and amino acid variants with increased substrate turnover (e.g. in *CYP2B6*, *CYP2C8*). Surprisingly few polymorphisms affect clearly the substrate selectivity or the inducibility of drug metabolic pathways. Important polymorphisms of drug metabolizing CYPs with functional and clinical correlates are summarized in Table 1.

The CYP-specific drug oxidation phenotype can be determined in vivo using selective model substrates (Walsky & Obach, 2004; Fuhr et

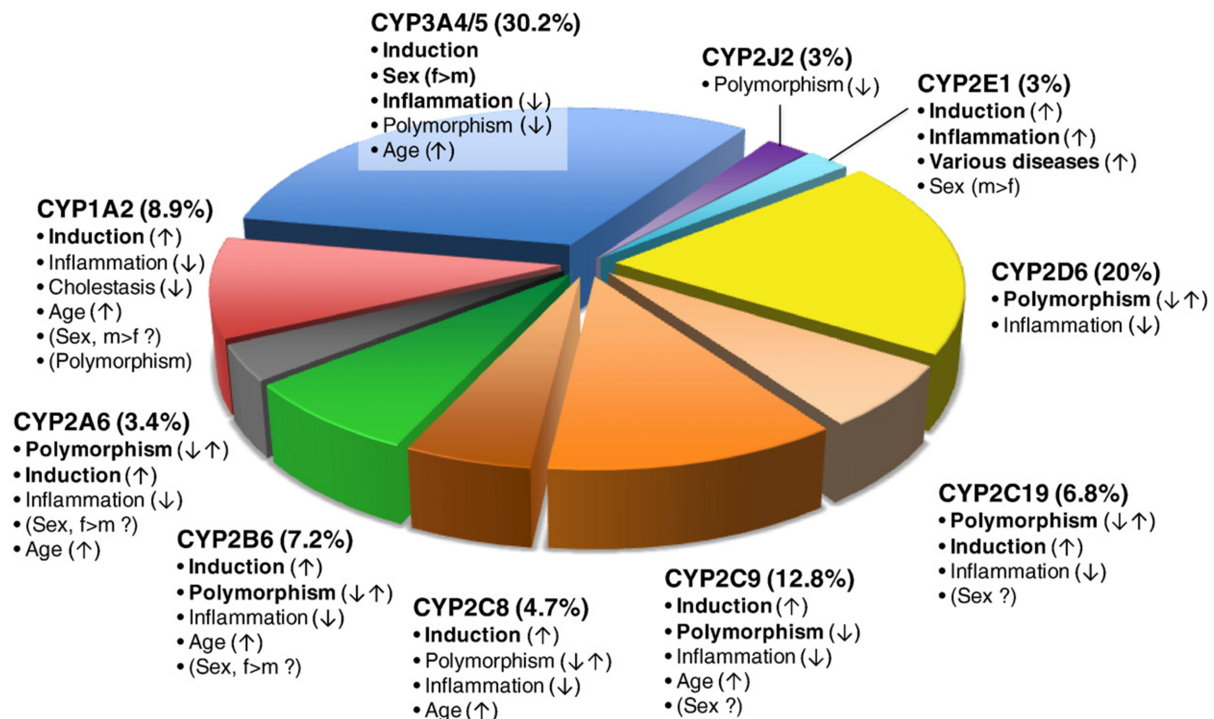

Fig. 1. Fraction of clinically used drugs metabolized by P450 isoforms and factors influencing variability. A total of 248 drug metabolism pathways with known CYP involvement (Table 3; chemicals and endogenous substrates excluded) were analyzed. Each metabolic pathway was only counted once for the major contributing CYP isoform. Important variability factors are indicated by bold type with possible directions of influence indicated (↑, increased activity; ↓, decreased activity; ↑↓, increased and decreased activity). Factors of controversial significance are shown in parentheses.

al., 2007). Different terms are in use for the associated pharmacokinetic phenotypes. In the case of the classical polymorphisms of the *CYP2D6* and *CYP2C19* genes, which were discovered by the phenotypic variation they elicit in drug-treated subjects,"poor metabolizer" (PM) refers to homozygous or compound heterozygous carriers of alleles with complete lack of function (null allele); "extensive metabolizer" (EM) refers to the "normal" phenotype, usually representing the major proportion of the population; "intermediate" metabolizers (IM) carry only one normal or functionally deficient allele, resulting in impaired drug oxidation capacity; and the "ultrarapid" metabolizer (UM) phenotype originates from gain-of-function variants (Fig. 2). Severe loss-of-function alleles and functional gene duplications are rare among CYPs 1A1, 1A2, 2C8, 2E1, 2J2, and 3A4, and terms like "slow metabolizer" and "rapid metabolizer" should here only be used in the context of phenotypic differences.

The clinical impact of polymorphism in a drug metabolising enzyme must be considered within its pharmacological context. Loss-of-function variants will lead to reduced clearance and increased plasma concentrations, while gain-of-function variants will lead to increased clearance and lower drug concentrations. If the drug is pharmacologically active, this results in increased and decreased drug effect, respectively, and potentially in drug-related toxicity due to overdosing. If the drug is metabolically activated (prodrug), the contrary is to be expected, and the pharmacological activity or toxicity of the metabolite(s) must be considered, as for example in the case of CYP2D6-dependent morphine formation from codeine. The influence of genetic polymorphisms on CYP expression and function, as well as their clinical impact will be discussed for each CYP below.

2.2. Epigenetic influences on drug metabolism

Some heritable changes in gene function are not based on DNA sequence variations, and the term epigenetics has been coined to describe such phenomena. Two important mechanisms are DNA methylation and histone protein modification. Whereas DNA methylation is involved in normal cellular control of gene expression, histone modification affects the accessibility and transcriptional activity of the chromatin within the cell. The term epigenetics further comprises gene regulatory mechanisms by microRNAs (miRNAs). Epigenetic patterns are principally reversible and may be tissue-specific and influenced by host factors (sex, age) and environmental factors. The influence of epigenetic processes on pharmacologically relevant genes and drug response is a rather new area of research that has recently been summarized (Ingelman-Sundberg & Gomez, 2010). A global analysis of differential gene expression in the human HepG2 hepatoma cell line following treatment with 5-aza-2′-deoxycytidine to inhibit DNA methylation and trichostatin A to inhibit histone deacetylation demonstrated widespread effects on more than 1500 and 500 genes, respectively, including induction of *CYP3A* genes and other cytochromes P450, as well as several transcription factors (Dannenberg & Edenberg, 2006). Examples studied in more detail include primarily *CYP1* genes. *CYP1A1* promoter methylation in human lung tissue was lowest among heavy tobacco smokers and highest in non-smokers, providing an example of environmental influence on DNA methylation patterns (Anttila et al., 2003). In *CYP1A2* an inverse correlation between mRNA and extent of methylation at two CpG sites near the transcription start site was observed in human liver samples (Ghotbi et al., 2009). Promoter methylation at multiple CpG sites in the *CYP1B1* gene promoter has been detected and associated with tamoxifen response (Widschwendter et al., 2004) and decreased inducibility (Beedanagari et al., 2010).

Recent research has also illuminated the impact of miRNAs on ADME gene expression. A current problem of miRNA information management relates to the large number of miRNAs, estimated at over 1000 different molecules per mammalian species and their poorly defined binding specificities, which allows for a vast number of potential miRNA-target gene interactions (Friedman et al., 2009). Various databases have been developed, using different algorithms to predict potential binding sites (Laganà et al., 2009; Xiao et al., 2009; Rieger et al., 2011). However the integration of these datasets is a difficult task and dedicated software programs, e.g. MIRNA-DISTILLER, allow the compilation of miRNA predictions from different databases to facilitate data management (Rieger et al., 2011). Direct regulation by miRNAs was shown for CYP1B1 and CYP3A4 by miR-27b (Tsuchiya et al., 2006; Pan et al., 2009), and CYP2E1 by miR-378 (Mohri et al., 2010). Nuclear receptors are also targets of miRNAs as shown for the xenosensor pregnane X receptor (PXR, NR1I2), which was shown to be under control of miR-148a, thereby influencing CYP3A4 and CYP2B6 expression levels and the metabolism of xenobiotic drug substrates of these enzymes (Takagi et al., 2008). Hepatocyte nuclear factor 4 alpha (HNF4α) is regulated by miR-24 and miR-34a and overexpression of these miRNAs results in decrease of HNF4α and downregulation of its target genes (Takagi et al., 2010). The vitamin D receptor (VDR), another transcriptional regulator of CYP3A4, is also regulated by the CYP3A4-targeting miR-27b, resulting in an indirect and a direct mechanism for miRNA regulation of CYP3A4 (Pan et al., 2009). The same miRNA miR-27b also regulates the peroxisome proliferator-activated receptor PPARγ (Karbiener et al., 2009; Jennewein et al., 2010) and the liver X receptor (LXR) was shown to be regulated by miR-613 (Ou et al., 2011), further supporting an important role of miRNAs in hepatic gene regulation.

Of special interest for pharmacogenetic aspects are SNPs in miRNAs and miRNA binding sites, as well as miRNA copy number variations, which may affect their expression and function and thus influence target gene expression (Schmeier et al., 2011; Wei et al., 2012). For example, the dihydrofolate-reductase (DHFR) gene harbors a socalled miRSNP in its 3′-UTR, which was found to cause loss of miR-24 binding leading to DHFR overexpression and association with methotrexate (MTX) resistance (Bertino et al., 2007; Mishra et al., 2007). Although the field of epigenetic regulation of drug metabolism and drug response genes is relatively new, these examples demonstrate an important impact of miRNAs on ADME gene regulation and potential relevance for drug response.

2.3. Nongenetic host factors

Sex influences a number of pharmacokinetically important parameters including body weight, fat distribution, liver blood flow, as well as expression of drug metabolizing enzymes and transporters (Beierle et al., 1999; Gandhi et al., 2004). Sex-specific expression of cytochromes P450 is common in laboratory animals including rats and mice and was found shown to be controlled by the different secretion profiles of growth hormone in female versus male animals (Dhir & Shapiro, 2003; Waxman & Holloway, 2009). In humans the differences are more subtle and their relevance for drug treatment is a matter of continuous concern (Gandhi et al., 2004; Schwartz, 2007; Waxman & Holloway, 2009). A recent genome-wide gene expression profiling study in 112 male and 112 female livers identified more than 1300 genes whose mRNA expression was significantly affected by sex, with 75% of them showing higher expression in females (Zhang et al., 2011). Among these were 40 ADME/ADME-related genes including *CYP1A2*, *CYP3A4* and *CYP7A1* showing female bias, and *CYP3A5*, *CYP27B1*, and *UGT2B15* showing male bias. Most clinical studies indicate that women metabolize drugs more quickly than men. This is particularly the case for substrates of the major drug metabolizing cytochrome P450, CYP3A4 (e.g. antipyrine, alfentanil, erythromycin, midazolam, verapamil; Cotreau et al., 2005). Analyses of CYP3A4 in human liver have indeed shown ~2-fold higher levels of protein in female compared to male liver tissue (Schmidt et al., 2001; Wolbold et al., 2003; Lamba et al., 2010; Yang et al., 2010). This pronounced difference is also apparent on the mRNA level, and

Table 1
Selected genetic polymorphisms of human cytochromes P450 and POR.

CYP allele designation[a]	Key mutation(s)[b] rs number	Location, protein effect	Allele frequencies[c]	Functional effect	Clinical correlations
*CYP1A1*2C*	2454A>G (rs1048943)	I462V	gMAF 0.120 0.0–0.04 Af, AA 0.20–0.26 As 0.03–0.07 Ca 0.18–0.43 Hs 0.17 Pc	↑ Activity (17β-estradiol and estrone)	↑ Lung cancer risk in Chinese; ↑ breast cancer risk in Caucasians; ↑ prostate cancer risk
*CYP1A2*1C*	−3860G>A (rs2069514)	Promoter	gMAF 0.188 0.26–0.40 AA, Af 0.21–0.27 As, Pc 0.01–0.08 Ca 0.20–0.30 Hs	↓ Inducibility (smokers)	May influence susceptibility to certain cancers
*CYP1A2*1F*	−163C>A (rs762551)	Intron 1	gMAF 0.35 (A>C) 0.5–0.8 all ethnicities	↑ Inducibility (smokers, omeprazole)	↑ Susceptibility to cancer in Caucasians; ↑ oral clearance olanzapine; possible modifier for risk of coronary heart disease
*CYP1B1*6*	142C>G (rs10012); 355G>T (rs1056827); 4326C>G (rs1056836)	R48G A119S L432V	gMAF 0.32–39 0.5–0.85 AA, Af 0.09–0.13 As 0.23–0.40 Ca	↑ Km, ↓ Vmax (17β-estradiol, recombinant)	↑ Prostate cancer risk for L432V in Asians
*CYP2A6*2*	1799T>A (rs1801272)	L160H	gMAF 0.013 0.00–0.01 AA, Af 0.00–0.025 As 0.04–0.10 Ca	No activity	↓ Nicotine metabolism & influence on cigarette consumption, nicotine dependence, smoking cessation response; ↑ lung cancer risk in Caucasians; ↓ oral clearance of tegafur
*CYP2A6*4A to *4H*	Recombination	CYP2A6 deleted	0.01–0.02 AA 0.05–0.24 As 0.01–0.04 Ca	*Null* allele	
*CYP2A6*7*	6558T>C (rs5031016)	I471T	gMAF 0.04 0.00 AA, Af 0.06–0.13 As 0.00 Ca	↓ Activity	
*CYP2A6*9*	−48T>G (rs28399433)	Promoter, TATA-box	gMAF 0.13 0.04–0.12 AA, Af 0.16–0.27 As 0.04–0.05 Ca	↓ Activity	
*CYP2A6*17*	5065G>A (rs28399454)	V365M	gMAF 0.025 0.04–0.50 AA, Af 0.00 As 0.00–0.02 Ca	↓ Activity	
*CYP2B6*4*	18053A>G (rs2279343)	K262R (isolated)	gMAF 0.26 0.00 AA, Af 0.05–0.12 As 0.04 Ca	↑ Expression & activity	↑ Drug clearance (bupropion, efavirenz, cyclophosphamide)
*CYP2B6*5*	25505C>T (rs3211371)	R487C	gMAF 0.05 0.01–0.04 AA, Af 0.01–0.04 As 0.09–0.12 Ca	↓ Expression & activity	Possibly decreased drug clearance
*CYP2B6*6*	15631G>T (rs3745274); 18053A>G (rs2279343)	Q172H K262R	gMAF 0.27 0.33–0.5 AA, Af 0.10–0.21 As 0.14–0.27 Ca 0.62 Pc	↓ Expression ↓ Activity (efavirenz, nevirapine) ↑ Activity (cyclophosphamide)	↓ Drug clearance & ↑ adverse events including treatment discontinuation (efavirenz, nevirapine, *S*-methadone)
*CYP2B6*18*	21011T>C (rs28399499)	I328T	gMAF 0.02 0.04–0.08 AA 0.05–0.12 Af 0.01 Hs 0.00 As, Ca, Pc	↓↓ Expression & activity	

*CYP2B6*22*	−82T>C (rs34223104)	Promoter, TATA-box	gMAF 0.012 0.00–0.025 AA, Af, As 0.024 Ca, Hs	↑ Expression & activity ↑ Inducibility	Possibly increased drug clearance
*CYP2C8*2*	11054A>T (rs11572103)	I269F	gMAF 0.039 0.10–0.22 AA, Af 0.00 As, Ca	↓ Activity	Controversial clinical effects
*CYP2C8*3*	2130G>A (rs11572080); 30411A>G (rs10509681)	R139K K399R	gMAF 0.065 0.00 AA, Af, As 0.65–0.14 Ca, Hs	↓ Activity (paclitaxel) ↑ Activity (antidiabetics)	
*CYP2C8*4*	11041C>G (rs1058930)	I264M	gMAF 0.026 0.00–0.01 AA, Af, As, Pc 0.03–0.07 Ca, Hs	↓ Activity (paclitaxel)	
*CYP2C9*2*	3608C>T (rs1799853)	R144C	gMAF 0.069 0.00–0.02 AA, Af 0.00–0.02 As, Pc 0.10–0.17 Ca 0.065 Hs	↓ Activity	↓ Drug clearance & ↑ risk of bleeding (anticoagulants warfarin, acenocoumarol, phenprocoumone); ↓ drug clearance & ↑ adverse events (sulfonylurea hypoglycemic drugs, NSAIDS); ↓ drug clearance & ↑ adverse events (sulfonylurea hypoglycemic drugs, NSAIDS)
*CYP2C9*3*	42614A>C (rs1057910)	I359L	gMAF 0.043 0.00–0.01 Af, AA 0.02–0.06 As 0.06 Ca	↓↓ Activity	
*CYP2C19*2*	19154G>A (rs4244285)	Splicing defect	gMAF 0.199 0.10–0.17 AA, Af 0.22–0.32 As, Pc 0.06–0.15 Ca 0.15 Hs	*Null* allele	↓ Clearance & ↑ efficacy of PPIs in *Helicobacter pylori* eradication therapy; ↓ anticoagulation effect of clopidogrel & ↑ cardiovascular events; ↓ clearance & ↑ risk of ADRs for antidepressants (amitriptypine, citalopram, clomipramine, moclobemide), antimalarials (proguanil), antifungals (voriconazole)
*CYP2C19*3*	17948G>A (rs4986893)	W212X	gMAF 0.014 0.00–0.01 Af, Ca, Hs 0.03–0.07 As, Pc	*Null* allele	
*CYP2C19*17*	−806C>T (rs12248560)	Promoter	gMAF 0.15 0.15–0.27 AA, Af 0.00–0.02 As 0.21–0.25 Ca	↑ Expression & activity	↑ Clearance of PPIs & risk of subtherapeutic concentrations; ↑ risk of bleeding with clopidogrel
*CYP2D6*3*	2549delA (rs35742686)	Frameshift	gMAF 0.009 ~0.01 all ethnicities	*Null* allele	↓ Clearance & ↑ risk of ADRs for many antiarrhythmics, antidepressants, antipsychotics; ↓ metabolic activation & analgesic effect of opioids (codeine, dihydrocodeine, oxycodone, tramadol); ↓ metabolic activation & efficacy of tamoxifen
*CYP2D6*4*	1846G>A (rs3892097)	Splicing defect	gMAF 0.106 0.01–0.10 AA, Af, As, Hs 0.15–0.25 Ca	*Null* allele	
*CYP2D6*5*	Recombination	Deletion	0.03–0.06 all ethnicities	*Null* allele	
*CYP2D6*6*	1707delT (rs5030655)	Frameshift	gMAF 0.01 ~0.01 all ethnicities	*Null* allele	
*CYP2D6*10*	100C>T (rs1065852)	P34S	gMAF 0.26 0.08–0.12 AA, Af 0.40–0.70 As 0.02 Ca	↓ Expression & activity	
*CYP2D6*17*	1023C>T (rs28371706); 2850C>T (rs16947)	T107I R296C	gMAF 0.049 (for 1023C>T) 0.14–0.24 Af 0.00 As, Ca	↓ Expression & activity	
*CYP2D6*41*	2988G>A (rs28371725)	Splicing defect	gMAF 0.055 0.01–0.06 Af, As, Pc, Hs 0.09 Ca	↓ Expression & activity	
*CYP2D6*Nxn*	Recombination	Copy number variations	Up to 0.30 Af, Ar 0.01–0.09 Ca	↑ Expression & activity	↑ Toxicity of opioids

(continued on next page)

Table 1 (*continued*)

CYP allele designation[a]	Key mutation(s)[b] rs number	Location, protein effect	Allele frequencies[c]	Functional effect	Clinical correlations
*CYP2J2*7*	−76G>T (rs890293)	SP1-binding to promoter decreased	gMAF 0.073 0.10–0.17 AA, Af 0.02–0.13 As 0.055–0.08 Ca	↓ Expression & activity	No conclusive clinical associations
*CYP3A4*1B*	−392A>G (rs2740574)	Promoter	gMAF 0.20 0.50–0.82 AA, Af 0.00 As 0.03–0.05 Ca, Hs, SA	Probably no effect on transcription	↑ Prostate cancer disease progression
*CYP3A4*22*	15389 C>T (rs35599367)	Intron 6	gMAF 0.021 0.043 AA 0.043 As 0.025–0.08 Ca	↓ Expression & activity	↓ Metabolism of simvastatin & ↑ lipid-lowering response; ↓ daily-dose requirement for tacrolimus
*CYP3A5*3*	6986A>G (rs776746)	Intron 3, splicing defect	gMAF 0.312 0.37 AA 0.12–0.35 Af 0.66–0.75 As, Hs 0.88–0.97 Ca	↓↓ Expression & activity	↓ Metabolism & dose requirements for selected drugs with a preference for metabolism by CYP3A5 over CYP3A4 (e.g., tacrolimus, saquinavir)
*CYP3A5*6*	14690A>G (rs10264272)	Exon 6, K208, splicing defect	gMAF 0.045 0.15–0.25 Af 0.12 AA 0.00 As, Ca, His	↓↓ Expression & activity	
*POR*28*	31696C>T (rs1057868)	A503V	gMAF 0.287 0.08–0.50 AA, Af 0.38–0.42 As 0.29–0.33 Ca 0.32–0.35 Pc	Various substrate- and CYP-dependent effects in vitro	↓ Enzyme activity of major CYP enzymes in patients with rare *POR* deficiency; ↑ CYP3A4 enzyme activity with midazolam

[a] According to the CYPallele nomenclature homepage (http://www.cypalleles.ki.se).
[b] Genomic positions are given with corresponding rs numbers in parentheses.
[c] gMAF, global allele frequency of the minor allele as reported in the 1000Genome phase 1 genotype data (released May 2011). Selected frequencies of individual ethnicities (AA, African American; Af African; As Asian; Ar, Arab; Ca Caucasian; Hs, Hispanic; In, Indian; Pc, Pacific; SA, South American) were compiled from dbSNP (build 137) at http://www.ncbi.nlm.nih.gov/projects/SNP/; from the Allele Frequency Database ALFRED at http://alfred.med.yale.edu/alfred/index.asp; and from the references cited in the text.

translates into apparently substrate-dependent pharmacokinetic differences in the order of 20 to 50%. For other CYPs the issue of sex-biased expression has not been finally clarified and some contradictory data have been published from different studies, as discussed below.

Age is a well established influential factor for drug metabolism capacity, particularly at the extremes of life, where drug metabolism capacity appears to be substantially lower. In neonates, this is due to immaturity of several enzyme systems including cytochromes P450 (Kinirons & O'Mahony, 2004; Koukouritaki et al., 2004; Stevens, 2006; Stevens et al., 2008), which fully develop only during the first year of life. In addition, there are some peculiarities in the expression of specific isoforms, e.g. CYP3A7 is primarily a fetally expressed form of the CYP3A subfamily. In the elderly population, the ability to clear drugs is clearly decreased. This is particularly relevant for drugs with narrow therapeutic window, including antipsychotics and antidepressants, anticoagulants, and betablockers. Clearance of paracetamol and benzodiazepines is also lower in older people. However, this does not seem to be a consequence of lower expression or activity of drug metabolizing enzyme systems. Studies in human liver have found a modest increase in expression and activity for most CYPs during life, particularly CYP2C9, which remained significant after correcting for multiple testing, while the influence of age on CYPs 1A2, 2A6, 2B6, 2C8, and 3A4 partially interacted with sex (Yang et al., 2010). Other reasons for limited drug clearance in the elderly are polypharmacy, i.e. inhibition of enzymes due to the concomitant intake of several potentially interacting drugs, as well as reduced liver blood flow and renal function (Cotreau et al., 2005). Age-associated changes in expression of genes involved in xenobiotic metabolism have also been identified in rats (Mori et al., 2007) and in long-lived mutant mice (Amador-Noguez et al., 2007).

Disease states generally have a negative effect on drug metabolism capacity. In liver cirrhosis changes in the architecture of the liver resulting in reduction of blood flow, loss of functional hepatocytes, and decreased drug metabolizing enzymes contribute to decreased drug metabolism capacity and lower synthesis of serum proteins, leading on the one hand to decreased clearance but on the other to increased unbound drug levels due to decreased plasma protein binding (Elbekai et al., 2004; Edginton & Willmann, 2008).

During infection, inflammation and cancer, circulating proinflammatory cytokines such as interleukin (IL)-1β, TNF-α and IL-6, which act as signaling molecules to elicit marked changes in liver gene expression profiles, lead to severe downregulation of many drug metabolizing enzymes (Slaviero et al., 2003; Aitken et al., 2006). The mechanism of these effects has been shown to be at least in part due to transcriptional suppression (Jover et al., 2002; Aitken et al., 2006; Aitken & Morgan, 2007). Alcoholic and non-alcoholic fatty liver disease (NAFLD) are conditions characterized by the abnormal retention of large amounts of triglycerides which are accumulated in fat vesicles. NAFLD is associated with diabetes, obesity and metabolic syndrome and in severe cases proceeds to steatohepatitis (NASH). While the majority of studies on drug metabolism in NAFLD were carried out in overweight rat or genetically obese db/db mouse models, human studies are rare. Available data show moderately reduced expression for most but not all CYP1-3 enzymes (Naik et al., 2013). Notably, CYP2E1 and fatty-acid metabolizing CYP4A proteins are upregulated and likely contribute to in the generation of free radicals, lipid peroxidation, mitochondrial damage and hepatic fibrosis (Gómez-Lechón et al., 2009; Buechler & Weiss, 2011). Overall the data suggest that drug metabolism is only moderately affected by steatosis, whereas in NASH it may be more strongly affected, comparable to other inflammatory conditions (Lake et al., 2011). The influence of further disease states has been reviewed by others (Villeneuve & Pichette, 2004; Kim & Novak, 2007).

3. Family *CYP1*: *CYP1A1*, *CYP1A2*, *CYP1B1*

3.1. Regulation and variability of gene expression

The *CYP1* family comprises three functional genes in two subfamilies. The highly conserved *CYP1A1* and *CYP1A2* genes consist of seven exons and six introns and are located on chromosome 15q24.1, whereas *CYP1B1* consists of only three exons located on chromosome 2p22.2, which however encode the largest human P450 in terms of mRNA size

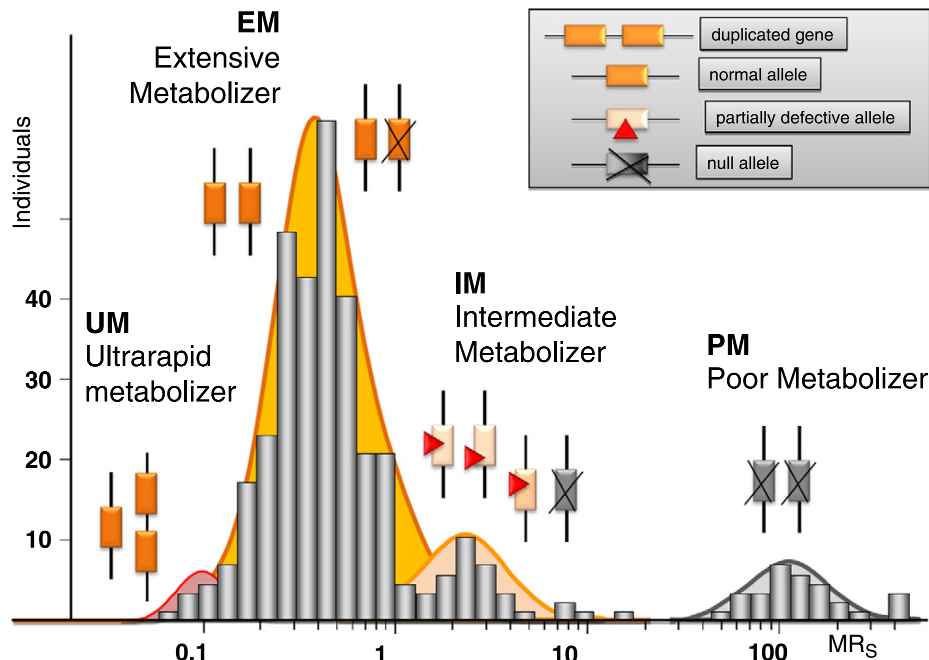

Fig. 2. Sparteine oxidation phenotype and genotype distribution in a German population (n = 308). MR_S: urinary metabolic ratio for sparteine (Raimundo et al., 2004; Zanger, 2008). Reproduced by permission of The Royal Society of Chemistry.

and number of amino acids (Murray et al., 2001; Nelson et al., 2004). In humans CYP1A2 is constitutively expressed at higher levels only in liver (Table 2). Estimations of the average abundance range from ~18 to 25 pmol per mg of microsomal protein determined by mass spectrometry (Kawakami et al., 2011; Ohtsuki et al., 2012) up to 65 pmol/mg determined immunologically (Shimada et al., 1994; Klein et al., 2010), representing ~4–16% of the total hepatic P450 pool (Table 2). In contrast, CYP1A1 and CYP1B1, both of which are primarily extrahepatically expressed enzymes (Ding & Kaminsky, 2003; Du et al., 2006; Paine et al., 2006; Bièche et al., 2007; Dutheil et al., 2008; Michaud et al., 2010), are found in liver at levels below 3 pmol/mg (Stiborová et al., 2005) or at undetectable levels (Chang et al., 2003), respectively.

The *CYP1A1* and *CYP1A2* genes are oriented head-to-head, sharing a 23 kb bi-directional promoter, which contains at least 13 Ah-receptor (AhR) response elements, some which appear to regulate transcription of both genes coordinately (Ueda et al., 2006; Jorge-Nebert et al., 2010). Consequently, both genes are highly inducible by numerous xenobiotics which act as AhR ligands such as methylcholanthrene and other polycyclic aromatic hydrocarbons, dioxins, β-naphthoflavone (Table 3; Nebert et al., 2004), as well as atypical inducers including omeprazole and primaquine which regulate transcription through the same response elements, but without binding to the AhR (Yoshinari et al., 2008). Typical exogenous sources of AhR activators are natural combustion products, dietary constitutents (e.g. in broccoli), and chemical manufacturing by-products (e.g. dioxins). Induction of CYP1A2 by smoking is well established and has been confirmed in recent in vivo studies (Ghotbi et al., 2007; Dobrinas et al., 2011). Numerous endogenous ligands such as eicosanoids have also been proposed to regulate expression of *CYP1* genes (Nebert & Karp, 2008). Interestingly, both CYP1A1 and 1A2 are also inducible by phenobarbital, and transactivation of human *CYP1A* promoter constructs by the human constitutive androstane receptor (CAR) was shown to be mediated through a common ER8 cis-element (Yoshinari et al., 2010). In contrast, PXR-dependent regulation of *CYP1A2* appears to be negligible as shown in vivo with the prototypical PXR ligand rifampin (Backman et al., 2006) and in human hepatocytes, where CYP1A2 was refractory to induction by statins (Feidt et al., 2010). Although CYP1B1 is principally regulated in similar ways, its promoter is distinct from that of the two related *CYP1A* genes, but also contains AhR binding sites as well as AhR-independent response elements, to which heterodimers between ARNT and the hypoxia response factor Hif-1α can bind (Schults et al., 2010).

A number of nongenetic factors influence CYP1A2 in vivo activity and/or hepatic expression levels. Decreased expression was found in liver donors with elevated liver function parameters, increased C-reactive protein (a marker of inflammation), and cholestasis (Klein et al., 2010). CYP1A2 activity in vivo was reported to be higher in men than in women for several substrates including the conversion of caffeine to paraxanthine (Relling et al., 1992; Ou-Yang et al., 2000). However recent studies failed to confirm such a difference in vivo (Ghotbi et al., 2007; Dobrinas et al., 2011) and in human liver tissue at the protein level (Klein et al., 2010) and at the mRNA level (Zhang et al., 2011). A possible explanation for the discrepant results may be that strong confounders of CYP1A2 activity, such as smoking and oral contraceptives (inhibition, see below), have not been consistently considered in all studies. The issue of a sex-bias in CYP1A2 expression and/or function thus remains controversial.

Evidence for epigenetic regulation of CYP1A2 expression was shown by measuring the extent of DNA methylation of a CpG island close to the translation start site, which was inversely correlated to hepatic CYP1A2 mRNA levels (Ghotbi et al., 2007; Dobrinas et al., 2011). Despite the common inducible regulation of CYP1A1 and 1A2, their ontogenic patterns differ substantially in that CYP1A1 is expressed earlier in embryogenesis and both CYP1A1 and CYP1B1 are primarily found in extrahepatic tissues (Table 2). Notably, CYP1B1 is expressed in various cell types of the human and mouse eye, where it plays a still undefined role in the development of primary congenital glaucoma, an inheritable disease leading to blindness (Vasiliou & Gonzalez, 2008). CYP1B1 has furthermore been found at higher levels in tumorous compared to normal tissues and has been proposed as an early stage tumor marker (Murray et al., 1997, 2001). CYP1B1-null mice were resistant to cancerogenic toxicity by 7,12-dimethylbenz[*a*]anthracene because they lacked metabolic activation to the procarcinogenic 3,4-dihydrodiol metabolite in fibroblasts, emphasizing the importance of extrahepatic CYP1B1 for carcinogenesis (Buters et al., 1999).

3.2. Role of CYP1 enzymes in drug metabolism

Catalytic activities of the CYP1 enzymes are overlapping and include hydroxylations and other oxidative transformations of many polycyclic aromatic hydrocarbons and other aromatic substances. Whereas CYP1A1 prefers planar aromatic hydrocarbons, CYP1A2 shows a preference for aromatic amines and heterocyclic compounds (Table 3). The crystal structure of CYP1A2 in complex with α-naphthoflavone revealed a rather compact active site with a cavity volume of 375 Å^3, which is larger than that of CYP2A6 (260 Å^3) but much smaller compared to CYPs 3A4 and 2C8 (~1400 Å^3; Sansen et al., 2007). Prototypical biotransformations catalyzed by CYP1A2 include 7-ethoxyresorufin *O*-deethylation, phenacetin *O*-deethylation, and caffeine *N3*-demethylation to paraxanthine, which are commonly used for in vitro or in vivo phenotype determination (Fuhr et al., 2007; Zhou et al., 2009). Due to its relatively high expression in liver, CYP1A2 plays a significant role in the metabolism of several clinically important drugs (Gunes & Dahl, 2008; Zhou et al., 2009). These include analgesics and antipyretics (acetaminophen, phenacetin, lidocaine), antipsychotics (olanzapine, clozapine), antidepressants (duloxetine; Lobo et al., 2008), anti-inflammatory drugs (nabumetone; Turpeinen et al., 2009), cardiovascular drugs (propranolol, guanabenz, triamterene), the cholinesterase inhibitor tacrine used for the treatment of Alzheimer's disease, the muscle relaxant tizanidine (Granfors et al., 2004), the hypnotic zolpidem used in the short term treatment of insomnia, the drug riluzole used to treat amyotrophic lateral sclerosis, the 5-lipoxygenase inhibitor zileuton, among others (Table 3). Some drugs are bioactivated by CYP1A2, including the antiandrogen flutamide (Kang et al., 2008). Endogenous substrates include arachidonic acid, prostaglandins, oestrogens, melatonin and retinoic acid (Nebert & Dalton, 2006). In addition, benzo[*a*]pyrene and diverse other procarcinogens such as arylarenes, nitroarenes, and arylamines, present in charbroiled food and industrial combustion products are bioactivated by CYP1 enzymes to reactive and carcinogenic intermediates able to cause DNA damage. Drug treatment with CYP1A2 substrates is sensitive to drug-interactions caused by reversible or irreversible inhibition of the enzyme by several small molecule inhibitors that fit the active site, or by AhR-mediated gene induction (Table 3). Some of the most potent inhibitors are α-naphtoflavone ($Ki<50$ nM) and the selective serotonin reuptake inhibitor (SSRI), fluvoxamine (Ki~0.2 μM; Hiemke & Härtter, 2000).

3.3. Genetic polymorphisms and functional impact

Common polymorphisms in the *CYP1* family have been found to be of limited impact on drug metabolism. Due to the role of all CYP1 enzymes in procarcinogen bioactivation many studies investigated their association to various forms of cancer. Rare variants at the *CYP1B1* locus result in primary congenital glaucoma although no consistent correlation has been observed between the severity of the glaucoma phenotype and the molecular CYP1B1 genotype (Vasiliou & Gonzalez, 2008).

Table 2
Hepatic and extrahepatic expression profiles of human cytochromes P450 and POR.

CYP	Liver abundance (pmol/mg)	% of hepatic P450 pool	Adrenal	Brain (cortex)	Heart	Kidney	Lung	Ovary	Placenta	Prostate	Skin/keratinocytes	Small intestine	Testis
CYP1A1	<3[a]	<1	R[b]	RP[c]	R[d]	R[b]	R[e,b]	N.Q.[b]	R[b]	R[b]	R[f]	RP[g]	R[b]
CYP1A2	17.7–65[h,i, k,l]	4.4–16.3	R[b]	N.D.[m]	N.D.[b]	R[b]	N.D.[b]	N.D.[b]	N.D.[b]	R[b]	N.D.[f]	N.D.[b,p]	R[b]
CYP1B1	N.D.[n]	0	R[b]	RP[c,m]	R[b]	R[b]	R[e,b]	R[b]	R[b]	R[b]	R[f]	R[b,p]	R[b]
CYP2A6	14–56[h,o,k,l]	3.5–14	R[b]	N.D.[c,m]	N.D.[b]	R[b]	R[e]	R[b]		R[b]		N.D.[p]	R[b]
CYP2B6	6.9–21[q,r,s,k,l]	1.7–5.3	R[b]	RP[t,m]	R[d]	RPA[u,b]	R[e,b]	R[b]	RA[v]	R[b]	N.D.[f]	N.D.[p]	R[b]
CYP2C8	29.3–30[w,k,l]	~7.5	R[b]	R[c,m]	RPA[x,d]	R[b]	R[e,b]	R[b]	R[b]	R[b]		R[y,b,p]	R[b]
CYP2C9	18–116[q,z,A,k,l]	4.5–29	R[b]	N.Q.[m]	R[x,d]	R[b]	R[b]	R[b]	R[b]	R[b]	R[f]	RPA[y,g,b,p]	R[b]
CYP2C19	3.6–15[z,k,l]	0.9–3.8	R[b]	N.D.[m]		R[b]	R[b]	R[b]	R[b]	R[b]	R[f]	RPA[y,g,b,p]	R[b]
CYP2D6	5–17[h,B,C,k,l]	1.3–4.3	R[b]	RP[D,E,m]		R[b]	R[e,b]	R[b]	R[b]	R[b]	R[f]	RP[g,b,p]	R[b]
CYP2E1	22–66[h,k,l]	5.5–16.5	R[b]	RP[m]	R[d]	R[b]	R[e,b]	R[b]		R[b]	R[f]	R[b,p]	R[b]
CYP2J2	1–2[F]	<1	R[b]	RP[m]	RP[x,b,d]	R[b]	R[e,b]	R[b]	R[b]	R[b]		RP[g,b,p]	R[b]
CYP3A4	58–146[h,G,H,k,l,M]	14.5–37	R[b]	N.D.[m]	N.D.[d]	RPA[u,b]	R[e,b]	N.Q.[b]	N.D.[b]	R[b]	R[f]	RPA[b,g,p]	R[b]
CYP3A5	3.5–4[G,k,l]	~1	R[b]	R[m]	N.D.[d]	RPA[u,b,K]	R[e,b]	R[b]	R[b]	R[b]		RP[G,b,g,p]	R[b]
POR	56–72[L,l]	0.14–0.18	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous	Ubiquitous

R, RNA detected by real-time PCR (N.D., not detectable; very low values reported as N.Q., not quantifiable); P, protein detected by Western blot, immunohistochemistry, or mass spectrometry (average hepatic P450 pool assumed as 0.4 nmol/mg microsomal protein); A, enzyme activity detected using appropriate probe drug. Data compiled from a, Stiborová et al., 2005; b, Bièche et al., 2007; c, Dutheil et al., 2008; d, Michaud et al., 2010; e, Ding & Kaminsky, 2003; f, Du et al., 2006; g, Paine et al., 2006; h, Shimada et al., 1994; i, Klein et al., 2010; k, Kawakami et al., 2011; l, Ohtsuki et al., 2012; m, Dutheil et al., 2009; n, Chang et al., 2003; o, Haberl et al., 2005; p, Thelen & Dressman, 2009; q, Coller et al., 2002; r, Lamba et al., 2003; s, Hofmann et al., 2008; t, Miksys et al., 2003; u, Aleksa et al., 2005; v, Wang et al., 2010a; w, Naraharisetti et al., 2010; x, DeLozier et al., 2007; y, Läpple et al., 2003; z, Koukouritaki et al., 2004; A, Rettie & Jones, 2005; B, Zanger et al., 2001; C, Langenfeld et al., 2009; D, Siegle et al., 2001; E, Miksys et al., 2002; F, Yamazaki et al., 2006; G, Lin et al., 2002; H, Wolbold et al., 2003; K, Bolbrinker et al., 2012; L, Gomes et al., 2009; M, Westlind-Johnsson et al., 2003.

3.3.1. CYP1A1

Of four common variants originally termed m1 to m4, only the nonsynonymous m2 variant (*CYP1A1**2C*, 2454A>G, Ile462Val) has been clearly associated with 6- to 12-fold higher enzymatic activity towards 17β-estradiol and estrone (Kisselev et al., 2005). This variant has a global minor allele frequency (gMAF) of 12% but it is more common among Asians and Hispanics than in other populations (Table 1).

3.3.2. CYP1A2

Brøsen and colleagues investigated the heritability of caffeine metabolic ratio as a CYP1A2 activity marker in a large cohort (n = 378) of mono- and dizygotic twins selected to exclude the influence of smoking, oral contraceptives and sex and they found indication for a strong overall heritability of 0.72 (Rasmussen et al., 2002). The CYPallele website (last accessed: December 2012) lists 21 defined alleles and numerous haplotype variants, some of which are associated with altered expression or inducibility, or code for proteins with altered enzyme activity. The Arg431Trp substitution (*CYP1A2**6*), which is located in the "meander" peptide, a region critical for maintenance of protein tertiary structure, was shown to result in nonfunctional protein (Zhou et al., 2004). However due to their rare occurrence this and other amino acid variants (Palma et al., 2010) are of limited clinical value. The 5′-upstream variant 3860G>A (*CYP1A2**1C*) was linked to decreased inducibility by smoking based on promoter analyses and to decreased caffeine 3-demethylation in Japanese smokers (Nakajima et al., 1999). The intron 1 polymorphism −163C>A (*CYP1A2**1F*) located downstream of the untranslated first exon was associated with increased enzyme inducibility in German (Sachse et al., 1999) and Swedish (Ghotbi et al., 2007) smokers and in Swedish and Serbian heavy coffee consumers (Djordjevic et al., 2010). The opposite effect of the two variants is consistent with the findings that carriers of the combined genotype *CYP1A2**1C/*1F* were not induced by omeprazole (Han et al., 2002). However there are also several controversial studies and thus it is so far unclear whether the SNP rs762551 (Table 1) represents the causal variant or whether linkage to other variants may be responsible for the different reported results across various populations. It should also be noted that the C-allele is considered as the reference allele, even though it is the rarer allele in most populations, and that some authors use the opposite allele designation. Additional *CYP1A2* SNPs but so far no copy number variants were found in recent studies where *CYP1A2* has been resequenced in individuals from different populations (Jiang et al., 2005; Browning et al., 2010).

Despite this multiplicity of *CYP1A2* polymorphisms, attempts to explain the suggested heritability in *CYP1A2* phenotype by relating common SNPs to phenotype remained disappointing and it was suggested that no single SNP or haplotype in the *CYP1A2* gene has a clear predictive value (Jiang et al., 2006). Klein and coworkers investigated the influence of nongenetic factors and of 136 gene polymorphisms in the *CYP1A* locus (15 SNPs) and in 16 other candidate genes from different pathways on hepatic CYP1A2 mRNA and protein expression as well as phenacetin *O*-deethylase activity phenotypes (Klein et al., 2010). Remarkably, 10 SNPs in the ARNT, AhRR, HNF1α, IL1β, SRC-1, and vitamin D receptor (VDR) genes, but none of the *CYP1A*-locus showed consistent associations by univariate analysis. Multivariate linear modeling indicated that genetic polymorphisms explained about 35% of hepatic CYP1A2 activity variation, whereas slightly more than 40% of the variation was explained by nongenetic and genetic factors together. This study indicated that additional genetic factors outside the *CYP1A* locus may have a greater influence on CYP1A2 phenotype than polymorphisms within the *CYP1A* locus.

3.3.3. CYP1B1

CYP1B1 was identified by genetic linkage analysis and mutation studies as causative gene of primary congenital glaucoma, an inheritable neurodegenerative disease leading to blindness (Vasiliou & Gonzalez, 2008). Over 80 mutations, mostly missense or nonsense mutations, deletions, insertions and/or duplications, were identified in patients with various forms of glaucoma. Some of them are

Table 3
Chemical interaction profiles of human hepatic drug metabolizing cytochromes P450.

CYP isoform, substrate structural characteristics	Substrates/pathways[a]	Inhibitors[b]	Inducers[c]
CYP1A2	Acetanilide 4-hydroxylation (2E1)	α-naphthoflavone	Aminoglutethimide
Planar, aromatic, polyaromatic and heterocyclic amides and amines	**Caffeine *N3*-demethylation**	Cimetidine	Antipyrine
	Chlorpromazine *N*-demethylation and 5-sulfoxidation (CYP3A4)	Ciprofloxacin	Bilirubin
	Clozapine *N*-demethylation (3A4/5)	Disulfiram	Carbamazepine
	Estradiol 2-hydroxylation (3A4/5, 1A1)	Enoxacin	Coffee
	7-ethoxyresorufin *O*-deethylation (in vitro)	Fluvoxamine	Cruciferous vegetables (e.g. broccoli)
	Flutamide 2-hydroxylation (3A4/5, 2C19)	**Furafylline**	Nelfinavir
	Genistein 3′hydroxylation (2E1)	Mexiletine	Omeprazole
	Guanabenz *N*-hydroxylation	Moricizine	Phenobarbital and other barbiturates
	Lidocaine *N*-deethylation and 3′-hydroxylation (3A4, 2B6)	Oral contraceptives	Phenytoin
	Melatonin 6-hydroxylation (1A1, 2C19)	Tolfenamic acid	Polycyclic aromatic hydrocarbons (PAHs, charbroiled meat, cigarette smoke)
	Mianserin *N*-demethylation + *N*-oxidation (3A4/5)		Polychlorinated biphenyls
	Nabumetone, 6-methoxy-2-naphthylacetic acid formation		Primaquine
	Naproxen *O*-demethylation (2C9, 2C8)		Rifampicine
	NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) hydroxylation (most other CYPs)		Ritonavir
	Olanzapine *N*-demethylation + 2-/7-hydroxylation (2D6)		Sulfinpyrazone
	Perphenazine *N*-dealkylation (3A4/5, 2C9/19, 2D6)		2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)
	Phenacetin *O*-deethylation (1A1, 2A13)		
	Propafenone *N*-dealkylation (3A4/5)		
	Propranolol *N*-desisopropylation		
	Riluzole *N*-hydroxylation		
	Tacrine 1-hydroxylation		
	Theophylline 8-hydroxylation and *N3*-demethylation		
	Triamterene 4′-hydroxylation		
CYP2A6	Bilirubin oxidation to biliverdin	Decursinol angelate	Artemisinin
Nonplanar low MW molecules usually with 2 hydrogen bond acceptors; includes ketones and nitrosamines	**Cotinine 3′-hydroxylation**	(R)-(+) menthofuran	Carbamazepine
	Coumarin 7-hydroxylation	**8-methoxypsoralen**	Dexamethasone
	1,7-dimethylaxanthine 8-hydroxylation	Pilocarpine	Estrogens
	Efavirenz 7-hydroxylation (2B6)	Selegiline	Phenobarbital
	Letrozole, carbinol formation (3A4/5)	**Tranylcypromine**	Rifampicin
	Nicotine 5′-oxidation and *N*-demethylation (2B6)		
	Pilocarpine 3-hydroxylation		
	Tegafur, 5-fluorouracil formation (1A2, 2C8)		
CYP2B6	Artemether *O*-demethylation (3A4/5)	Bergamottin	Artemisinine-type antimalarials
Neutral or weakly basic, mostly lipophilic non-planar molecules with 1 to 2 hydrogen bond acceptors; includes anaesthetics, insecticides and herbicides	Artemisinin reductive cleavage (3A4/5)	Clopidogrel	Baicalin
	Benzphetamine *N*-demethylation	Clotrimazole	Carbamazepine
	7-Benzyloxyresorufin *O*-debenzylation (3A4/5)	Imidazoles	Cyclophosphamide
	Bupropion 4-hydroxylation	Mifepristone (RU486)	N,N-diethyl-m-toluamide (DEET)
	Chlorpyrifos desulfuration (3A4/5, 1A2, 2C9/19)	**2-phenyl-2-(1-piperdinyl)propane**	Efavirenz
	Cyclophosphamide 4-hydroxylation (2C19, 3A4/5, 2C9, 2A6)	Raloxifene	17-α-ethinylestradiol
	N,N-diethyl-m-toluamide (DEET) ring methyl hydroxylation	Sertraline	Hyperforin
	Efavirenz 8-hydroxylation (1A2, 3A4/5)	**thioTEPA**	Metamizole
	Endosulfan S-oxidation (3A4)	Ticlopidine	Nelfinavir
	7-ethoxy-4-trifluoromethylcoumarin (7-EFC) O-deethylation	Voriconazole	Nevirapine
	Hexane 2-hydroxylation (2E1)		Phenobarbital
	Ifosfamide 4-hydroxylation (3A4/5)		Phenytoin
	Ketamine *N*-demethylation (3A4/5, 2C9)		Rifampicin
	S-mephenytoin *N*-demethylation (2C9)		Ritonavir
	S-mephobarbital *N*-demethylation		Statins (e.g. atorvastatin)
	Meperidine *N*-demethylation (3A4/5, 2C19)		Vitamin D
	Methadone *N*-demethylation (CYP2C, 3A4)		St. John's Wort
	Methamphetamine 4-hydroxylation and *N*-demethylation		

	N-methyl-3,4-methylenedioxyamphetamine (MDMA, ecstasy)		
	N-demethylation (1A2)		
	Nevirapine 3-hydroxylation		
	Propofol hydroxylation (CYP2C9)		
	Selegiline *N*-demethylation and N-depropargylation (1A2)		
	Sertraline *N*-demethylation (2C19, 2C9, 3A4/5)		
	Temazepam *N*-demethylation		
	Testosterone 16α- and 16β-hydroxylation (3A4/5)		
	Tramadol *N*-demethylation (3A4/5)		
CYP2C8	Amiodarone *N*-deethylation (3A4/5)	Gemfibrozil	Cyclophosphamide
Relatively large and weakly acidic molecules;	**Amodiaquine *N*-desethylation**	**Montelukast**	Dexamethasone
includes antimalarials and oral antidiabetics	Cerivastatin 6-hydroxylation and *O*-demethylation (3A4/5)	Trimethoprim	Fibrates (e.g. gemfibrozil)
	Chloroquine *N*-deethylation (3A4/5)		Hyperforin
	Imatinib *N*-demethylationn (3A4/5)		Imatinib
	Montelukast 36-hydroxylation (3A4/5, 2C9)		Lithocholic acid
	Nicardipine debenzylation (3A4/5)		Nelfinavir
	Paclitaxel 6α-hydroxylation		Paclitaxel
	Pioglitazone hydroxylation (1A2, 2D6)		Phenobarbital
	Retinoic acid 4-hydroxylation (3A7, 3A4, 2C9)		Phenytoin
	Rosiglitazone *N*-demethylation and p-hydroxylation (2C9)		Rifampicin
	Troglitazone oxidation (3A4/5)		Ritonavir
			Statins (e.g. atorvastatin)
CYP2C9	Acenocoumarol 6- and 7-hydroxylation (1A2, 2C19)	Amiodarone	Aprepitant
Weakly acidic molecules with a hydrogen bond	Candesartan *O*-deethylation	Fluconazole	Avasimibe
acceptor; includes most NSAIDs	Chlorpropamide 2-hydroxylation (2C19)	Naringenin	Barbiturates
	Celecoxib methylhydroxylation (3A4/5)	**Sulphaphenazole**	Bosentan
	Dapsone *N*-hydroxylation (2C8)	**Tienylic acid**	Carbamazepine
	Diclofenac 4′-hydroxylation	Voriconazole	Cyclophosphamide
	Etodolac 6- and 7-hydroxylation		Dexamethasone
	Fluoxetine *N*-demethylation (2D6, 2C19, 3A4/5)		Glutethimide
	Flurbiprofen 4′-hydroxylation		Hyperforin
	Glibenclamide hydroxylation		Nelfinavir
	Glimepiride hydroxylation		Nifedipine
	Ibuprofen 2- and 3-hydroxylation (2C8, 3A4/5)		Norethindrone
	Indomethacine *O*-demethylation (2C8)		Phenobarbital
	Irbesartan hydroxylation		Prednisone
	Ketobemidone *N*-demethylation (3A4/5)		Rifampicin
	Lornoxicam 5′-hydroxylation		Ritonavir
	Losartan 2-step oxidation of –CH2OH (3A4/5)		Statins (e.g. atorvastatin)
	Meloxicam 5′-methylhydroxylation (3A4/5)		St. John's Wort
	Phenobarbital p-hydroxylation (2C19)		
	Phenytoin 4-hydroxylation (2C19)		
	Piroxicam 5′-hydroxylation		
	Rosuvastatin *N*-demethylation		
	Sulfamethoxazole N-hydroxylation		
	S-warfarin 7-hydroxylation (4F2)		
	Tetrahydrocannabinol 11-hydroxylation (3A4/5)		
	Tienilic acid *S*-oxidation		
	Tolbutamide 4′-hydroxylation (2C19)		
	Valproic acid 4-hydroxylation (2B6, 2A6)		
	Valsartan 4-hydroxylation		
	Zaltoprofen sulfoxidation		
CYP2C19	Amitriptyline *N*-demethylation (2C8, 2C9)	**(−)-N-3-benzyl-phenobarbital**	Acetylsalicylic acid
Neutral or weakly basic molecules or amides with	Clomipramine 8-hydroxylation (1A2)	Clopidogrel	Antipyrine
2 or 3 hydrogen bond acceptors; includes most	Clopidogrel, 2-oxo-clopidogrel formation (3A4/5, 2B6, 1A2)	Fluoxetine	Artemisinin-type antimalarials
proton pump inhibitors	Hexobarbital 3′-hydroxylation	Fluvoxamine	Baicalin

(continued on next page)

Table 3 (*continued*)

CYP isoform, substrate structural characteristics	Substrates/pathways[a]	Inhibitors[b]	Inducers[c]
	Imipramine *N*-demethylation	Naringenin	Barbiturates
	Lansoprazole 5-hydroxylation (3A4/5)	(+)-N-3-benzyl-nirvanol	Carbamazepine
	Melatonin *O*-demethylation (1A2)	Omeprazole	Dexamethasone
	Nelfinavir *tert*-butylamide-hydroxylation (M8)	Ticlopidine	Efavirenz
	Omeprazole 5-hydroxylation (3A4/5)	Voriconazole	Hyperforin
	Pantoprazole sulfoxidation (3A4/5)		Nelfinavir
	Progesterone 21-hydroxylation (2C9, 3A4/5)		Rifampicin
	Proguanil isopropyl oxidation and cyclization to cycloguanil (3A4/5)		Ritonavir
	R-mephobarbital 4-hydroxylation (2B6)		St. John's Wort
	Ranitidine *N*-demethylation (1A2, 2D6)		
	S-mephenytoin 4′-hydroxylation		
	Venlafaxin *N*-demethylation (2C9, 3A4/5)		
	Voriconazole *N*-oxidation (3A4/5)		
CYP2D6	Amitriptyline 10-hydroxylation (3A4/5)	Bupropion	No significant induction by prototypical P450 inducers
Basic molecules with protonatable nitrogen atom 4–7 Å from the metabolism site; includes many plant alkaloids and antidepressants	Amphetamine 4-hydroxylation	Celecoxib	
	Aprindine 5-hydroxylation	Flecainide	
	Aripiprazole dehydrogenation (3A4/5)	Fluoxetine	
	Atomoxetine 4-hydroxylation and *N*-demethylation	Haloperidol	
	Bufuralol 1′-hydroxylation (1A2, 2C19)	Methadone	
	Carvedilol 4′- and 5′-hydroxylation	Paroxetine	
	Chlorpromazine 7-hydroxylation (1A2)	**Quinidine**	
	Clomiphene 4-hydroxylation (2B6)		
	Codeine *O*-demethylation		
	Debrisoquine 4-hydroxylation		
	Desipramine 2-hydroxylation (2C19, 1A2)		
	Dextromethorphan *O*-demethylation (2C9/19)		
	Dihydrocodeine *O*-demethylation		
	Diphenhydramine *N*-demethylation (1A2, 2C9, 2C19)		
	Dolasetron 6-hydroxylation (3A4/5)		
	Donepezil *O*-demethylation (3A4/5)		
	Duloxetine 4-, 5-, 6-hydroxylations (1A2)		
	Flecainide meta-*O*-dealkylation (1A2)		
	Galantamine *N*-demethylation		
	Hydrocodone *O*-demethylation (3A4/5)		
	Imipramine 2-hydroxylation (2C19, 1A2)		
	Loratadine oxidation to desloratadine (3A4/5)		
	Metoclopramide *N*-deethylation (3A4/5)		
	Metoprolol α-hydroxylation and *O*-demethylation		
	Mexiletine p-, m-, and 2-methylhydroxylation (1A2)		
	Mianserin 8-hydroxylation (2B6, 3A4/5)		
	Minaprine 4-hydroxylation		
	Mirtazapine 8-hydroxylation (1A2, 3A4/5)		
	N-methyl-3,4-methylenedioxyamphetamine (MDMA, ecstasy) demethylenation (1A2)		
	Nortriptyline 10-hydroxylation (3A4/5)		
	Ondansetron 7- and 8-hydroxylation (3A4/5)		
	Oxycodone *O*-demethylation		
	Paroxetine demethylenation		
	Perhexiline hydroxylation		
	Procainamide *N*-hydroxylation		
	Promethazine hydroxylation		
	Propafenone 5-hydroxylation		
	Propranolol 4- and 5-hydroxylation (Masubuchi 1994)		
	Risperidone 9-hydroxylation (3A4/5)		
	Sparteine C-oxidation		
	Tamoxifen 4-hydroxylation (2C9)		
	Thioridazine sulfoxidation (3A4/5)		

	Timolol hydroxylation (2C19)		
	Tramadol O-demethylation		
	Tropisetrone 5- and 6-hydroxylation (3A4/5)		
	Venlafaxin *O*-demethylation (2C19, 2C9)		
	Zuclopenthixol *N*-dealkylation (3A4/5)		
CYP2E1	Aniline 4-hydroxylation	Clomethiazole	Acetone
Small, generally neutral and hydrophilic, planar molecules;	Arachidonic acid ω-1-hydroxylation (1A1, 2D6)	**Diethyldithiocarbamate**	Ethanol
includes aliphatic alcohols and halogenated alkanes	Benzene hydroxylation and hydrochinone formation	**Disulfiram**	Isoniazid
	Butadiene 1,2-epoxidation (2A6)	**4-methylpyrazole**	Pyrazole
	Chlorzoxazone 6-hydroxylation (1A2)	Orphenadrine	Various other solvents and chemicals
	N,N-dimethylnitrosamine *N*-demethylation (2A6)		
	Enflurane oxidation and dehalogenation		
	Ethanol oxidation (major: ADH1)		
	Halothane hydroxylation (2A6, 3A4/5)		
	Isoflurane dehalogenation		
	Lauric acid (omega-1)-hydroxylation (4A11)		
	***Para*-nitrophenol 2-hydroxylation**		
	Salicylic acid 5-hydroxylation (3A4/5)		
	Sevoflurane hydroxylation		
	Styrene 7,8-epoxidation		
	Tetrachloromethane dehalogenation (3A4/5)		
	Toluene benzylic hydroxylation (2B6, 2C8, 1A2)		
	Vinylchloride epoxidation		
CYP2J2	Albendazole *S*-oxidation	Arachidonic acid	None known
Active site can accommodate large substrates similar	**Amiodarone 4-hydoxylation**	α-naphthoflavone	
to CYP3A4 but more restrictive catalytic function	Arachidonic acid epoxidation (mainly in heart; other CYPs)	**Danazol**	
	Astemizole *O*-demethylation	Hydroxyebastine	
	Cyclosporine A hydroxylation (major: 3A4/5)	Ketoconazole	
	Ebastine *t*-butyl hydroxylation (3A4/5)	Terfenadone	
	Danazol hydroxylation	Tranylcypromine	
	Mesoridazine sulfoxidation (major: CYP3A4)	Troglitazone	
	Terfenadine hydroxylation		
CYP3A4/5	L-α-acetylmethadol (LAAM) *N*-demethylation (2B6)	**Azamulin**	Amprenavir
Large and lipophilic molecules of very diverse structures;	Aflatoxin B1 3α-hydroxylation and 8,9-epoxidation (1A2)	Claritromycin	Aprepitant
includes over 50% of all clinically used drugs	**Alfentanil *N*-dealkylation**	Diltiazem	Artemisinine-type antimalarials
	Alprazolam α-hydroxylation	Erythromycin	Avasimibe
	Antipyrine 4-hydroxylation (1A2)	Ethinylestradiol	Baicalin
	Aprepitant *N*- and *O*-dealkylation (1A2, 2C19)	Grapefruit juice	Baribiturates
	Atorvastatin *o*- and *p*-hydroxylation	Isoniazid	Bosentan
	Budesonide 6β-hydroxylation	Irinotecan	Carbamazepine
	Buprenorphine *N*-demethylation (2C8)	**Ketoconazole**	Dexamethasone
	Buspirone 6′-hydroxylation	Mibefradil	Efavirenz
	Carbamazepine 10,11-epoxidation (2C8)	Mifepristone (RU486)	Etravirine
	Cholesterol 4β-hydroxylation	Naringenin	Ginkgo biloba
	Cisapride N-dealkylation (2A6)	Nicardipine	Glucocorticoids
	Citalopram *N*-demethylation (2C19, 2D6)	Ritonavir	Hyperforin
	Clarithromycin 14-(R)-hydroxylation and *N*-demethylation	Troleandomycin	Imatinib
	Clindamycin *S*-oxidation	Verapamil	Miconazole
	Codeine *N*-demethylation (2B6)	Voriconazole	Mitotane
	Cortisol 6β-hydroxylation		Moricizine
	Cyclobenzaprine (1A2, 2D6)		Nafcillin
	Cyclophosphamide *N*-dechloroethylation		Nevirapine
	Cyclosporine A hydroxylation (M1 and M17 formation)		Oxcarbazepine
	Dasatinib *N*-dealkylation		Phenobarbital
	Dexamethasone 6-hydroxylation		Phenylbutazone
	Dextromethorphan *N*-demethylation (2B6, 2C9/19))		Phenytoin

(continued on next page)

Table 3 (*continued*)

CYP isoform, substrate structural characteristics	Substrates/pathways[a]	Inhibitors[b]	Inducers[c]
	Dextropropoxyphene *N*-demethylation		Rifabutin
	Diazepam 3-hydroxylation and *N*-demethylation (2C19)		Rifampicin
	Dihydrocodeine *N*-demethylation		Rifapentin
	Diltiazem *N*-demethylation (2C8, 2C9)		Ritonavir
	Docetaxel hydroxylation		Statins
	Dolasetron *N*-oxidation		St. John's Wort
	Donezepil *O*-dealkylation (2D6)		Sulfinpyrazone
	Ebastine *N*-dealkylation		Topiramate
	Erlotinib *O*-demethylation (1A1/2)		Troglitazone
	Erythromycin *N*-demethylation (2B6)		Valproic acid
	Eszopiclone oxidation and *N*-demethylation (2E1)		Vinblastine
	17α-ethinyl estradiol 2-hydroxylation		
	Etoposide catechol metabolite formation		
	Felodipine oxidation to pyridine		
	Fenofibrate deesterification		
	Fentanyl *N*-dealkylation		
	Fluticasone 17β-carboxylic acid formation		
	Gefitinib *O*-demethylation (1A1/2D6)		
	Glyburide hydroxylation (2C9)		
	Granisetron *N*-demethylation		
	Haloperidol *N*-dealkylation (2D6)		
	Hydromorphone *N*-demethylation (2C9)		
	Ifosfamide *N*-dechloroethylation (2B6)		
	Ilaprazole sulfone formation		
	Irinotecan (CPT-11) oxidation to APC		
	Isotretinoin (13-cis- retinoic acid) 4-hydroxylation (2C8)		
	Lithocholic acid 6α-hydroxylation		
	Lopermide *N*-demethylation (2B6)		
	Midazolam 1′-hydroxylation		
	Mifepristone (RU-486) *N*-demethylation		
	Mirtazapine *N*-demethylation and *N*-oxidation		
	Morphine *N*-demethylation (2C8)		
	Nevirapine 2-hydroxylation		
	Nifedipine oxidation to pyridine		
	Oxycodone *N*-demethylation		
	Paracetamol oxidation to NAPQI (2E1, 2A6, 1A2, 2D6, 2C9/19)		
	Quetiapine *N*-dealkylation		
	Quinine 3-hydroxylation		
	Quinidine 3-hydroxylation and *N*-oxidation		
	Sildenafil *N*-demethylation (2C9)		
	Simvastatin 6′-β-hydroxylation (2C8)		
	Sirolimus 16-*O*- and 39-*O*-demethylation and various hydroxylations		
	Tacrolimus *O*-demethylation		
	Teniposide *O*-demethylation		
	Testosterone 6β-hydroxylation (2C9, 1A1)		
	Tetrahydrocannabinol 7- and 8-hydroxylation		
	Tilidine *N*-demethylation		
	Tramadol *N*-demethylation (2B6)		
	Trazodone *N*-dealkylation to mCPP		
	Triazolam α- and 4-hydroxylation		
	Verapamil *Nn*demethylation to norverapamil (2C8)		
	Vincristine M1-formation (3A5>3A4)		
	Ziprasidone sulfoxidation (2C19)		
	Zolpidem hydroxylation (1A2)		

Data were compiled from Anzenbacher & Zanger, 2012, and from the references cited in the text.

[a] Substrates/pathways are grouped by the major metabolizing P450 enzyme in liver with other contributing enzymes given in parentheses. Drugs selectively metabolized by one form and used for phenotyping are printed in bold-type. Endogenous substrates are underlined.

[b] Inhibitors listed have shown to inhibit the respective P450 significantly in vivo or in human liver microsomes; isoenzyme-selective inhibitors are shown in bold-type.

[c] Inducers that have been shown to induce the respective P450 significantly in vivo or in human hepatocytes; isoenzyme-selective inducers are shown in bold-type.

predicted to interrupt the open reading frame and some were shown to lead to severely compromised enzyme function (Jansson et al., 2001; Chavarria-Soley et al., 2008; Choudhary et al., 2008; Vasiliou & Gonzalez, 2008). Because these mutations are rare in the general population, their value as tumor markers or markers of altered metabolism of drugs appears to be of limited value. More common polymorphisms include five amino acid variants in different combinations. Functional analysis of variant proteins coexpressed with P450 reductase in *E. coli* showed threefold increased Km towards 17β-estradiol for the Leu432Val (*CYP1B1**3*) variant but little influence of the Arg48Gly, Ala119Ser and Asn453Ser variants (Li et al., 2000). This finding was however not reproduced in a yeast expression study using the same substrate, whereas decreased Vmax and increased Km towards 17β-estradiol was observed in combination alleles *CYP1B1**6* and *CYP1B1**7* (Aklillu et al., 2002). The *CYP1B1.7* variant was also found to have lower benzo[a]pyrene hydroxylase activity. The Leu432Val variant was correlated to changed urinary estrogen metabolites, indicating in vivo contribution of CYP1B1 to estrogen catabolism (Napoli et al., 2009). These studies suggest that the common amino acid variations have moderate to low substrate-dependent effects on the catalytic properties of the enzyme.

3.4. Clinical impact of genetic variation

Because of the role of CYP1A and CYP1B enzymes in the metabolism of procarcinogens and cellular signalling molecules, their polymorphisms have been extensively studied as susceptibility factors in the context of various cancers (examples shown in Table 1). As this topic is not systematically covered here, the reader is referred to reviews and meta-analyses by others (Shi et al., 2008; Kaur-Knudsen et al., 2009b; Sergentanis & Economopoulos, 2009; Shaik et al., 2009; Economopoulos & Sergentanis, 2010; Yao et al., 2010a; Cui et al., 2012; Li et al., 2012a; Wang et al., 2012).

DNA damage caused by CYP1A-activated tobacco smoke mutagens may contribute to the development of coronary heart disease. Cornelis and colleagues investigated this hypothesis by genotyping 873 Costa Rican subjects with myocardial infarction (MI) for *CYP1A1* and *CYP1A2* genotypes (Cornelis et al., 2004). While *CYP1A1* genotype had no influence, individuals homozygous for the low inducibility –163C allele had increased risk, but surprisingly this was independent of smoking status. The authors reasoned that activation of tobacco smoke mutagens by CYP1A2 may not play a significant role in CHD but that an unknown compound, e.g. a coffee ingredient detoxified by CYP1A2, may contribute to MI. This finding was however not reproduced in a Tunisian population (Achour et al., 2011). The controversial association between coffee intake and risk of MI was investigated with respect to the *CYP1A2* –163C/A polymorphism by the same researchers (Cornelis et al., 2006). Intake of coffee was associated with an increased risk of MI only among individuals with the low-inducibility (−163C) allele in a dose-dependent way. This effect was independent of smoking status and the authors suggested that an unknown CYP1A2 substrate that is detoxified rather than activated may play a role in CHD.

As CYP1A2 is the rate-limiting enzyme for metabolism of caffeine, the most widely consumed psychoactive substance worldwide, *CYP1A2* polymorphism could play a role in habitual caffeine intake, which is also regarded as a model for addictive behavior. Indeed, twin studies suggest heritability estimates for heavy caffeine use of up to 77% (Dvorak et al., 2003). Several genome-wide association studies (GWAS) and GWAS meta-analyses involving many thousands of subjects identified SNPs in the regulatory region of the *CYP1A* locus (rs2472304, rs2472297) as well as SNPs in the AhR gene regulatory region (rs4410790, rs6968865) along with genes related to addictive behavior to be associated with habitual coffee intake (Dvorak et al., 2003; Cornelis et al., 2011; Sulem et al., 2011). It would be highly interesting to identify the causal variants for these associations. The *CYP1A2* low-inducibility –163C allele may also modify the risk of hypertension in coffee drinkers, as suggested by one study (Palatini et al., 2009).

These data collectively support a role of CYP1A2 polymorphism in the metabolism and disposition of caffeine. Data concerning clinical drug use are generally less convincing although some studies reported a significant influence. *CYP1A2**1F*/*1F* genotype was associated with a 22% reduction of olanzapine serum concentration, which was independent of any inducing agents, indicating a moderately increased activity of the **1F* allele per se (Laika et al., 2010). In this study higher olanzapine concentrations were correlated to better improvement of paranoid and depressive symptoms in patients with schizophrenic disorders. In contrast, although CYP1A2 is the major P450 enzyme for the metabolism of the antipsychotic, clozapine, clinical studies did not confirm an influence of *CYP1A2* genotype (Van der Weide et al., 2003; Jaquenoud Sirot et al., 2009). This was quite surprising since smoking behavior strongly influenced clozapine clearance and daily dose requirement.

In conclusion, the currently known polymorphisms in the *CYP1A2* gene explain only a small fraction of the CYP1A2 variability in expression and function. GWAS and candidate gene studies indicate that genetic determinants in other genes contribute to CYP1A2 activity.

4. Family *CYP2*

The *CYP2* family contains 16 full-length genes, which all have 9 exons and 8 introns. Several of the most important hepatic drug metabolizing CYPs but also extrahepatic enzymes and several "orphan" P450s (Guengerich & Cheng, 2011) with still unclear function are found in this family. The genes are spread over different chromosomes and organized in multi-gene clusters containing one or several subfamilies (Hoffman et al., 2001; Nelson et al., 2004). The three largest gene clusters are the *CYP2ABFGST* cluster on chromosome 19q13.2, which contains the *CYP2A6* and *CYP2B6* genes, the CYP2C cluster on chromosome 10q23.33 with the *CYP2C8*, *CYP2C9*, and *CYP2C19* genes, and the *CYP2D* cluster on chromosome 22q13.1-2 with the only functional gene *CYP2D6*. In the evolution of rodents, many of the *CYP2* subfamilies expanded tremendously, making the identification of true orthologues between mouse and human P450s especially challenging (Nelson et al., 2004). Most pharmacologically important *CYP2* genes are highly polymorphic, in particular *CYP2A6*, *CYP2B6*, *CYP2C9*, *CYP2C19*, and *CYP2D6*. In this chapter, we focus on the description of those genes and enzymes that are of highest importance for xenobiotic metabolism.

4.1. Subfamily CYP2A: CYP2A6, CYP2A7, CYP2A13

4.1.1. Regulation and variability of gene expression

The three full-length human *CYP2A* genes *2A6*, *2A7*, and *2A13* and a split pseudogene *CYP2A18P* are found on a 370 kb gene cluster on chromosome 19q13.2 that contains genes and pseudogenes of the *CYP2A*, *2B*, *2F*, *2G*, *2S* and *2T* subfamilies (Hoffman et al., 2001; Nelson et al., 2004 Only *CYP2A6* and *CYP2A13* are functional whereas *CYP2A7* apparently encodes a nonfunctional gene, although *CYP2A7* cDNA generates an immunoreactive protein unable to incorporate heme (Ding et al., 1995; Hoffman et al., 2001). Human CYP2A6 is mainly expressed in liver (Table 2), where mean expression levels corresponding to ~4% of the hepatic P450 pool were found by Western blot analysis (Shimada et al., 1994; Haberl et al., 2005) while mass spectrometric studies found much higher levels of ~50 pmol/mg (Ohtsuki et al., 2012). Significantly increased protein and mRNA levels were observed in female liver donors (Al Koudsi et al., 2010) and decreased levels of protein and activity in Japanese compared to Caucasian liver donors (Shimada et al., 1996).

Transcriptional regulation of *CYP2A6* involves several response pathways. In human hepatocytes, the PXR and CAR activators

rifampin and phenobarbital induce CYP2A6 mRNA via several DR4 elements (Itoh et al., 2006). Furthermore glucocorticoid receptor-mediated activation of CYP2A6 transcription by dexamethasone was reported to depend on HNF4α (Onica et al., 2008). In vivo, estrogen-containing oral contraceptives can increase CYP2A6 activity as measured by nicotine and cotinine clearance (Benowitz et al., 2006). In vitro data indicate transcriptional upregulation of CYP2A6 via an estrogen receptor-dependent pathway (Higashi et al., 2007). *CYP2A13* codes for a catalytically active protein expressed at low levels predominantly in the respiratory tract including the lung, where expression levels decrease from nasal mucosa to peripheral lung tissues (Leclerc et al., 2010; Raunio & Rahnasto-Rilla, 2012).

4.1.2. Role of CYP2A enzymes in drug metabolism

Human CYP2A6 has been recognized as the major isoform involved in the oxidative metabolism of the psychoactive tobacco ingredient nicotine to the inactive cotinine (Raunio & Rahnasto-Rilla, 2012). Further metabolism of cotinine to 3′-hydroxycotinine is also exclusively catalyzed by CYP2A6 in humans and in agreement with higher expression of hepatic CYP2A6 in females, metabolism of nicotine to cotinine, and the trans-3′-hydroxycotinine/cotinine ratio were significantly higher in women than in men (Benowitz et al., 2006).

The 7-hydroxylation of coumarin is a selective marker activity for CYP2A6 (Pelkonen et al., 2000; Fuhr et al., 2007). Major racial differences exist, e.g. only 1% of white subjects but to up to 20% of Asians were characterized as poor metabolizers (Shimada et al., 1996; Raunio et al., 2001). CYP2A6 was identified as the main isoenzyme responsible for bioactivation of the cancer prodrug tegafur to 5-FU (Komatsu et al., 2000), efavirenz 7-hydroxylation, a minor pathway compared to the major 8-hydroxylation catalyzed by CYP2B6 (Desta et al., 2007), and the biotransformation of the aromatase inhibitor, letrozole, to its major, pharmacologically inactive carbinol metabolite, 4,4′-methanol-bisbenzonitrile (Murai et al., 2009). Furthermore, CYP2A6 contributes to the metabolism of a number of clinically used drugs such as disulfiram, fadrozole, halothane, osigamone, methoxyflurane, pilocarpine, promazine, and valproic acid (Di et al., 2009). An endogenous substrate of CYP2A6 that was only recently identified is bilirubin (Abu-Bakar et al., 2012). CYP2A13 has similar substrate specificity and also metabolizes coumarin and nicotine, but has been shown to be the most efficient metabolic activator of NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), a major tobacco procarcinogen (Su et al., 2000).

4.1.3. Genetic polymorphisms and functional impact

Both increased and decreased gene expression and enzyme activity have been associated with genetic variation in the *CYP2A6* gene. At present, 38 distinct star-alleles with deleted or duplicated genes, gene conversions, nucleotide deletions and insertions, as well as coding and non-coding SNPs are described on the CYPalleles website. Some of these variants were shown to change mRNA and/or protein expression levels or to affect the structure and function of the protein (Table 1). The prevalence of low-activity or loss-of-function *CYP2A6* alleles was estimated to be ~9% in Caucasians, ~22% in Africans and up to 50% in Asians (Nakajima et al., 2006; di Iulio et al., 2009). A detailed compilation of the known structural changes and their functional impact was presented by Mwenifumbo and Tyndale (2009).

Loss-of-function alleles include the *CYP2A6***2*[Leu160His] and the **4A-H* deletion alleles, that have been shown to dramatically reduce enzyme activity in vivo in homozygous or hemizygous combination, resulting in the poor metabolizer phenotype in affected individuals (Table 1). The most frequent null alleles in Asians are the **4A to* **4H* hybrid-deleted alleles which consist of a *CYP2A7*-derived 5′ part and a 3′ part of *CYP2A6* origin. The decreased gene copy number associated with these gene deletions appears to be correlated to decreased expression and activity (Haberl et al., 2005; Mwenifumbo et al., 2010). The **4A* deletion variant is rare in Caucasians and Africans but present at up to ~20% frequency in Asian populations (Table 1).

*CYP2A6***2*[Leu160His] encodes an unstable protein that fails to incorporate heme. Its frequency is ~1–5% in Caucasians and lower in Africans and Asians. In a study involving 156 liver samples from Caucasians, resequencing revealed 33 haplotypes of which two (**9B*, containing a -48T>G TATA-box polymorphism, and the 2A7/2A6 recombination allele **12B*) were major genetic determinants associated with decreased hepatic expression (Haberl et al., 2005). Additional alleles with functional impact include *CYP2A6***7*, **10*, **17*, and **35* associated with reduced enzyme activity in homozygous or hemizygous individuals. The **7*[Ile471Thr] and **10* [Ile471Thr; Arg485Leu] alleles are Asian-specific and **17* [Val365Met] was only found in African Americans. The *CYP2A6***5*, **6*, **11*, **19*, and **20* alleles were shown to result in reduced activity by heterologous expression. Further variants shown to affect expression or function include several promoter variants that result in decreased expression (Von Richter et al., 2004b). Apart from the low copy number variants with deleted *CYP2A6*, increased copy number variants termed **1X2A* and **1X2B* appear to be correlated to increased activity (Fukami et al., 2007).

4.1.4. Clinical impact of genetic variation

Most pharmacogenetic studies involving *CYP2A6* were carried out to study the effect of genotype either on nicotine metabolism, smoking behavior, nicotine withdrawal symptoms or lung cancer risk (Benowitz et al., 2006; Nakajima et al., 2006; Mwenifumbo & Tyndale, 2007; Rossini et al., 2008). For example, compared to subjects with reference genotype (**1*/**1*), heterozygotes of alleles **9* and **12* had on average 80% of normal activity, whereas **4* heterozygotes or carriers of two low-activity alleles had ~50% nicotine C-oxidation activity (Benowitz et al., 2003). Because of its major contribution to nicotine metabolism, the enzyme has been proposed as a novel target for smoking cessation. In a nicotine-replacement clinical trial, the group with low-activity alleles had 50% reduced CYP2A6 activity before treatment and reached 44% higher steady-state plasma levels of nicotine (Malaiyandi et al., 2006). Moreover, severe nicotine withdrawal symptoms related to nicotine dependence during smoking cessation were higher in *CYP2A6*-genotyped Japanese high-activity subjects (50.0%) compared to the low-activity group (22.2%; (Kubota et al., 2006). Recent studies investigated *CYP2A6* and the *CHRNA5-CHRNA3-CHRNB4* nicotinic acetylcholine receptor gene polymorphisms in relation to smoking behavior and lung cancer risk. In ever-smokers of European ancestry (417 lung cancer patients) versus control subjects, increased cigarette consumption, nicotine dependence, and lung cancer risk were independently and additively associated with genetic variation in *CYP2A6* and the acetylcholine receptor gene cluster. The combined risk group exhibited the greatest lung cancer risk with an odds ratio of ~2 (Wassenaar et al., 2011). *CYP2A6* variants were also associated to smoking behaviour (cigarettes smoked per day) at genome-wide significance (Thorgeirsson et al., 2010).

The significance of CYP2A6 polymorphism for drug therapy is emphasized by the following two examples. CYP2A6 is a major enzyme for the bioactivation of the cancer prodrug tegafur to 5-FU (Komatsu et al., 2000). A prospective pharmacokinetic study in Japanese patients with advanced cancers revealed that *CYP2A6* variants determined oral clearance of tegafur as shown by multivariate regression analysis and that tegafur clearance was lowest in homozygous or compound heterozygous *CYP2A6* variant allele carriers (Fujita et al., 2008). Another example is efavirenz, an antiretroviral drug with the major metabolic pathway catalyzed by CYP2B6, which leads to 8-hydroxy efavirenz. As initially shown in human liver microsomes, the minor 7-hydroxy-efavirenz metabolite is mainly formed by CYP2A6 (Desta et al., 2007). While the wide interindividual variability in efavirenz plasma exposure is largely explained by *CYP2B6* polymorphisms, the CYP2A6-dependent accessory pathway becomes critically limiting for drug clearance in

patients with genetically impaired *CYP2B6* (Di Iulio et al., 2009). As combined *CYP2B6* and *CYP2A6* genetic deficiency occurs at significant frequency in various human populations, the *CYP2A6* polymorphism may be a clinically relevant determinant of extremely high efavirenz exposure in HIV patients. A more recent pharmacogenetic study found that CYP2A6 genotype is also a predictor for plasma letrozole concentrations in postmenopausal women with breast cancer (Desta et al., 2011).

4.2. Subfamily CYP2B: CYP2B6

4.2.1. Regulation and variability of gene expression

The functional *CYP2B6* gene and the nonfunctional pseudogene *CYP2B7P* are located in a tandem head-to-tail arrangement within the large *CYP2ABFGST* gene cluster on chromosome 19 (Nelson et al., 2004). Although the genomic structures of the human and rodent *CYP2B* genes are very different with more functional genes expressed in the animals, strong inducibility by phenobarbital is a hallmark of *CYP2B* genes, and similar mechanisms apply in humans and animals. The major discovery in this field was the identification of the orphan nuclear receptor CAR (NR1I3) as the major regulator of CYP2B6 by drugs and other xenobiotics via a phenobarbital-responsive enhancer module (PBREM) at –1.7 kb of the *CYP2B6* promoter (Sueyoshi et al., 1999). Later it was found that PXR (NR1I2) also contributes to CYP2B6 induction via a distal xenobiotics-responsive enhancer module (XREM, −8.5 kb; (Wang et al., 2003). CYP2B6 inducers (Table 3) are typically ligands of either of these receptors, such as rifampicin and barbiturates, or substances that activate both receptors (Faucette et al., 2004, 2006). In human hepatocytes inducibility of CYP2B6 was reported for cyclophosphamide (Gervot et al., 1999), artemisinine (Burk et al., 2005), carbamazepine, efavirenz and nevirapine (Faucette et al., 2007), metamizole (Saussele et al., 2007), the insect repellent N,N-diethyl-m-toluamide DEET; (Das et al., 2008), and several statins (Feidt et al., 2010).

In humans CYP2B6 belongs to the minor hepatic P450s, contributing on average ~2–5% to the total hepatic P450 pool (Table 2), but it exhibits ~300-fold variability of expression (Lang et al., 2001; Lamba et al., 2003; Desta et al., 2007; Hofmann et al., 2008; Ohtsuki et al., 2012). Expression in fetal liver appears to be considerably lower with up to 36% of pediatric liver samples having undetectable levels (Croom et al., 2009). According to this study CYP2B6 increases about 2-fold within the first month of life. Although most studies did not find a significant sex difference in CYP2B6 expression, the issue remains controversial as in some studies higher expression in females versus males was found, depending on ethnicity (Lamba et al., 2003). In another study 1.6-fold higher expression in female livers was observed in all samples but there was no difference when samples from drug-treated donors were excluded (Hofmann et al., 2008). Inflammation has also been recognized as an influential factor for CYP2B6 expression, as shown by downregulation in human hepatocytes in response to IL-6 and interferon γ (Aitken & Morgan, 2007).

CYP2B6 was detected at the level of RNA and protein in human brain, where it was reported to be higher in samples of smokers and alcoholics (Miksys et al., 2003), a result that awaits confirmation. Low levels of CYP2B6 transcripts were found in several extrahepatic tissues including kidney (Aleksa et al., 2005), heart (Michaud et al., 2010), placenta (Wang et al., 2010a), and in various tissues of the respiratory tract including lung and nasal mucosa (Ding & Kaminsky, 2003). In contrast, expression in skin or keratinocytes (Du et al., 2006) and intestine (Paine et al., 2006) appears to be low or absent (Table 2).

4.2.2. Role of CYP2B6 in drug metabolism

The CYP2B6 substrate selectivity comprises many diverse chemicals, including not only clinically used drugs but also a large number of environmental chemicals (Table 3). Therapeutically important drugs metabolized mainly by CYP2B6 include the prodrug cyclophosphamide, which is converted to the direct precursor of the cytotoxic metabolites, phosphoramide mustard and acrolein, by 4-hydroxylation; the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz; the atypical antidepressant and smoking cessation agent bupropion; the antimalarial artemisinin; the anaesthetics propofol and ketamine; the μ-opioid agonist methadone, and others (Zanger et al., 2007; Turpeinen & Zanger, 2012). Suitable probe drugs for CYP2B6 include S-mephenytoin N-demethylation and bupropion hydroxylation, of which the latter one was shown to be more selective (Faucette et al., 2000; Fuhr et al., 2007) and is now most often used. Another potentially useful in vivo probe drug is efavirenz, based on in vitro investigations (Ward et al., 2003; Desta et al., 2007). CYP2B6 also metabolizes the *N*-demethylation of the recreational drug “ecstasy” (MDMA), which leads to potentially neurotoxic metabolites (Kreth et al., 2000), and it plays a minor role in nicotine metabolism (Yamazaki et al., 1999; Yamanaka et al., 2005). Numerous studies have furthermore documented an important role of CYP2B6 in the metabolism of pesticides and several other environmental chemicals and pollutants (Hodgson & Rose, 2007), in particular the activating oxidation of organophosphorus insecticides to their more toxic oxon metabolites. Examples are the organophosphorus insecticide, chlorpyrifos (Crane et al., 2012), the insecticide and endocrine disruptor methoxychlor, and the extensively used insect repellent DEET, among many others (Hodgson & Rose, 2007). Recent studies have revealed the crystal structure of CYP2B6 in complex with various inhibitors, providing first views into its active site and ligand binding properties (Gay et al., 2010; Shah et al., 2011).

4.2.3. Genetic polymorphisms and functional impact

The *CYP2B6* gene is extensively polymorphic with numerous variants in the coding and noncoding regions of the gene (Lang et al., 2001; Lamba et al., 2003; Lang et al., 2004; Klein et al., 2005; Zukunft et al., 2005; Zanger et al., 2007). The CYPalleles website currently lists 29 distinct star-alleles with variant amino acid sequence or with proven functional effect. More than 30 SNPs code for amino acid changes which occur in different combinations and additional haplotype variants and SNPs not yet assigned to particular alleles exist. The most common allele is *CYP2B6*6* with two amino acid changes Gln172His and Lys262Arg, in combination with other identified changes mainly in the promoter. The **6* allele occurs with frequencies between 15 and 60% across different populations (Table 1) and is associated with 50 to 75% decreased hepatic liver protein expression (Lang et al., 2001; Lamba et al., 2003; Desta et al., 2007). The major causal variant for decreased expression was identified as the 15631G>T [Gln172His] polymorphism, which was shown to cause incorrect splicing of the CYP2B6 pre-mRNA leading to a shorter mRNA that lacks exons 4 to 6 (Hofmann et al., 2008). This polymorphism represents an example of a nonsynonymous variant leading to major effects that are unrelated to the amino acid exchange but instead to changes on the mRNA level (Zanger & Hofmann, 2008; Sadee et al., 2011). Importantly, only appropriately designed RT-PCR assays will detect the qualitative and quantitative mRNA changes associated with this particular genetic variant (Hofmann et al., 2008). *CYP2B6* genotyping by testing for 15631G>T as a marker of the **6* allele appears to be straightforward. However, it should not be forgotten that this results in the detection of a mixture of related complex haplotypes with additional upstream region SNPs (–1456T>C and -750T>C) and the second nonsynonymous variant 18053A>G [K262R]. Only marginal changes appear to be associated with the promoter variants (Lamba et al., 2003; Hesse et al., 2004; Hofmann et al., 2008), but differential functional effects conferred by the K262R amino acid variant have been reported. The K262R variant (**4* allele, frequency ~2–6%) was associated with higher activity towards several substrates including bupropion (Kirchheiner et al., 2003), nicotine (Johnstone et al., 2006), efavirenz (Rotger et al., 2007), artemether (Honda et al., 2011), and selegiline (Watanabe et al., 2010).

However expressed K262R variant was unable to metabolize 17-α-ethynylestradiol (Bumpus et al., 2005) and further studies indicated altered active site topology of the variant resulting in more uncoupled reaction kinetics (Bumpus & Hollenberg, 2008). In contrast cyclophosphamide activation was found to be enhanced by the recombinant Q172H variant but decreased by the K262R variant (Xie et al., 2003; Ariyoshi et al., 2011; Raccor et al., 2012). These data strongly emphasize the need to perform detailed genotyping of the involved *CYP2B6* variants in order to obtain conclusive results in particular from in vivo studies. Further differential effects of the amino acid variants were reported with respect to enzyme inactivation. In contrast to the wild-type enzyme the recombinantly expressed K262R variant was not inactivated by efavirenz, but both enzymes were irreversibly inhibited by 8-hydroxyefavirenz (Bumpus et al., 2006). Lower susceptibility to inhibition of the K262R variant and the *6 (Q172H/K262R) double variant was also found with respect to sertraline and clopidogrel and several other potent drug inhibitors of CYP2B6 (Talakad et al., 2009). Taken together, the low-expressor phenotype of the 15631G>T variant is partially compensated for by higher specific catalytic activity at least for some substrates, which explains some conflicting data regarding observations made in liver microsomes, heterologous expression systems, or studies in vivo. This also appears to be the case for the *5 variant (25505C>T [R487C]) which expresses very low levels of an apparently highly active enzyme with bupropion (Lang et al., 2001) as well as efavirenz (Desta et al., 2007), which explains why it was not associated with efavirenz pharmacokinetics in patients (Burger et al., 2006).

Another important functionally deficient allele is *CYP2B6*18* (21011T>C [I328T]), which occurs predominantly in African subjects with allele frequencies of 4–12% (Mehlotra et al., 2007; Li et al., 2012b). The variant cDNA did not form a functional protein in transfected mammalian cells tested with bupropione (Klein et al., 2005) and lack of activity was also found in vitro for 7-EFC and selegiline (Watanabe et al., 2010) as well as artemether (Honda et al., 2011). The *18 allele is thus phenotypically a *null* allele. At least 12 additional null or low-activity alleles have been described and analyzed with various substrates (Lang et al., 2004; Klein et al., 2005; Rotger et al., 2007; Watanabe et al., 2010; Honda et al., 2011). Although they are rather rare in all investigated populations they may have profound effects on drug metabolism if present in compound heterozygous genotypes e.g. in combination with *6 or *18 (Rotger et al., 2007). The *CYP2B6*22* allele is a gain-of-function variant associated with increased transcription in vitro (Zukunft et al., 2005) and with increased activity in vivo (Rotger et al., 2007). It was shown that a −82T>C exchange alters the TATA-box into a functional CCAAT/enhancer-binding protein binding site that causes increased transcription from an alternative downstream initiation site (Zukunft et al., 2005). Interestingly, the −82T>C polymorphism also confers synergistically enhanced CYP2B6 inducibility by the PXR ligand rifampicin in human primary hepatocytes (Li et al., 2010).

4.2.4. Clinical impact of genetic variation

A major clinical role of *CYP2B6* polymorphism was established in HIV therapy, following the identification of CYP2B6 as the major enzyme responsible for 8-hydroxylation of efavirenz and its further hydroxylation to 8, 14-dihydroxyefavirenz (Ward et al., 2003). The potent first-generation NNRTI of HIV-1is recommended as initial therapy with two NRTIs in highly active antiretroviral therapy (HAART) regimes, but patients with subtherapeutic plasma concentrations can develop resistance and treatment failure, whereas those with too high plasma levels are at increased risk of CNS side effects, which can lead to treatment discontinuation in a fraction of patients (King & Aberg, 2008). Several *CYP2B6* low activity alleles have been associated with increased efavirenz plasma levels in numerous studies investigating HIV-infected adults and children. Homozygosity for the 15631T [Q172H] variant is associated with several-fold higher median efavirenz AUC compared to carriers of only one or no T-allele as shown in numerous clinical studies (see reviews King & Aberg, 2008; Telenti & Zanger, 2008; Rakhmanina & van den Anker, 2010). Compound heterozygotes of 15631T and another low activity allele (e.g. *11, *18, *27, *28) also predict high efavirenz plasma levels (Rotger et al., 2007; Ribaudo et al., 2010). Three *CYP2B6* polymorphisms, 15631G>T, 21011T>C and intron 3 rs4803419, were independently associated with efavirenz pharmacokinetics at genome-wide significance (Holzinger et al., 2012). In addition to CYP2B6 polymorphism, CYP2A6 and CYP3A4/5 variants also influence clearance, in particular when CYP2B6 is impaired (Arab-Alameddine et al., 2009). The 15631T [Q172H] variant was furthermore associated with increased neurotoxicity and other CNS side effects (Haas et al., 2004; King & Aberg, 2008; Lubomirov et al., 2010; Ribaudo et al., 2010; Maimbo et al., 2011) with highly active antiretroviral therapy (HAART)-induced liver injury (Yimer et al., 2012), and with efavirenz treatment discontinuation and the associated risk of developing drug resistance (Ribaudo et al., 2006; Lubomirov et al., 2011; Wyen et al., 2011). In prospective, genotype-based dose adjustment studies the therapeutic dose of efavirenz could be successfully reduced and CNS-related side effects decreased (Gatanaga et al., 2007; Gatanaga & Oka, 2009). Using pharmacokinetic modelling and simulation it was suggested that *a priori* dose reduction in homozygous *CYP2B6*6* patients would maintain drug exposure within the therapeutic range in this group of patients (Nyakutira et al., 2008).

In addition to efavirenz, CYP2B6 genotype also affects plasma levels of the antiretroviral drug nevirapine (Penzak et al., 2007; Mahungu et al., 2009). The impact of the 15631G>T polymorphism on nevirapine exposure was confirmed and quantified in a pharmacometric analysis of nevirapine plasma concentrations from 271 patients genotyped for 198 SNPs in 45 ADME genes and covariates (Lehr et al., 2011). Moreover, nevirapine-related cutaneous adverse events, which are most likely MHC class I-mediated, were significantly influenced by *CYP2B6* polymorphism while hepatic side effects, most likely MHC class II-mediated, were unaffected by *CYP2B6* (Yuan et al., 2011).

While efavirenz pharmacokinetics appears to be largely explained by low expression of *CYP2B6*6* in liver, other substrates may be additionally influenced by altered catalytic functions of CYP2B6 protein variants as outlined above. Bioactivation of the widely used anticancer and immunosuppressant prodrug cyclophosphamide to 4-hydroxycyclophosphamide is highly variable in cancer patients and has been attributed mainly to CYP2B6 in vitro and in vivo with contributions from CYP2C19 and CYP3A4 (Chang et al., 1993; Raccor et al., 2012). There is growing evidence that cyclophosphamide bioactivation and response to therapy depend on *CYP2B6* genotype (Xie et al., 2006; Nakajima et al., 2007; Rocha et al., 2009; Bray et al., 2010; Melanson et al., 2010; Yao et al., 2010b; Raccor et al., 2012). As mentioned above, allele-effects, particularly for *4 and *6, appear to differ for cyclophosphamide, most likely due to substrate-specific effects of amino acid substitutions (Ariyoshi et al., 2011; Raccor et al., 2012). Furthermore, the *5 (R487C) variant, not found to be related to efavirenz disposition, was significantly associated with lower rate of overall toxicity and higher rate of relapse in patients who received high dose CPA treatment (Black et al., 2012). However, data concerning cyclophosphamide from in vivo and in vitro studies are so far not consistent. In part this may be explained by lack of consistency in allele definition and genotype information among studies (Helsby & Tingle, 2011).

CYP2B6 allele variants were also investigated in the context of the synthetic μ-opioid receptor agonist, methadone, which is metabolized by CYPs 3A4/5, 2B6, and 2D6, and used as a maintenance treatment for opioid addiction. In *6/*6 carriers (S)-methadone plasma levels were increased leading to potentially higher risk of severe cardiac arrhythmias and methadone associated deaths (Crettol et al., 2005; Eap et al., 2007; Bunten et al., 2011). Methadone dose requirement for effective treatment of opioid addiction was shown to be significantly reduced in carriers of this genotype (Levran et al., 2011).

In conclusion, the clinical impact of *CYP2B6* pharmacogenetics has not yet been fully explored but an increasing number of studies suggest clinical relevance for different drug substrates. Importantly, the relationship between *CYP2B6* genotype and in vivo drug metabolism function is complex due to the combined effects of the involved variants on both expression and catalytic properties, the latter of which additionally depend on the substrate.

4.3. Subfamily CYP2C: CYP2C8, CYP2C9, CYP2C18, CYP2C19

4.3.1. Regulation and variability of gene expression

The human *CYP2C* subfamily consists of the four highly homologous genes *CYP2C18-CYP2C19-CYP2C9-CYP2C8* which are localized in this order (from centromere to telomere) in a ~390 kb gene cluster on chromosome 10q23.3. Although CYP2C18 mRNA is highly expressed in liver, the transcript is not efficiently translated into protein and does not make significant contributions to drug metabolism. CYP2C9 is the highest expressed member being expressed at similar or even higher protein levels compared to CYP3A4, while CYP2C8 and CYP2C19 are expressed at ~2-fold and 10-fold lower levels (Coller et al., 2002; Koukouritaki et al., 2004; Rettie & Jones, 2005; Naraharisetti et al., 2010; Ohtsuki et al., 2012). The dramatic expression difference between CYP2C9 and 2C19 was found to be at least in part due to the inability of the CYP2C19 promoter to be activated by HNF4α, despite the presence of similar HNF4α binding sites in both gene promoters (Kawashima et al., 2006). In addition to HNF4α, constitutive expression of the CYP2C genes in liver requires several other liver-enriched transcription factors including HNF3γ and C/EBPα (Chen & Goldstein, 2009) and the liver-enriched factor GATA-4 (Mwinyi et al., 2010b). All three expressed CYP2C enzymes are inducible by ligands of the PXR/CAR, glucocorticoid (GR) and vitamin D (VDR) nuclear receptor pathways through different response elements in their 5′-flanking regions (Chen & Goldstein, 2009; Jover et al., 2009; Helsby & Burns, 2012). However, the genes show different relative inducibility. CYP2C8 is the most strongly inducible member, e.g. by statins (Feidt et al., 2010). Although distal PXR/CAR binding sites have been identified, the precise reason for the high inducibility of CYP2C8 has not been elucidated. Maximal induction of CYP2C9 requires cross-talk between distal CAR/PXR sites and proximal HNF4α binding sites in the CYP2C9 promoter which may be mediated by a mega-complex of HNF4α-associated cofactors including PGC-1α, SRC-1, and NCOA6 (Jover et al., 2009). Recently regulation of CYP2C19 (Mwinyi et al., 2010a) and CYP2C9 (Mwinyi et al., 2011) transcription by estrogen receptor alpha (ERα)-ligands was shown to be mediated by newly discovered response elements at ~150 bp upstream of the transcriptional start site, probably contributing to the known inhibition of these enzymes by oral contraceptives.

In a humanized *CYP2C18/CYP2C19* transgenic mouse line only CYP2C19, but not CYP2C18 was expressed in liver to yield a catalytically active enzyme. Interestingly, adult male mice expressed much higher CYP2C18 and CYP2C19 mRNA levels in liver and kidney compared with female mice (Löfgren et al., 2009). This appears to reflect the generally more pronounced sex effects on expression in mice compared to humans. Sex differences of human CYP2C9 and CYP2C19 have been investigated in only a few studies which so far do not seem to support the existence of marked sex-biased activity (Gandhi et al., 2004). At lower levels functional CYP2C enzymes are also expressed in extrahepatic tissues, e.g. in human small intestine and in cardiovascular tissues (Delozier et al., 2007). Together with CYP3A, the CYP2Cs represent the major intestinal CYPs, accounting for ~80% and 18%, respectively, of total immunoquantified CYPs (Paine et al., 2006; Thelen & Dressman, 2009).

4.3.2. Role of CYP2C enzymes in drug metabolism

Given the strong relatedness in DNA and protein sequence (>82%) and common mechanisms of transcriptional regulation of the CYP2C enzymes, it is surprising how unique each enzyme is in terms of substrate specificity and role in drug metabolism (Table 3). The major enzyme CYP2C9 accepts weakly acidic substances including the anticoagulant warfarin, the anticonvulsants phenytoin and valproic acid, the angiotensin receptor blockers candesartan and losartan, oral antidiabetics like glibenclamide and tolbutamide, and most nonsteroidal anti-inflammatory drugs (NSAIDs; (Lee et al., 2002). Commonly used substrates for CYP2C9 phenotyping are diclofenac and tolbutamide. The CYP2C9 enzyme also metabolizes endogenous substances, in particular arachidonic acid and some steroids. The crystal structure of CYP2C9 has been resolved both unliganded and in complex with warfarin showing evidence for an additional substrate binding pocket (Williams et al., 2003). CYP2C9 is inhibited by several substances (Table 3) and this can be clinically important as in the case of warfarin treatment (Lu et al., 2008).

CYP2C8 is mainly responsible for the metabolism of the antidiabetics rosiglitazone and pioglitazone, the antiarrhythmic amiodarone, the natural anticancer drug paclitaxel, and the antimalarial amodiaquine, which is now commonly used as a selective marker activity. In addition to amodiaquine, CYP2C8 has a major role in metabolizing other antimalarials such as chloroquine and dapsone (Kerb et al., 2009). Additional drugs metabolized primarily by CYP2C8 include some retinoic acid drugs used in acne and cancer treatment. Some overlap in substrate specificity with CYP2C9 occurs, e.g. in the case of ibuprofen and others (Table 3; Goldstein, 2001; Lai et al., 2009). The clinical significance of CYP2C8 inhibition became apparent after its involvement in fatal drug interactions was described, which were in part due to its potent inhibition by gemfibrozil acyl-glucuronide, ultimately leading to rhabdomyolysis (Backman et al., 2002; Ogilvie et al., 2006). Additional potent CYP2C8 inhibitors at clinically relevant concentrations have meanwhile been described (Lai et al., 2009).

CYP2C19 was the first CYP2C enzyme to be discovered by its marked genetic polymorphism resulting in the *S*-mephenytoin PM and EM phenotypes (Küpfer & Preisig, 1984). The CYP2C19 enzyme was later shown to be the major enzyme for the inactivating metabolism of proton pump inhibitors (PPI) including omeprazole and pantoprazole, and for the metabolic activation of the anticoagulant clopidogrel to the active 2-oxo metabolite (Hulot et al., 2006; Kazui et al., 2010; Dansette et al., 2011; Boulenc et al., 2012). CYP2C19 has also a prominent role in the metabolism of several antidepressants of the first and second generation (Brøsen, 2004). Endogenous substrates of CYP2C19 include progesterone and melatonin (Table 3).

4.3.3. Genetic polymorphisms and functional impact

4.3.3.1. CYP2C8. Apart from rare variants with no (*5, *7), reduced (*8) or unknown activity, three alleles with amino acid changes, *CYP2C8*2* and **3* (Dai et al., 2001), and **4* (Bahadur et al., 2002) are more common and have potential clinical relevance (Table 1). *CYP2C8*2* [I269F] has been found practically only in Africans and African Americans at frequencies of ~10 to 22%. Slower conversion of the antimalarial drug amodiaquine to its metabolite *N*-desethylamodiaquine (DEAQ) in carriers of CYP2C8*2 has been reported (Li et al., 2002; Parikh et al., 2007). The heterologously expressed 2C8.2 variant had 2-fold lower intrinsic clearance for paclitaxel due to increased Km. *CYP2C8*3* [R139K + K399R] occurs more frequently in white subjects but is almost absent in Africans and Asians. The CYP2C8.3 variant was initially shown to have reduced metabolic activity toward arachidonic acid (~40%) and paclitaxel (~80%) (Dai et al., 2001). A more recent comparison of protein variants expressed in yeast revealed lower activity of 2C8.2, 2C8.3 and 2C8.4 and altered IC50 values towards inhibitors compared to 2C8.1 (Gao et al., 2010). Some functional effects of *CYP2C8*3* appear to be substrate dependent, e.g. for repaglinide and rosiglitazone higher metabolic capacity of this variant was observed (Daily & Aquilante, 2009). Similarly, a recent study showed 40% increased activity with pioglitazone as substrate of liver microsomes genotyped as *CYP2C8*3/*3* compared to **1/*1* (Muschler et al., 2009).

A point of concern is that there is significant linkage disequilibrium (LD) between the *CYP2C* gene polymorphisms, due to their close distances. In particular *CYP2C8*3* is in partial LD to *CYP2C9*2*, which may account in part for the association between *CYP2C8*3* and *CYP2C9*2* and **3* alleles with reduced clearance of ibuprofen (Garcia-Martin et al., 2004). CYP2C8 pharmacogenetics has recently been reviewed (Daily & Aquilante, 2009).

4.3.3.2. CYP2C9. Among the 35 distinct alleles listed on the CYPalleles website, the initially discovered alleles **2* [R144C] and **3* [I359L] are the best investigated ones (Goldstein, 2001; Rettie & Jones, 2005). The global MAFs of two variants are ~7% and ~4%, respectively, but their frequency in African and Asian populations is generally low, whereas **2* is present in >10% in some Caucasian populations (Table 1). The replacement of the positively charged arginine by cysteine in the 2C9.2 variant appears to affect the interaction of the protein with POR (Crespi & Miller, 1997). Expressed mutant CYP2C9.2 and CYP2C9.3 proteins have reduced intrinsic clearance, although the degree of activity reduction appears to depend on the particular substrate. For example, the Vmax/Km values of yeast-expressed 2C9.1 and 2C9.2 variants for seven different substrates including diclofenac, tolbutamide and piroxicam varied from 3.4-fold to 26.9-fold (Takanashi et al., 2000). The 359Leu variant had higher Km values than did the wild-type for all the reactions studied. Remarkably, the widely used marker substrate diclofenac was not a sensitive substrate to detect the **2/*3* activity difference either in this study or in vivo (Shimamoto et al., 2000). Compared to the **2* allele the **3* allele is more severely affected in its activity which can be 70–90% reduced for some substrates. In vivo, this results in clearance reductions of more than 70% in **3/*3* homozygotes and in about half of the clearance for heterozygotes. Other more rare alleles with decreased function include **5*, **6*, **8*, and **11*, although **8* was recognized as the most frequent *CYP2C9* variant among African Americans (Scott et al., 2009). Promoter variants may contribute to expression variability as shown in a study which resequenced the upstream region and investigated numerous known and novel variants using a reporter gene assay (Kramer et al., 2008). On the other hand a large resequencing study in 400 Chinese subjects identified only 3 novel variants of unknown functional significance, indicating that probably most of the genetic variation in *CYP2C9* is already known, at least among Asians (Xiong et al., 2011).

4.3.3.3. CYP2C19. The *CYP2C19* or "S-mephenytoin polymorphism" was discovered during the early 1980s and was since then established as one of the clinically most relevant P450 polymorphisms (Küpfer & Preisig, 1984; Wrighton et al., 1993; De Morais et al., 1994a; Meyer & Zanger, 1997; Goldstein, 2001; Rosemary & Adithan, 2007). The existence of fairly common null alleles explains the large variability and strong phenotype–genotype correlations found for *CYP2C19*. About 2 to 5% of white and black populations but up to ~25% of Asians are CYP2C19 PMs (Table 1). The two most important null alleles are *CYP2C19*2*, which occurs almost exclusively in Caucasians, and *CYP2C19*3*, which occurs primarily in Asians. The causal mutation of **2* is located in exon 5 and leads to aberrant splicing (De Morais et al., 1994b), whereas that of **3* in exon 4 creates a premature stop codon (De Morais et al., 1994a). A further clinically relevant variant is the promoter variant −806C>T (**17*) which appears to increase expression and activity toward mephenytoin and omeprazole by a still unclear mechanism (Sim et al., 2006). Additional rare null alleles *CYP2C19*4–*8* and variants with unknown phenotypic penetrance are listed on the CYPalleles nomenclature website.

4.3.4. Clinical impact of genetic variation

4.3.4.1. CYP2C8. Drug interaction studies support the importance of CYP2C8 for the hypoglycemic agent repaglinide. However, the impact of *CYP2C8* pharmacogenetics on repaglinide pharmacokinetics and clinical consequences is unclear. Some pharmacokinetic studies reported that individuals heterozygous for *CYP2C8*3* showed higher drug clearance and up to 60% lower plasma levels of repaglinide compared with *CYP2C8*1* carriers (Niemi et al., 2003; Rodríguez-Antona et al., 2008). Recently, a healthy volunteer study indicated that *CYP2C8*3* did not affect the pharmacokinetics as well as pharmacodynamic parameters like changes in insulin and glucose concentration of repaglinide (Tomalik-Scharte et al., 2011). Confounding by genetic variants of the organic anion transporting polypeptide 1B1 (SLCO1B1), which mediates the uptake of repaglinide into cells, could be excluded in this study. *CYP2C8* variants were reported to moderately alter pharmacokinetics and effects of PPAR-γ agonists such as rosiglitazone and pioglitazone (Kirchheiner et al., 2006; Tornio et al., 2008; Yeo et al., 2011) but this contention is also controversially discussed by others (Pedersen et al., 2006).

The same conclusion is true for the anticancer drug paclitaxel frequently used in treatment of women with ovarian or breast cancer (Henningsson et al., 2005; Bergmann et al., 2011a, 2011b; Leskelä et al., 2011). Whether subjects carrying CYP2C8 variants are at increased risk of amodiaquine-related severe ADRs is also still a matter of discussion (Kerb et al., 2009).

4.3.4.2. CYP2C9. Genetic variation in *CYP2C9* is a recognized factor for ADRs as many of its drug substrates have a narrow therapeutic index. Numerous studies demonstrated the clinical significance of the *CYP2C9*2* and **3* polymorphisms for most drug substrates mentioned above. Due to their common occurrence in Caucasians, there are about 1 to 2% of homozygous (**2/*2*, **3/*3*) and hemizygous (**2/*3*) carriers that are at risk to experience more dramatic effects, but even for the heterozygous carriers higher incidence of ADRs were reported. This includes, for example, hypoglycaemia as a result from treatment with hypoglycaemic drugs (Holstein et al., 2005; Xu et al., 2009), gastrointestinal bleeding from NSAIDs (see below) and serious bleedings from anticoagulant treatment. Vitamin K antagonists such as warfarin, acenocoumarol, and phenprocoumone are commonly used to prevent thrombosis in several situations. The anticoagulant warfarin is probably the most thoroughly studied clinical application of *CYP2C9* pharmacogenetics. In addition to the vitamin K epoxide reductase complex subunit 1 (*VKORC1*), variants of *CYP2C9* affect warfarin dosing and response (Jonas & McLeod, 2009). However its contribution to anticoagulant response is rather low. In a study of 539 white patients on steady-state warfarin therapy 9% of variability in warfarin dose could be explained by *CYP2C9* variants, compared to 25% by variants of *VKORC1* (Rieder et al., 2005). Between 50 and 60% of the variability in maintenance dose of warfarin in Caucasians could be explained by variants of *CYP2C9* and *VKORC1* in combination with other patient factors (e.g. body size, age; (Klein et al., 2009). Different distribution of *CYP2C9* and *VKORC1* variants as a function of ancestry resulted in highest dose requirement of warfarin in Africans compared to Asians requiring lowest doses. In 2007 pharmacogenetic information on *CYP2C9* and *VKORC1* genetic polymorphisms as a predictor of response was included in the warfarin labeling by the FDA, and was revised in 2010 to include specific dosing recommendations. Currently various pharmacogenetics-guided warfarin dosing algorithms are available (Jonas & McLeod, 2009; Schwab & Schaeffeler, 2011). Interindividual dosage variation for the anticoagulants acenocoumarol (Teichert et al., 2009) and phenprocoumon (Teichert et al., 2011) has also been associated with *CYP2C9* genotype at genome-wide significance.

The influence of *CYP2C9* polymorphisms on the metabolism of first- and second generation sulfonylurea hypoglycaemic drugs (e.g., glibenclamide, tolbutamide, glyburide, glimepiride) has been well-established by several studies with consequences on pharmacokinetics and in part on therapeutic response (e.g., HbA1C decrease, secondary failure of therapy, hypoglycemic events; (Manolopoulos et al., 2011). For example, type 2 diabetes mellitus patients responded

better to treatment with glibenclamide when they had variant alleles of *CYP2C9* as compared to those with normal genotype (Surendiran et al., 2011).

CYP2C9 polymorphism affects the metabolism of several NSAIDs, which is of increasing importance in aging populations, due to dose-dependent ADRs (He et al., 2011). Association of NSAID exposure and risk for gastrointestinal bleeding with *CYP2C9* genetic variants has been reported by several studies (Pilotto et al., 2007; Carbonell et al., 2010). However, due to limited data available and the fact that the published studies show substantial methodological limitations current evidence is still controversial (Estany-Gestal et al., 2011).

Finally, the fact that CYP2C9 catalyzes arachidonic acid epoxygenation and that it is expressed in endothelial cells suggested a role in ischemic heart disease and vascular homeostasis (Chehal & Granville, 2006). However in three independent studies totaling more than 52,000 individuals, no association between *CYP2C9*2* and *3* polymorphisms and risk of atherosclerosis, ischemic vascular disease or death after ischemic heart disease was found (Kaur-Knudsen et al., 2009a).

4.3.4.3. CYP2C19. The clinical significance of *CYP2C19* has been extensively documented (Goldstein, 2001; Desta et al., 2002; Furuta et al., 2007; Rosemary & Adithan, 2007; Lee, 2013). The effect of the *CYP2C19* polymorphism on *H. pylori* eradication therapy in patients with ulcers is a special but intriguing example of clinical pharmacogenetics (Furuta et al., 2004; Klotz, 2006). The common eradication strategy involves application of different antibiotics (e.g., amoxicillin, clarithromycin, metronidazole), together with a proton pump inhibitor, which contributes to accelerated ulcer healing and increases effectiveness of the antibiotics. Since CYP2C19 contributes significantly to the metabolism of the PPIs omeprazole, lansoprazole, and pantoprazole and to minor extent to the metabolism of rabeprazole, pharmacokinetics, the PPI-induced increase in intragastric pH and treatment outcome depend on *CYP2C19* genotype (Furuta et al., 1998; Klotz et al., 2004; Furuta et al., 2007). For instance, PM subjects showed 4- to 15-fold increased AUC values for omeprazole and lansoprazole compared with EMs resulting in significantly higher *H. pylori* eradication rates compared to EMs. Accordingly, the PPI-induced increase in intragastric pH depends on the *CYP2C19* polymorphism. In several studies with PPI based dual, triple and quadruple therapy in Asia and Europe it was shown that PM subjects benefit from their lower metabolism rate because their drug levels stay higher for a longer time resulting in a stronger acid inhibition and higher intragastric pH (Furuta et al., 2007; Yang & Lin, 2010). Since PPI are used also for the treatment of non-ulcer dyspepsia, reflux oesophagitis, gastroesophageal reflux disease (GERD), the Zollinger–Ellison syndrome, and prevention and treatment of NSAID-associated damage, healing rates of these diseases are also impacted by *CYP2C19* genotype (Schwab et al., 2004, 2005). The *CYP2C19* PM genotype does however not appear to be a risk factor for omeprazole-associated visual disorders (Lutz et al., 2002).

Pharmacokinetic effects associated with *CYP2C19* genotype have also been reported for several antidepressants, including clomipramine (Nielsen et al., 1994), citalopram (Tai et al., 2002), amitriptyline (Steimer et al., 2005), moclobemide (Yu et al., 2001), as well as for benzodiazepines like diazepam (Bertilsson et al., 1989) and clobazam (Kosaki et al., 2004). Moreover, the *CYP2C19* gene has substantial impact on the pharmacokinetics of the antifungal agent voriconazole and its interaction with other drugs (Mikus et al., 2011) and of the antimalarial drug proguanil (Kerb et al., 2009). Although pharmacokinetic alterations were sometimes related to ADRs, an influence of *CYP2C19* genotype on clinical pharmacodynamic outcome for most of these drugs remains so far controversial.

Important recent studies investigated *CYP2C19* as a genetic determinant of the efficacy of the platelet aggregation inhibiting thienopyridine, clopidogrel (Plavix). Both, treatment and prevention of atherothrombotic events after percutaneous coronary revascularization in patients with coronary artery disease with clopidogrel is complicated because a significant proportion of patients is resistant and experiences insufficient platelet inhibition resulting in cardiovascular (re-)events including stent thrombosis (Zuern et al., 2010). Numerous clinical studies have confirmed that *CYP2C19* PMs have significantly lower anticoagulation effect of clopidogrel, which is associated with an increased risk of major adverse cardiovascular events (Collet et al., 2009; Mega et al., 2009; Simon et al., 2009; Sofi et al., 2011). Already in 2009, the FDA added a *Boxed Warning* to the label for Plavix alerting patients and health care professionals that the drug can be less effective in genetically determined *CYP2C19* PMs. However, recent meta-analyses drew an inconsistent picture. No significant or consistent influence of *CYP2C19* genotype on the clinical efficacy of clopidogrel was found in one analysis (Bauer et al., 2011), association with clopidogrel metabolic concentration and platelet reactivity responsiveness but no overall association with cardiovascular events in another one (Holmes et al., 2011), while the most recent study, which analyzed 16 clinical studies, confirmed significant associations with major cardiovascular endpoints, i.e. increased risk of cardiac death, myocardial infarction, and stent thrombosis (Jang et al., 2012).

Several clinical studies investigated the clinical impact of the gain-of-function allele *CYP2C19*17* (Zabalza et al., 2011). With clopidogrel, no association with platelet aggregation was found (Geisler et al., 2008) while another study reported increased risk of bleeding events (Sibbing et al., 2010). The homozygous *17/*17 genotype has been found to accelerate omeprazole metabolism resulting in subtherapeutic drug exposure (Baldwin et al., 2008). In another example, homozygous *CYP2C19*17* genotype was associated with lower serum concentration of escitalopram, which might imply an increased risk of therapeutic failure (Tai et al., 2002). Moreover, treatment outcome of tamoxifen in postmenopausal breast cancer women has been associated with the *CYP2C19*17* allele, although the magnitude of effect appears to be considerably smaller compared to loss of function alleles (Schroth et al., 2007; Li-Wan-Po et al., 2010). However, not all studies have identified a significant effect of *CYP2C19*17* (Kurzawski et al., 2006; Ohlsson Rosenborg et al., 2008).

4.4. Subfamily CYP2D: CYP2D6

4.4.1. Regulation and variability of gene expression

CYP2D6 is the only protein-coding gene of the *CYP2D* subfamily. The *CYP2D* locus on chromosome 22q13.1also harbors two pseudogenes, *CYP2D7* and *CYP2D8P* (Kimura et al., 1989; Heim & Meyer, 1992). *CYP2D7* is expressed as mRNA in liver (Endrizzi et al., 2002), but the presence of an insertion in the first exon disrupts the reading frame, preventing expression of protein. In contrast, *CYP2D8P* is a true pseudogene which has accumulated several gene-disrupting mutations. Because *CYP2D6* is considered to be essentially a noninducible gene not significantly influenced by smoking, alcohol consumption or sex (Bock et al., 1994; Glaeser et al., 2005), its transcriptional regulation has not been studied very thoroughly. It should be mentioned, however, that phenotypically determined induction by rifampicin in vivo was reported (Caraco et al., 1997). An initial promoter analysis revealed the presence of a positive DR-1 element which bound and responded to HNF4α which was antagonized by COUP-TF-I. It was concluded that the balance between HNF4α and COUP-TF-I may contribute to expression variability (Cairns et al., 1996). HNF4α also mediates downregulation of CYP2D6 during inflammation by nitric oxide through the same proximal DR-1 site (Hara & Adachi, 2002). The regulation of CYP2D6 by HNF4α was further investigated in a CYP2D6-humanized transgenic mouse line which expressed CYP2D6 protein in the liver, intestine, and kidney (Corchero et al., 2001). Conditional inactivation of the HNF4α gene in this mouse line decreased debrisoquine 4-hydroxylase activity by more than 50% demonstrating that HNF4α regulates CYP2D6 activity in vivo. The influence of HNF4α on CYP2D6 activity in vivo was further shown in a recent population-based polymorphism study which showed that the rare HNF4α variant G60D was unable to bind and activate the CYP2D6 promoter (Lee et al., 2008b).

Hepatic *CYP2D6* protein content varies dramatically from person to person mainly due to its genetic polymorphism (Zanger et al., 2001). A recent quantitative comparison of hepatic CYP2D6 protein by Western blot and mass spectrometric analysis demonstrated comparability of the results which ranged from undetectable in genetic PMs up to ~70 pmol/mg of microsomal protein in carriers of three alleles (Langenfeld et al., 2009). *CYP2D6* and the *CYP2D7* pseudogene are found at low mRNA levels in most extrahepatic tissues (Table 2), and expression of protein has been shown in the gastrointestinal tract (Glaeser et al., 2005) and in different areas of the human brain (Table 2; Siegle et al., 2001; Miksys et al., 2002; Gaedigk et al., 2005; Dutheil et al., 2009; Ferguson & Tyndale, 2011). At the RNA level, CYP2D6 expression is characterized by the occurrence of numerous splice variants. However, with the exception of the effect of polymorphic splice variants (see below) the functional significance of alternative splicing of CYP2D6 pre-mRNA has not been clarified. In foetal liver CYP2D6 is virtually undetectable but expression surges within hours after birth (Cresteil, 1998). Investigation of CYP2D6 and CYP3A4 activity in healthy infants by using dextromethorphane as probe drug revealed that the CYP2D6-dependent *O*-demethylation activity was detectable and concordant with genotype by 2 weeks of age and showed no relationship with gestational age, whereas the CYP3A4-dependent *N*-demethylation developed more slowly over the first year of life (Blake et al., 2007). In a large (n = 222) set of pediatric liver samples it was found that gestational age influenced CYP2D6 protein expression and activity in prenatal samples whereas postnatal samples were influenced by age and genotype (Stevens et al., 2008).

4.4.2. Role of CYP2D6 in drug metabolism

The number of drugs metabolized primarily by CYP2D6 is very large in comparison to its relatively minor expression in liver and includes ~15–25% of all clinically used drugs from virtually all therapeutic classes, like antiarrhythmics (e.g. propafenone, mexiletine, flecainide), tricyclic and second generation antidepressants (e.g. amitriptyline, paroxetine, venlafaxin), antipsychotics (aripiprazole, risperidone), β-blockers (bufuralol, metroprolol), as well as anti-cancer drugs, in particular the selective estrogen receptor modifier (SERM) tamoxifen, several opioid analgesics including codeine and tramadol, and many others (Table 3; Zanger et al., 2008; Stingl et al., 2012). Several highly selective test drugs have been used to determine the CYP2D6 drug oxidation phenotype, including debrisoquine, dextromethorphan, metoprolol, sparteine, and tramadol (Frank et al., 2007). Endogenous biotransformations include 5-methoxyindolethylamine O-demethylase (Yu et al., 2003a) and regeneration of serotonin from 5-methoxytryptamine (Yu et al., 2003b). CYP2D6 is also prone to inhibition by numerous compounds that need not be substrates but bind to the enzyme with high affinity, e.g. quinidine or methadone (Gelston et al., 2012; Table 3). Some of these inhibitors are strong enough to change the apparent phenotype of the patient, a phenomenon known as phenocopying. The structure–activity relationships for CYP2D6 substrates and inhibitors were useful to develop pharmacophore models (Lewis et al., 2004). The crystal structure of the CYP2D6 protein has been resolved yielding further insights into the active site and the chemical requirements for binding and catalysis (Rowland et al., 2006).

4.4.3. Genetic polymorphisms and functional impact

The *CYP2D6* polymorphism is historically the best studied and one of the most intriguing examples of pharmacogenetics. *CYP2D6* shows the greatest impact of genetic polymorphism among all major drug metabolizing CYPs, due to its wide spectrum of genetic variants (from null alleles to several-fold gene amplification), comparably little influence by environmental and nongenetic factors, and its extraordinarily broad substrate spelectivity. Initial evidence for *CYP2D6* genetic polymorphism came from population and family pharmacokinetic studies in the 1970's which showed that deficient debrisoquine 4-hydroxylation (Mahgoub et al., 1977) and sparteine *N*-oxidation (Eichelbaum et al., 1979) occurs in 5 to 10% of European Caucasians as a monogenic recessive trait later shown to be the same for the two drugs and for many others that are polymorphically metabolized. In ethnicities other than Caucasian the deficiency occurs at much lower frequency (Gaedigk, 2000). The molecular studies that followed were reviewed previously (Meyer & Zanger, 1997; Zanger et al., 2004; Ingelman-Sundberg, 2005). Currently 105 distinct alleles and a large number of allele variants are listed on the CYPalleles website, many of them leading to absent or nonfunctional protein, or to decreased or increased expression (Table 1). Genotype–phenotype correlation analysis studies in Caucasians phenotyped with the probe drugs sparteine or debrisoquine have clearly demonstrated the impact of genetic polymorphism on CYP2D6 function in vivo (Fig. 2; Sachse et al., 1997; Griese et al., 1998; Raimundo et al., 2004).

In Caucasians the most frequent null alleles are the *CYP2D6*4* alleles, which all harbor a consensus splice site mutation (1846G>A) that leads to absence of detectable protein in the liver. The collective *CYP2D6*4* allele frequency among Caucasians is about 20 to 25%, accounting for 70 to 90% of genetically determined PMs (Sachse et al., 1997; Griese et al., 1998). The virtual absence of the **4* allele in Asian, African, and South American populations explains the low incidence of the PM phenotype in these populations, whereas African-Americans have an intermediate frequency. The *CYP2D6* gene deletion allele **5* is present at a frequency of 3 to 5% in most populations. The null alleles **3* and **6* are present at frequencies of ~1–3% in Caucasians whereas most other null alleles are even rarer. Nevertheless, collectively the low frequency alleles make a significant contribution to phenotype. Heterozygous carriers of one defective and one normal allele of *CYP2D6* tend to have a lower median enzyme activity, which is overlapping with that of carriers of two functional alleles (Fig. 2).

A separate phenotype model has been termed intermediate metabolizer (IM), which occurs in all major races, but interestingly the causative mutations are different. About 10 to 15% of Caucasians are carriers of one partially defective allele (e.g. **41*, **9*, **10*) in combination with another partially defective or null allele such as **4*, resulting in a distinct phenotypic subgroup with compromised sparteine oxidation capacity (Fig. 2). The mechanism of the **41* allele, which is more common among Caucasians, has been studied in detail and an intron 6 SNP that leads to erroneous splicing resulting in only a fraction of correctly spliced mRNA has been shown to be responsible for the low activity in vitro and in vivo (Toscano et al., 2006). In Africans and Asians other partially defective alleles termed **17* and **10*, respectively, are prevalent. The **17* allele is present at frequencies of up to 30% in Africans (Wennerholm et al., 2002) and the **10* variant occurs at up to 50% in Asians (Sakuyama et al., 2008). Due to their high frequencies, the partial activity conferred by these alleles leads to a shift of the metabolic drug oxidation capacity towards lower values which has clinical relevance (Kitada, 2003).

A large number of structural variations exists at the *CYP2D* locus (Schaeffeler et al., 2003; Gaedigk et al., 2010). Unequal crossing over between the highly homologous genes involving a certain repetitive sequence also present in the *c-myc* gene lead to variants with deleted, duplicated, or otherwise recombined genes. *CYP2D6* gene duplications were first identified in combination with the functional **2* allele (Bertilsson et al., 1993; Johansson et al., 1993; Johansson & Ingelman-Sundberg, 2008) and later shown to occur also with other alleles including **1*, **4*, **6*, **10*, **17*, **29*, **35*, **41*, **43*, **45*. This is important because not all duplications comprise functional genes, which complicates phenotype prediction (Schaeffeler et al., 2003; Gaedigk et al., 2012). The overall frequency of the gene duplications in Caucasians is between 1 and 5% whereas in some Arabian, Eastern African and Pacific populations it can reach 10 and even up to 50% and more. It was hypothesized, therefore, that the striking preference of CYP2D6 for plant alcaloids found in food of some of these ethnicities

may play a role in recent selection processes (Ingelman-Sundberg, 2005).

The presence of the pseudogenes, structural variants, and numerous SNPs at the *CYP2D* locus requires particular cautiousness in the design of genotyping assays. Coamplification of pseudogenes, unexpected recombination events, and failure to account for important variants, for example due to ethnic variation can lead to erroneous interpretation of genotype. Numerous genotyping assays and strategies were developed which, due to the complexity of variants, usually identify only one functionally dominant key mutation per allele. This possibly reduces the predictive power of genotyping for certain haplotypes. The most comprehensive commercially available platform for *CYP2D6* genotyping is the AmpliChip CYP450 test from Roche. This microarray has probes to identify 33 CYP2D6 alleles, including most confirmed variants responsible for absent or impaired enzyme activity and seven gene duplications, as well as two *CYP2C19* variant alleles (Jain, 2005; de Leon et al., 2009; Rebsamen et al., 2009).

4.4.4. Clinical impact of genetic variation

Numerous clinical studies document the clinical importance of the CYP2D6 polymorphism for response and/or ADRs to agents that are either inactivated or activated by this enzyme.

Several antiarrhythmic drugs including metoprolol, timolol, propafenone and others are metabolically inactivated by CYP2D6, leading to increased exposure and risk of adverse events for PMs/IMs, although clinical effects are still controversial (Fux et al., 2005; Darbar & Roden, 2006; Klotz, 2007; Mörike et al., 2008; Bijl et al., 2009; Rau et al., 2009). Many antidepressants and antipsychotics are substrates of CYP2D6 (Table 3) and oxidative metabolism usually leads to their inactivation and consequently a risk of overexposure in PMs/IMs and underexposure in UMs. Studies on clinical effects have however not been unanimous, in part due to inherently problematic dosing of these drugs. The area has been extensively reviewed (Kirchheiner et al., 2004; Bertilsson, 2007; Crisafulli et al., 2011; Stingl et al., 2012).

Several opioid drugs including codeine, dihydrocodeine, oxycodone, and tramadol used in pain management are metabolically activated by CYP2D6 and genotype was shown to affect their efficacy and safety (Stamer et al., 2010; Leppert, 2011; Madadi et al., 2012). The prodrug codeine is *O*-demethylated by CYP2D6 to the pharmacologically active analgesic morphine. In *CYP2D6* PMs there is no analgesic effect due to extremely low morphine plasma concentrations (Eckhardt et al., 1998). Conversely, increased effectiveness of codeine with sometimes life-threatening opioid intoxication was observed in patients with multiple CYP2D6 gene copies but also in neonates whose breastfeeding mothers were genetic *CYP2D6* UMs, consistent with higher rates of conversion to morphine in patients with UM phenotype (Gasche et al., 2004; Koren et al., 2006; Madadi et al., 2009). This scenario of morphine intoxication of neonates including further glucuronidation via UGT2B7 has been the subject of a computerized quantitative modeling study (Willmann et al., 2009). The physiologically based pharmacokinetic model was able to simulate the accumulation of morphine in the plasma of neonates during maternal codeine intake for different genotypes and to identify risk factors.

The selective estrogen receptor modulator (SERM) tamoxifen is extensively metabolized into at least 22 metabolites, two of which, 4-hydroxytamoxifen and the secondary metabolite endoxifen, are thought to be mainly responsible for the antiestrogenic effect because of their high affinity to the estrogen receptor (Johnson et al., 2004; Mürdter et al., 2011b). Because CYP2D6 is the major enzyme for the crucial 4-hydroxylation (Dehal & Kupfer, 1997; Coller et al., 2002; Johnson et al., 2004), *CYP2D6* genotype should be expected to influence plasma concentrations of these active metabolites and hence treatment outcome, with patients having functionally impaired CYP2D6 producing lower levels of active metabolites and thus profiting less from the treatment compared to patients with active enzyme (Brauch et al., 2009). This hypothesis has been scrutinized over the past decade, and initial retrospective studies found indeed that *CYP2D6* PMs show less benefit from adjuvant treatment of post-menopausal breast cancer with tamoxifen monotherapy (Goetz et al., 2007; Schroth et al., 2007). However, while several more recent studies confirmed an association of *CYP2D6* PM genotype with worse outcome (Schroth et al., 2009; Kiyotani et al., 2010; Madlensky et al., 2011) or demonstrated a beneficial therapeutic effect of genotype-guided treatment (Irvin et al., 2011; Kiyotani et al., 2012), other studies found no (Rae et al., 2012; Regan et al., 2012) or inconsistent allele-specific effects (Abraham et al., 2010). Possible explanations for inconsistent results include a number of confounding factors that have not been taken into account systematically, including previous chemotherapy, enzyme inhibition due to co-medication, menopausal status, but also differences in genotyping quality like limited *CYP2D6* allele coverage or use of tumor instead of germline DNA for genotyping (see discussion comments by Brauch et al., 2013; Nakamura et al., 2012; Pharoah et al., 2012; Stanton, 2012). Despite existing evidence, well-planned prospective studies seem to be inevitable to clarify the real value of CYP2D6 predictive genotyping for clinical utility.

A recent study investigated the chemically related SERM clomiphene, chemically closely related to tamoxifen, which is used as first line infertility treatment in women. Like tamoxifen, clomiphene is a prodrug and requires bioactivation by 4-hydroxylation. CYP2D6 was shown to be the key enzyme in the conversion of clomiphene to its active metabolites (E)-4-hydroxy-clomiphene and (E)-4-hydroxy-desethyl-clomiphene by human liver microsomes (Ghobadi et al., 2008; Mürdter et al., 2011a). A strong gene-dose effect was found for the formation rate of both metabolites in microsomes and in a pharmacokinetic study including healthy women genotyped for CYP2D6. Furthermore, both metabolites were shown to mediate clomiphene action through oestrogen receptor binding. Clinical studies are therefore warranted to prove the validity of *CYP2D6* genetics for individualization of clomiphene therapy in infertility.

In addition the gene has been studied as a risk factor for numerous diseases. Most of the epidemiological studies revealed conflicting results concerning pharmacogenetic association and the reader is referred to specialized articles, for example, regarding Parkinson's disease (Christensen et al., 1998), schizophrenia and other psychiatric diseases (Patsopoulos et al., 2005; Stingl et al., 2012), Alzheimer's disease (Scordo et al., 2006), and several forms of cancer (Agundez, 2004; Rodriguez-Antona et al., 2010).

4.5. Subfamily CYP2E: CYP2E1

4.5.1. Regulation and variability of gene expression

CYP2E1 is the only gene of the *CYP2E* subfamily located at chromosome 10q26.3. Its expression is undetectable in fetal liver. Within several hours after birth protein and activity rise considerably but independently of mRNA which remains quite low (Vieira et al., 1996). Stabilization of CYP2E1 protein by ketone bodies could explain the early neonatal rise at the protein level. During the following periods from one month to one year, accumulation of CYP2E1 mRNA is correlated with the methylation status of CpG residues in the 5′ flanking region. Transcriptional activators suggested to participate in the regulation of CYP2E1 expression include HNF1α and β-catenin (Gonzalez, 2007). Expression in liver is rather high (Table 2) and variability of CYP2E1 protein between individuals appears to be considerable and correlated to catalytic activity (Ohtsuki et al., 2012; Tan et al., 2001). One study reported one third greater clearance values for the probe drug, chlorzoxazone, in males compared to females (Kim & O'Shea, 1995). CYP2E1 transcript levels are not well or not at all correlated to protein, and this has been suggested

to be the consequence of strong regulation via translational repression by miR-378 (Mohri et al., 2010).

The CYP2E1 enzyme is inducible by many of its substrates (Table 3) as well as several hormones by complex mechanisms involving transcriptional, translational and posttranslational effects (Gonzalez, 2007). In humans induction by ethanol was shown to involve increased transcription which primarily takes place in perivenous hepatocytes (Takahashi et al., 1993). Significant and rapid induction of CYP2E1 activity was shown to occur already at moderate alcohol consumption which was rapidly reversed following alcohol withdrawal (Oneta et al., 2002). CYP2E1 is furthermore induced under diverse pathophysiological conditions including diabetes, obesity, fasting, alcohol and non-alcoholic liver disease where it is believed to play a pathophysiological role (Caro & Cederbaum, 2004; Aubert et al., 2011). Extrahepatic expression of CYP2E1 has been found at lower levels in brain, nasal mucosa, kidney cortex, testis, ovaries, the gastrointestinal tract and at somewhat higher levels in cardiac tissue (Lieber, 1997; Joshi & Tyndale, 2006; Thelen & Dressman, 2009; Michaud et al., 2010; Ferguson & Tyndale, 2011).

4.5.2. Role of CYP2E1 in drug metabolism and toxicology

CYP2E1 displays a substrate preference for low molecular weight molecules, including ethanol, acetone and other organic solvents, narcotics like halothane, and some drugs including chlorzoxazone and paracetamol (Table 3). Many known industrial chemicals and occupational and environmental toxicants as well as procarcinogens are also CYP2E1 substrates (Bolt et al., 2003; Lu & Cederbaum, 2008). Endogenous substrates of CYP2E1 are lauric acid and acetone, a product of fatty acid oxidation, which is oxidized to acetol and further to 1,2-propanediol in the propanediol pathway of gluconeogenesis. The role of CYP2E1 in ethanol oxidation depends on the conditions. The major enzyme for ethanol oxidation to acetaldehyde is alcohol dehydrogenase (ADH), whereas CYP2E1 plays a more important role at elevated concentrations and after chronic consumption due to induction (Caro & Cederbaum, 2004).

An important feature of ethanol oxidation via CYP2E1 is the generation of reactive oxygen species (ROS) which contributes to damage of liver cells. CYP2E1 is an effective generator of ROS such as the superoxide anion radical and hydrogen peroxide as a result of uncoupling of oxygen consumption with NADPH oxidation (Caro & Cederbaum, 2004). The fact that significant levels of CYP2E1 are located within the mitochondria could contribute further to its deleterious effects (Knockaert et al., 2011). A number of studies therefore implicated CYP2E1 as a causative player in alcoholic liver disease as well as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) probably through enhancement of hepatic lipid peroxidation (Cederbaum, 2006; Aubert et al., 2011). Furthermore, chronic alcohol consumption has been recognized as a major risk factor for esophageal cancer, probably due to carcinogenic and genotoxic effects of acetaldehyde and oxidative stress (Wang et al., 2009; Millonig et al., 2011).

4.5.3. Genetic polymorphisms and pharmacogenetics

The CYPalleles website lists only 7 distinct *CYP2E1* star-alleles and few variants compared to other *CYP2* genes, and for none of them could an important functional impact be demonstrated. Some studies suggested effects on expression for several 5′-upstream region polymorphisms, including an insertion of several repeats (*CYP2E1*1D*; McCarver et al., 1998) and polymorphic PstI (−1293G>C) and Rsa I (−1053C>T) sites (Neafsey et al., 2009; Tan et al., 2001). The latter two polymorphisms occur together on alleles **5A* and**5B*, the latter of which lacks an additional nucleotide change in intron 6 (7632T>A), which can be detected as a *DraI* RFLP. *CYP2E1*5A* has an approximate frequency 5% in Caucasians and up to 38% in Asians, whereas **5B* appears to be present only in Asians at ~2 to 8% frequency. Only few coding-region variants have been reported with little or no impact on enzyme function. A recent study analyzed 11 polymorphisms and their haplotypes in over 2600 individuals from population samples representing the major geographical regions of the world (Lee et al., 2008a). Similar to other genetic loci, *CYP2E1* haplotype diversity was much higher among African populations (6–10 common haplotypes) than in other parts of the world (about 1–6 common haplotypes).

Because of the particular relevance of CYP2E1 for toxicology due to its role in the metabolic activation of procarcinogens and chemical carcinogenesis, pharmacogenetic studies mostly focused on association with various cancers. For example, genetic polymorphisms in CYP2E1 have been associated with altered susceptibility to hepatic cirrhosis induced by ethanol and with increased risk of development of esophageal cancer and other malignant tumours. Likewise, long-term intake of CYP2E1 inducers has also been recognized as a risk factor for malignancy, in particular for carriers of certain variant *CYP2E1* alleles. As these studies are complex and often contradictory in their results, the reader is referred to some recent specialized reviews and meta-analyses on CYP2E1 and risk of chemically induced cancers (Trafalis et al., 2010), association with lung cancer risk (Wang et al., 2010b), and alcohol-related cancers (Druesne-Pecollo et al., 2009).

4.6. Subfamily CYP2J: CYP2J2

4.6.1. Regulation and variability of gene expression

The human *CYP2J* subfamily has only a single gene, *CYP2J2*, which encodes a 502 amino acid microsomal P450 protein. Like all other CYP2 members, the CYP2J2 gene comprises 9 exons and 8 introns, which are spread over a region encompassing about 40 kb on chromosome 1. The *CYP2J2* gene promoter lacks a TATA-box and its basal activity is regulated predominantly by Sp1, for which at least 4 different binding sites are present within the first 100 bp of 5′-upstream sequence (King et al., 2002). This promoter arrangement is consistent with a "housekeeping" nature of this P450 gene, which does not seem to be inducible by typical P450 inducers. CYP2J2 is expressed at high levels in the heart, especially in cardiac myocytes and in endothelial cells (Wu et al., 1996; Delozier et al., 2007; Michaud et al., 2010), and at lower levels it is also expressed in lung, gastrointestinal tract, and pancreas, as well as in selected brain regions (Table 2). In the liver CYP2J2 abundance is less than 1% of total P450 content, and similar estimations have been made regarding expression in small intestine (Paine et al., 2006; Yamazaki et al., 2006). Prenatal expression of CYP2J2 mRNA and protein was also observed in these tissues (Gaedigk et al., 2006).

4.6.2. Role of CYP2J2 in drug metabolism and toxicology

The role of CYP2J2 in drug metabolism has not been fully evaluated. Several antihistamine drugs including terfenadine, ebastine, and astemizole, have been identified as efficient substrates but the contribution of CYP2J2 to overall clearance is not clear and may strongly depend on the tissue (Table 3; Matsumoto et al., 2002; Lafite et al., 2007). One recent study screened 139 marketed drugs from different therapeutic classes and identified eight novel CYP2J2 substrates including amiodarone, cyclosporine, and other drugs typically metabolized by CYP3A4, however with different regioselectivity (Lee et al., 2010).

CYP2J2 is one of the major P450 enzymes to metabolize arachidonic acid (AA) predominantly via NADPH-dependent olefin epoxidation to 20-HETE and all four regioisomeric *cis*-epoxyeicosatrienoic acids, i.e. the 5,6-, 8,9-, 11,12-, and 14,15-EETs (Node et al., 1999; Xu et al., 2011). These AA metabolites play important roles in the regulation of renal, pulmonary, cardiac and vascular functions. In the heart some of the CYP2J2-generated products have anti-inflammatory and vascular-protective effects. For example the 11,12-EET exerts anti-inflammatory effects by inhibiting endothelial nuclear factor-κB, a

transcription factor that plays a key role in eliciting inflammatory responses in the vascular wall. The CYP2J2 products 8,9- and 11,12-EETs were also shown to activate anti-inflammatory functions by binding as ligands to PPARα (Wray et al., 2009).

Besides its cardioprotective functions, CYP2J2 is also being investigated for its role in cancer as it was found to be highly and selectively expressed in different human tumor tissues and cancer cell lines (Chen et al., 2009). Interestingly, CYP2J2 inhibitors structurally related to the drug terfenadine decreased EET production and inhibited proliferation and neoplastic phenotypes of human tumor cells and in murine xenograft models.

4.6.3. Genetic polymorphisms and pharmacogenetics

Considerable interindividual variation in CYP2J2 expression has been observed and investigated in relation to genetic polymorphism. The CYPalleles website lists 10 distinct star alleles, eight of which carry nonsynonymous SNPs. Some of these variants (**2*: T143A; **3*: R158C; **4*: I192N; **6*: N404Y) were shown to have decreased catalytic activity towards AA when tested recombinantly in an insect cell system (King et al., 2002). The significance of these amino acid variants for drug substrates of CYP2J2 has not been investigated, to our knowledge. The most common *CYP2J2* allele variant with functional relevance is *CYP2J2*7*, which occurs at frequencies of ~2–17% in different populations (Table 1). The key SNP rs890293 is located in the proximal promoter at (−76G>T) and disrupts one of the SP1 binding sites, which results in ~50% reduced promoter-activity relative to the wild-type promoter (Spiecker et al., 2004). Because of the assumed role of CYP2J2 in physiological processes of the heart, most pharmacogenetic studies analyzed *CYP2J2*7* in cohorts of patients with coronary artery disease, coronary heart disease, myocardial infarction, or hypertension. So far these studies did not result in conclusive associations, with many of them showing either no or controversial associations (Berlin et al., 2011; Xu et al., 2011). The in vivo relevance of *CYP2J2* polymorphism thus remains to be established.

5. Family CYP3: CYP3A4, CYP3A5, CYP3A7, CYP3A43

5.1. Regulation and variability of gene expression

The human *CYP3* family consists only of one subfamily, *CYP3A*, which is located on chromosome 7q22.1 and has a size of 231 kb. It comprises the four CYP genes *3A4*, *3A5*, *3A7*, and *3A43*. The mouse *Cyp3a* cluster contains 7 full length genes but there are no orthologous pairs between mouse and human, suggesting that a single *CYP3A* gene present in the common ancestor existed, which independently expanded during the last 75 MY (Nelson et al., 2004). CYP3A4 is in the majority of individuals abundantly expressed in liver but population variability is extremely high (>100-fold), although complete absence of expression has not been definitively proven to our knowledge. Average microsomal content has been estimated between ~60 pmol per mg of microsomal protein (Ohtsuki et al., 2012) to 110 pmol/mg (Klein et al., 2012) to ~146 pmol/mg (Westlind-Johnsson et al., 2003), representing on average about ~14–24% to the microsomal P450 pool (Shimada et al., 1994; Lin et al., 2002; Wolbold et al., 2003; Ohtsuki et al., 2012). Expression of the three minor isoforms, CYP3A5, CYP3A7, and CYP3A43 is generally lower compared to CYP3A4, although the contribution of CYP3A5 in carriers of *CYP3A5*1* may be substantial in low expressors of CYP3A4 (Hustert et al., 2001; Kuehl et al., 2001; Koch et al., 2002; Westlind-Johnsson et al., 2003; Daly, 2006). According to a recent mass-spectrometric quantification, the mean fractions of CYPs 3A4, 3A5, 3A7, and 3A43 proteins of the total microsomal CYP3A protein amount measured in 17 adult samples were 85.4% (range, 6.2–270 pmol/mg), 5.4% (2.5–17.1), 3.4% (≤9.4), and 5.8% (≤6.4), respectively (Ohtsuki et al., 2012). If one sample with high CYP3A5 expression (genotype was not determined) was omitted, CYP3A5 expression ranged from 2.5 to 4.3 pmol/mg. CYP3A7 is more abundantly expressed in fetal liver than in adult liver but the mechanism for this has not been studied in detail (Cresteil, 1998; Leeder et al., 2005). CYP3A4 is the major expressed P450 in intestinal enterocytes, with levels uncorrelated to those of liver, and contributes substantially to the first-pass metabolism of orally administered drugs (Ding & Kaminsky, 2003; von Richter et al., 2004a; Daly, 2006). In other extrahepatic tissues including the respiratory tract, brain, lung, and kidney, CYP3A5 expression appears to be predominant or similar to CYP3A4 (Table 2; Raunio et al., 2005; Daly, 2006; Dutheil et al., 2008; Pavek & Dvorak, 2008; Bolbrinker et al., 2012). Multiple signaling pathways contribute to the complex regulation of the CYP3A genes. Constitutive transcriptional regulation includes both positive and negative regulators, in particular C/EBPα and C/EBPβ (Jover et al., 2002; Rodriguez-Antona et al., 2003; Martinez-Jiménez et al., 2005), HNF1α and HNF3γ (Rodriguez-Antona et al., 2003), HNF4α (Tirona et al., 2003; Tegude et al., 2007; Jover et al., 2009), and USF (Biggs et al., 2007). Inducible transcriptional regulation in response to numerous xenobiotics (Table 3) is due to at least three major cis-acting modules: the proximal PXR responsive element prPXRE, the distal (−7.2 to −7.8 kb) xenobiotic-responsive enhancer module XREM, and the constitutive liver enhancer module CLEM4 (−11.4 to −10.5 kb; Matsumura et al., 2004; Jover et al., 2009; Qiu et al., 2010). The xenosensors PXR and CAR, which bind to these regions, translocate to the nucleus upon binding of structurally diverse drug ligands, including barbiturates, rifampicin, statins, and many other drugs and then heterodimerize with RXR to enhance transcription several-fold (Timsit & Negishi, 2007; Liu et al., 2008; Pascussi et al., 2008). These nuclear receptors were also shown to induce CYP3A5 in liver and intestine (Burk et al., 2004), which explains the observed coregulation between hepatic CYP3A4 and CYP3A5 (Lin et al., 2002). Additional ligand-dependent transcriptional regulators of CYP3A4 include the bile acid receptor FXR (Gnerre et al., 2004), the glucocorticoid receptor (Pascussi et al., 2008), the oxysterole receptor LXR (Duniec-Dmuchowski et al., 2007), and the vitamin D receptor (Matsubara et al., 2008). Recent studies indicate that PPARα also contributes to constitutive and inducible regulation of CYP3A4. In a genetic candidate gene approach (see below), PPARα SNPs were found to affect hepatic CYP3A4 phenotypes including atorvastatin hydroxylase activity (Klein et al., 2012) and in a systems biology approach genome-wide time-resolved data from human hepatocytes challenged with statins identified, among others, PPARα as an influential factor for CYP3A4 expression (Schröder et al., 2011). Validation experiments in these studies demonstrated ~3-fold induction of CYP3A4 in human hepatocytes by the potent PPARα agonist, WY14,643, while the antagonist MK886 and shRNA-mediated PPARα knock-down lead to marked repression. These studies together with an earlier transcriptional profiling study (Rakhshandehroo et al., 2009) clearly demonstrate an impact of the lipid homeostase regulator PPARα on CYP3A4.

Also of considerable importance is cytokine-mediated down-regulation of CYP3A4 in the course of the inflammatory response via JAK/STAT pathway (Jover et al., 2002). This is clinically relevant for example in cancer patients because tumors can be a source of systemically circulating cytokines which then lead to substantial down-regulation of CYP3A4 and other drug metabolizing enzymes and transporters (Slaviero et al., 2003; Aitken et al., 2006). Moreover, as summarized in chapter 3.3, CYP3A4 shows significant activity and expression differences in females versus males (Wolbold et al., 2003; Cotreau et al., 2005; Lamba et al., 2010). Recently, higher activity in females was also confirmed in women from Tanzania ($P<0.001$) and Korea ($P<0.00001$) by measuring the proposed endogenous CYP3A4/5 metabolite-marker 4β-hydroxycholesterol (Diczfalusy et al., 2011). The mechanistic basis for sex-biased expression of CYP3A4 and other CYPs has not been elucidated but may involve different growth hormone/Stat5b signaling (Waxman & Holloway, 2009). A recent investigation in human hepatocytes from female and male donors found more efficient hormone-dependent activation, greater extent of nuclear translocation, and stronger binding to DNA motifs of HNF4α and PXR in female compared to male hepatocytes (Thangavel et al., 2011).

5.2. Role of CYP3A enzymes in drug metabolism

The CYP3A subfamily enzymes play a major role in the metabolism of ~30% of clinically used drugs from almost all therapeutic categories (Fig. 1; Table 3; Bu, 2006; Liu et al., 2007; Zanger et al., 2008). The active site of CYP3A4 is large and flexible and can accommodate and metabolize many preferentially lipophilic compounds with comparatively large structures (Scott & Halpert, 2005; Hendrychová et al., 2011). Typical large substrates are immunosuppressants like cyclosporin A and tacrolimus, macrolide antibiotics like erythromycin, and anticancer drugs including taxol, but smaller molecules are also accepted including ifosfamide, tamoxifen, benzodiazepines, several statins, antidepressants, opioids and many more (Table 3). CYP3A4 is also an efficient steroid hydroxylase with an important role in the catabolism of several endogenous steroids including testosterone, progesterone, androstenedione, cortisol and bile acids. Although several probe drugs that measure general CYP3A activity are available, e.g. midazolam, erythromycin, alprazolam, and dextromethorphan (Fuhr et al., 2007; Liu et al., 2007), phenotyping data obtained with different CYP3A substrates are not generally well correlated to each other, a CYP3A4-typical feature that may be related to the occurrence of several overlapping substrate binding regions and the well-known allosteric regulation of CYP3A4 enzyme activity (Niwa et al., 2008; Foti et al., 2010; Roberts et al., 2011).

The high sequence similarity between the CYP3A isozymes (CYP3A4 and CYP3A5 share >85% primary amino acid sequence identity) leads to highly similar substrate selectivity between the isoforms (Williams et al., 2002). Nevertheless, some limited substrate and regioselectivity differences were observed. For example, aflatoxin B1 (AFB1) 3α-hydroxylation to AFQ1 is solely catalyzed by CYP3A4 and results in detoxification and subsequent elimination of AFB1, whereas CYP3A5 converts it to the genotoxic exo-8,9-epoxide AFBO (Kamdem et al., 2006). Another example is the aromatic *ortho*-hydroxylation of atorvastatin, which is 16-fold more efficiently catalyzed by CYP3A4 compared to CYP3A5 (Feidt et al., 2010).

5.3. Genetic polymorphisms and functional impact

5.3.1. CYP3A4

Drug oxidation phenotypes of CYP3A4 are strongly variable but unimodally distributed. Nevertheless there is indication of substantial heritability. For example, antipyrine 4-hydroxylation rate, which is mainly catalyzed by CYP3A4 (Engel et al., 1996), was reported to be largely inherited as shown in early twin studies (Penno et al., 1981). Moreover, a repeated drug administration approach lead Kalow and colleagues to conclude a high degree of heritability for CYP3A4 drug oxidation capacity towards several of its substrates (Ozdemir et al., 2000). The genetic basis for these observations remained obscure even though several resequencing and haplotype tagging studies have recently been carried out at the *CYP3A* locus in ethnically diverse populations (Thompson et al., 2006; Schirmer et al., 2007; Perera et al., 2009; Perera, 2010). A genome-wide association study carried out in 310 twins, who had been induced with St John's Wort, also failed to identify significant associations (Rahmioglu et al., 2012). The apparent "missing heritability" of CYP3A4 drug oxidation phenotype is thus an intriguing genetic problem (Sadee, 2012).

One of the more common and frequently studied polymorphisms is the proximal promoter variant *CYP3A4**1B* [-392A>G] which occurs in white populations at ~2 to 9% but at higher frequencies in Africans (Table 1). This SNP was initially found to be associated with higher tumor grade and stage in prostate cancer and showed higher nifedipine oxidase activity in human livers (Rebbeck et al., 1998). Association of *CYP3A4**1B* with markers of advanced disease was confirmed by some but not all further studies (Keshava et al., 2004; Perera, 2010). A functional effect of this variant could however not be established and remained controversial, despite several studies in vitro and in human liver (Wandel et al., 2000; Spurdle et al., 2002; Rodríguez-Antona et al., 2005; Klein et al., 2012).

A notable recent discovery is the intron 6 C>T variant rs35599367 (*CYP3A4**22*) which was found by a systematic screen for SNPs showing allelic expression imbalance in human liver and with decreased mRNA expression in cultured cells transfected with minigenes (Wang et al., 2011). These authors found that the effect of the variant was not confounded by sex or other variables and that it accounted for 7% of the mRNA expression variability in a cohort of 93 liver samples. In another recent liver study this variant was associated with decreased protein levels by univariate and multivariate analysis (Klein et al., 2012).

Another intronic variant rs4646450, located in the *CYP3A5* gene, has recently been associated with reduced tacrolimus dosage requirement in Japanese patients (Onizuka et al., 2010) and with reduced serum dihydroepiandrosterone sulfate concentrations (Zhai et al., 2011). This variant was also associated with decreased protein and activity of CYP3A4 in human liver, explaining about 3–5% of hepatic variability (Klein et al., 2012). This indicates that SNPs at the CYP3A locus exist that are likely to influence expression, and possibly there are more to be discovered.

Another possibility to explain the "missing heritability" of CYP3A4 variability is that polymorphic trans-acting genetic factors could account in part. Initial studies indicated that PXR variants may contribute to CYP3A4 expression differences (Lamba et al., 2005, 2008). Recently this hypothesis was explored more systematically using liver tissue banks. Several genome-wide association studies with a total number of >800 human liver samples failed however to identify novel significant markers of CYP3A4 expression and function (Schadt et al., 2008; Yang et al., 2010; Innocenti et al., 2011; Schröder et al., 2013; Glubb et al., 2012). This disappointing result is probably due to lack of power due to the statistical correction for the large number of tests. In contrast, two recent studies applied candidate-gene approaches to detect cis- and trans-SNPs influencing expression phenotypes. Lamba and colleagues phenotyped 128 livers by quantitative real-time PCR for expression of CYP3A genes and identified a functional CCT-repeat polymorphism in the *FoxA2* gene to be associated with higher expression of FoxA2 mRNA and its targets PXR and CYP3A4 (Lamba et al., 2010). Polymorphisms in *FoxA2*, *HNF4α*, *FoxA3*, *PXR*, *ABCB1*, and the *CYP3A4* promoter together explained 24.6% of the variation in hepatic CYP3A4 mRNA expression. However the study lacked information of the relevance of these variations for CYP3A4 protein and activity.

In a liver cohort study mentioned earlier, Klein and colleagues phenotyped 149 Caucasian liver samples for CYP3A4 mRNA and protein levels and for verapamil *N*-demethylase and atorvastatin hydroxylase activities (Klein et al., 2012). They identified SNPs in the Ah-receptor nuclear translocator (*ARNT*), glucocorticoid receptor (*GR*), progesterone receptor membrane component 2 (*PGRMC2*), and peroxisome proliferator activated receptor alpha (PPARα) to be consistently associated with CYP3A4 phenotype. Validation in an atorvastatin-treated volunteer cohort confirmed decreased atorvastatin-2-hydroxylation in carriers of PPARα SNP rs4253728. Moreover, homozygous carriers expressed significantly less PPARα protein in liver and shRNA-mediated PPARα gene knock-down in primary human hepatocytes decreased expression levels of CYP3A4 by more than 50%. Multivariate analysis revealed that two linked PPARα SNPs alone explained ~8–9% of the atorvastatin hydroxylase activity variation, whereas all genetic and nongenetic factors together accounted for ~33% of atorvastatin 2-hydroxylase variation (Klein et al., 2012).

5.3.2. CYP3A5

Expression of CYP3A5 in liver is polymorphic as only a fraction of about 5 to 10% of Caucasians, but 60% or more of Africans or African Americans have appreciable amounts expressed in their liver. These ethnic differences are largely explained by two alleles that result in aberrant splicing and deficient expression of the functional transcript.

The most common deficient allele *CYP3A5*3* harbors a mutation in intron 3 that leads to aberrant splicing and a truncated protein, and occurs in all ethnic groups studied, with large frequency differences between major races (Table 1; Kuehl et al., 2001). *CYP3A5*6* with an exon 7 mutation that also leads to an aberrantly spliced mRNA lacking exon 7 was only detected in populations of African origin (Kuehl et al., 2001; Roy et al., 2005). Another *null* allele, *CYP3A5*7*, includes a frame-shift mutation (Hustert et al., 2001). Taken together, only a small percentage of Caucasian subjects but considerably larger fractions of Asians and Africans have a functional copy of the *CYP3A5* gene (**1*). In these individuals, CYP3A5 could make a significant contribution to drug metabolism, particularly for substrates with preferential metabolism by CYP3A5 over CYP3A4 (e.g., tacrolimus) and in individual with a low expression of CYP3A4.

5.3.3. CYP3A7

The fetal-predominant form accounts for up to 50% of total P450 content in fetal livers (Cresteil, 1998; Leeder et al., 2005). Although expression shifts after birth from CYP3A7 to CYP3A4, it remains polymorphically expressed in some adult livers and in intestine (Burk et al., 2002). Most of the CYP3A7 mRNA high expressor phenotypes could be explained by the *CYP3A7*1C* promoter variant, which harbors a recombined promoter starting with −188G>T and extending to −129, which has been replaced by the corresponding CYP3A4 promoter from −210 to −250 bp. The mutant gene is more effectively transcribed due to increased binding and transactivation by HNF4α, PXR/RXR and CAR/RXR heterodimers to a polymorphic ER6 motif (Burk et al., 2002). Further studies with a specific antibody estimated the relative content of CYP3A7 to the total CYP3A pool to be between 9 and 36% for the ~10% of high expressors and about 10-fold lower in the low expressors (Sim et al., 2005). Additional alleles of the *CYP3A7* gene can be found on the CYPalleles website. Due to the large overlap in substrate specificity with other CYP3A enzymes the clinical significance *CYP3A7* polymorphism has not been well studied.

5.4. Clinical impact of genetic variation

5.4.1. CYP3A4

In agreement with a decreasing effect of the **22* variant on CYP3A4 expression, patients treated with atorvastatin, simvastatin, or lovastatin who were carriers of the T allele required 1.7- to 5-fold reduced statin doses compared to non-T carriers for optimal lipid control (Wang et al., 2011). Significant association of *CYP3A4*22* with decreased 2-OH-atorvastatin/atorvastatin $AUC_{0-\infty}$ ratio was observed in atorvastatin-treated volunteers (Klein et al., 2012). The association of *CYP3A4*22* with simvastatin lipid-lowering response was also shown in another clinical study (Elens et al., 2011a). Furthermore, renal transplant recipients who were carriers of the low-expressor T-allele had a 33% reduced mean daily-dose requirement to reach the same tacrolimus blood concentration compared to homozygotes for the wild type allele (Elens et al., 2011b) and 1.6 to 2.0-fold higher dose-adjusted trough blood levels of tacrolismus and cyclosporine in stable renal transplant patients (Elens et al., 2011c). Despite these consistent reports, the rather low frequency of this intron 6 variant (global minor allele frequency 2.1%, Caucasians 3–8%; Table 1) limits its contribution to overall CYP3A4 variability.

5.4.2. CYP3A5

Associations with *CYP3A5* genotype were reported, for example, for the immunosuppressant tacrolimus (Hesselink et al., 2003; Anglicheau et al., 2007; Elens et al., 2011b); the antihypertensive verapamil (Jin et al., 2007), and the HIV protease inhibitor saquinavir (Josephson et al., 2007). Tacrolimus-related nephrotoxicity is clinically highly relevant and dose adjustment of tacrolimus by therapeutic drug monitoring is common clinical practice in renal transplant patients as recommended by the European consensus conference report (Wallemacq et al., 2009). To elucidate underlying mechanisms several studies investigated the contribution of *CYP3A5* genetics demonstrating a strong association between the deficient allele *CYP3A5*3* and lower tacrolimus clearance, higher blood concentrations, and lower dose requirements (Staatz et al., 2010a, 2010b). In a large cohort of 'real-world' kidney transplant recipients (n = 446) on tacrolimus steady state concentrations, *CYP3A5*3* alone explained 39% of the variability of tacrolimus blood concentration to dose (C/D) ratio, compared to 46% explained by clinical covariates and *CYP3A5*3* together (Birdwell et al., 2012). In another trial a predictive model that included age, ethnicity and concomitant use of medications explained ~30% of the variability in tacrolimus dosing, which increased to 58% by including *CYP3A5*3* genotype (Wang et al., 2010c). Thus, clinical variables and *CYP3A5* pharmacogenetics explain approximately one-half of the interindividual variability in tacrolimus C/D ratio, suggesting that algorithms for pharmacogenetics-guided tacrolimus dosing should be helpful for clinical practice.

6. NADPH:cytochrome P450 oxidoreductase (*POR*)

NADPH:cytochrome P450 oxidoreductase (POR) is a microsomal flavoprotein which constitutes an essential component of several oxygenase enzyme complexes including heme oxygenase, squalene monooxygenase, 7-dehydrocholesterol reductase, and in particular all 50 microsomal cytochrome P450 (CYP) monooxygenases. The FMN/FAD flavogroups of the protein mediate the transfers of two single electrons originating from NADPH to the P450 prosthetic heme iron. Furthermore, POR can directly metabolize a number of drugs by 1-electron reduction reactions. This is particularly the case for drugs with quinone moieties, including several anticancer prodrugs such as menadione, mitomycin C, tirapazamine, and E09 used for the treatment of solid tumors (Hart et al., 2008).

In contrast to the multiplicity of CYPs, mammals have only a single *POR* gene. In humans the gene is located on chromosome 7q11.2 and spans about 72 kb, coding for a 680 amino acid protein which uses flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) as prosthetic groups. Complete deletion of the *por* gene in mouse is embryonically lethal most likely due to deficient adrenocortical steroidogenesis (Shen et al., 2002; Otto et al., 2003). In contrast, liver-specific knockout of *por* leads to phenotypically and reproductively normal mice that accumulate hepatic lipids and have a drastically diminished capacity for hepatic drug metabolism (Gu et al., 2003; Finn et al., 2007).

The amount of POR in human liver is stoichiometrically ~5 to 10-fold lower compared to the microsomal CYP pool, raising the possibility that it represents a limiting factor for monooxygenase function (Hart et al., 2008; Gomes et al., 2009). Although interindividual variability of POR expression in human liver is lower compared to most drug metabolizing microsomal CYP enzymes, it was shown to be significantly correlated to several CYP monooxygenase activities, supporting a possible rate-limiting role in catalysis (Backes & Kelley, 2003). POR expression variability is in part due to the inducibility of the *POR* gene by both PXR and CAR (Maglich et al., 2002), as well as hormonal influences on transcription (Tee et al., 2011), whereas other nongenetic factors including sex, age, smoking and drinking habits do not appear to be of significant influence in liver (Hart et al., 2008; Gomes et al., 2009). Following the discovery of an untranslated first exon, the human POR promoter was located and binding of transcription factors Smad3/Smad4, as well as thyroid hormone receptor TRα and TRβ was confirmed by chromatin immunoprecipitation (Tee et al., 2011).

In recent years rare POR missense mutations in humans were discovered that cause disordered steroidogenesis, ambiguous genitalia, and Antley–Bixler syndrome (Flück et al., 2004; Huang et al., 2005; Flück et al., 2008). The CYPalleles website currently lists 41 distinct star-alleles, most of which represent vary rare variants identified in patients with clinical manifestations of POR deficiency (Sim et al., 2009). The causative mutations in these alleles either result in

amino acid changes that severely damage POR function or in erroneous splicing or translation. The clinical and developmental aspects of these rare POR variants have been recently reviewed (Flück & Pandey, 2011).

Using a cocktail phenotyping approach in a family with genetic POR deficiency, subnormal activities of CYP1A2, CYP2C9, CYP2D6 and CYP3A4 were observed in a heterozygous patient with congenital adrenal hyperplasia, demonstrating that POR activity can be limiting in vivo at least for these P450 enzymes (Tomalik-Scharte et al., 2010).

Common *POR* polymorphisms also exist in addition to the rare disease-causing mutations (Huang et al., 2005, 2008a). In particular a A503V variation (*POR**28*) is present at high frequencies ranging from 19% to 37% in all major ethnicities and has been studied most extensively (Table 1). In a recombinant system the variant retained >50% of the wild type activity towards several CYPs (Huang et al., 2008b; Sandee et al., 2010), while in an analysis of 150 human liver microsome samples it was not associated with significant changes in any of 11 measured CYP activities (Gomes et al., 2009). Nevertheless an in vivo study found that *POR**28* TT genotype was associated with a 1.6-fold increase in CYP3A midazolam 1′-hydroxylase activity compared with *POR**28* C carriers, a finding that could be replicated in an independent cohort (Oneda et al., 2009). Similarly, in a cohort of allograft recipients under tacrolimus therapy, *POR**28* T-allele carriers had significantly higher tacrolimus dose requirements compared to noncarriers but only if they were genotypic *CYP3A5* expressors (i.e. presence of at least one *CYP3A5**1* allele; (De Jonge et al., 2011). Thus, the effect of this common *POR* variant appears to depend on both CYP and substrate analyzed.

Numerous additional missense mutants that influence P450 activities in a CYP- and substrate specific manner have been identified more recently (Hart et al., 2008; Huang et al., 2008a; Kranendonk et al., 2008; Marohnic et al., 2010). In a large scale sequencing study, Miller and colleagues sequenced the POR gene in 842 normal persons from 4 ethnic groups and detected 140 SNPs of which 43 occurred at >1% frequency and 13 were novel nonsynonymous variants (Huang et al., 2008a). Moreover, polymorphisms in the promoter and in introns could affect transcription and/or splicing, but have not yet been investigated systematically. In the above-mentioned study, twelve promoter variants were detected. One polymorphism at −152 bp was described to result in decreased transcription in cell lines (Tee et al., 2011). In addition, two common 5′-flanking region SNPs (−173C>A, -208C>T) and the intron 2 SNP rs2868177 were significantly associated with variations in warfarin maintenance dose, in addition to several known factors, in a study of 122 male patients, who had attained a stable warfarin dose. A study in human liver microsomes identified three intronic POR variants that affected several CYP activities as determined by multivariate analysis, in concert with the donor's sex (Gomes et al., 2009). An effect of intron 11 variant rs2302429G>A on CYP1A2 activity but not inducibility was recently demonstrated in an in vivo study (Dobrinas et al., 2012). Taken together these recent advances indicate that POR variants are a complex but potentially relevant source of genetic variation for steroid hydroxylation and drug oxidation (Miller et al., 2011).

7. Conclusions and future perspectives

The scientific literature cited in this review, and many more articles we could not mention, demonstrate the tremendous progress that has been made in understanding the drug metabolizing cytochromes P450 with respect to their functional properties and differences, regulation of gene expression, population variability, genotype–phenotype correlation, and clinical impact. Regulation of all CYPs is clearly multifactorial with sex, age, hormonal and disease states and inhibition or induction-type drug–drug interactions contributing to inter- and intraindividual variability. Nevertheless, genomic markers have a confirmed impact on several CYPs, approximately in the order CYP2D6 > CYP2C19 ~ CYP2A6 > CYP2B6 > CYP2C9 > CYP3A4/5.

Future directions should include basic as well as clinical aspects. In basic research it will be interesting to see how many rare mutations exist in these genes in various populations, and what their contribution to the total variability is. In this review we focused on common variants, but because rare variants often have stronger impact on phenotype, their collective role for complex phenotypes may be significant. Rare variants with strongly decreased function can be particularly important for phenotype if present in combination with another allele or haplotype of moderately decreased function, as shown for example in the case of efavirenz-treated HIV patients (Rotger et al., 2007). Although earlier studies have shown that genotyping of only few common variants is sufficient to predict the major phenotypes (Sachse et al., 1997; Griese et al., 1998), it should be remembered that even in the case of CYP2D6 this conclusion was based on very few probe drugs (i.e. debrisoquine, sparteine) that have no clinical significance today. For other substrates the situation may be different.

Current progress in the 1000-genomes project and by targeted re-sequencing suggests that the number of unknown rare polymorphisms and “private” mutations can make significant contributions to interindividual as well as interethnic variability, because these mostly unknown variants show increased population-specificity and are enriched for functional variants (Gamazon et al., 2009; Marth et al., 2011; MacArthur et al., 2012). However, the task is a difficult one, because available in vitro test systems for CYP enzyme and gene variants are time-consuming and unreliable and in vivo testing on the other hand is impractical due to the low SNP frequencies. In silico prediction tools to filter out potentially functional SNPs for further study may thus be a promising approach, although functional effects of intronic and promoter variants remain especially difficult to predict (Pang et al., 2009).

Polymorphisms in *trans*-acting genes, for example genes that influence monooxygenase activity (e.g., NADPH:cytochrome P450 reductase, cytochrome b_5) or in the numerous regulatory genes involved in transcriptional, posttranscriptional and posttranslational regulation have only been occasionally investigated so far but these studies have shown potential to develop predictive multigenetic gene signatures for CYP1A2 (Klein et al., 2010) and CYP3A4 (Klein et al., 2012; Lamba et al., 2010). Furthermore, the contribution of CNVs for drug metabolic phenotypes has also not been evaluated in a systematic way, although several examples with functional impact, including CYPs 2A6 and 2D6, as well as several phase II genes are known (Johansson & Ingelman-Sundberg, 2008; Gamazon et al., 2011). These directions may ultimately reveal the true genetic contribution to variable CYP-dependent drug metabolism phenotype.

Concerning clinical aspects, it must be noted that translation of this knowledge into clinical practice has been slow and not on a broad front. The reasons for this are manifold and mostly not directly related to P450 research but rather to organizational, medical, ethical and legal issues which have been discussed in other reviews (Frueh & Gurwitz, 2004; Woelderink et al., 2006; Pirmohamed, 2009; Lunshof & Gurwitz, 2012). Future directions should focus on the proper evaluation of clinical outcomes and properly designed clinical studies to assess the clinical utility as well as practicality of *CYP* genotyping. A pharmacogenetic test is considered clinically useful when it can be shown to improve drug therapy in terms of efficacy or safety, whereas practicality requires development of a suitable infrastructure, including testing facility, instructed personel, and incorporation into the general health care system. It is further necessary to realize that *CYP* genotyping alone can not be the answer. For each drug, the relevant genes have to be defined and tested, along with other factors (sex, age, health and nutritional condition, and many more), in order to exploit the full potential of pharmacogenetics for drug therapy. Systems biology approaches, in particular physiology-based pharmacokinetic

and pharmacodynamic modeling of the complex interplay between the many levels and facets of drug-organism interactions should also be expected to make major contributions in the future towards implementing pharmacogenetic testing in personalized medicine (Rostami-Hodjegan & Tucker, 2007; Eissing et al., 2011; Holzhütter et al., 2012).

Conflict of interest statement

U.M. Zanger named as coinventor of several patent applications directed to the detection of specific CYP polymorphisms for diagnostic purposes and is entitled to share in any net income derived from licensing these patent rights under standard academic institutional policies. M. Schwab declares no conflict of interest.

Acknowledgments

Work in the authors' laboratory is supported by the German Federal Ministry of Education and Research (Virtual Liver Network grant 0315755 and grant 03 IS 2061C), the Deutsche Forschungsgemeinschaft (grant SCHW 858/1-1), the FP7 EU Initial Training Network Program "FightingDrugFailure" (grant PITN-GA-2009-238132), and the Robert-Bosch Foundation, Stuttgart, Germany. These funding agencies had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

Abraham, J. E., Maranian, M. J., Driver, K. E., Platte, R., Kalmyrzaev, B., Baynes, C., et al. (2010). CYP2D6 gene variants: association with breast cancer specific survival in a cohort of breast cancer patients from the United Kingdom treated with adjuvant tamoxifen. *Breast Cancer Res 12*, R64.

Abu-Bakar, A., Arthur, D. M., Wikman, A. S., Rahnasto, M., Juvonen, R. O., Vepsäläinen, J., et al. (2012). Metabolism of bilirubin by human cytochrome P450 2A6. *Toxicol Appl Pharmacol 261*, 15–58.

Achour, A., Zaag, I., Gueddah, L., Trimeche, B., Slama, F. B. H., & Zemni, R. (2011). Role of CYP1A1 (T6235C) polymorphism and cigarette smoking in the development of coronary heart disease in Tunisian population. *J Genet 90*, 303–307.

Agundez, J. A. G. (2004). Cytochrome P450 gene polymorphism and cancer. *Curr Drug Metab 5*, 211–224.

Aitken, A. E., & Morgan, E. T. (2007). Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes. *Drug Metab Dispos 35*, 1687–1693.

Aitken, A. E., Richardson, T. A., & Morgan, E. T. (2006). Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu Rev Pharmacol Toxicol 46*, 123–149.

Aklillu, E., Oscarson, M., Hidestrand, M., Leidvik, B., Otter, C., & Ingelman-Sundberg, M. (2002). Functional analysis of six different polymorphic CYP1B1 enzyme variants found in an Ethiopian population. *Mol Pharmacol 61*, 586–594.

Al Koudsi, N., Hoffmann, E. B., Assadzadeh, A., & Tyndale, R. F. (2010). Hepatic CYP2A6 levels and nicotine metabolism: impact of genetic, physiological, environmental, and epigenetic factors. *Eur J Clin Pharmacol 66*, 239–251.

Aleksa, K., Matsell, D., Krausz, K., Gelboin, H., Ito, S., & Koren, G. (2005). Cytochrome P450 3A and 2B6 in the developing kidney: implications for ifosfamide nephrotoxicity. *Pediatr Nephrol 20*, 872–885.

Amador-Noguez, D., Dean, A., Huang, W., Setchell, K., Moore, D., & Darlington, G. (2007). Alterations in xenobiotic metabolism in the long-lived Little mice. *Aging Cell 6*, 453–470.

Anglicheau, D., Legendre, C., Beaune, P., & Thervet, E. (2007). Cytochrome P450 3A polymorphisms and immunosuppressive drugs: an update. *Pharmacogenomics 8*, 835–849.

Anttila, S., Hakkola, J., Tuominen, P., Elovaara, E., Husgafvel-Pursiainen, K., Karjalainen, A., et al. (2003). Methylation of cytochrome P4501A1 promoter in the lung is associated with tobacco smoking. *Cancer Res 63*, 8623–8628.

Anzenbacher, P., & Zanger, U. M. (Eds.). (2012). *Metabolism of drugs and other xenobiotics*. Wiley-VCHWeinheim.

Arab-Alameddine, M., Di Iulio, J., Buclin, T., Rotger, M., Lubomirov, R., Cavassini, M., et al. (2009). Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. *Clin Pharmacol Ther 85*, 485–494.

Ariyoshi, N., Ohara, M., Kaneko, M., Afuso, S., Kumamoto, T., Nakamura, H., et al. (2011). Q172H replacement overcomes effects on the metabolism of cyclophosphamide and efavirenz caused by CYP2B6 variant with Arg262. *Drug Metab Dispos 39*, 2045–2048.

Aubert, J., Begriche, K., Knockaert, L., Robin, M. A., & Fromenty, B. (2011). Increased expression of cytochrome P450 2E1 in nonalcoholic fatty liver disease: mechanisms and pathophysiological role. *Clin Res Hepatol Gastroenterol 35*, 630–637.

Backes, W. L., & Kelley, R. W. (2003). Organization of multiple cytochrome P450s with NADPH-cytochrome P450 reductase in membranes. *Pharmacol Ther 98*, 221–233.

Backman, J. T., Granfors, M. T., & Neuvonen, P. J. (2006). Rifampicin is only a weak inducer of CYP1A2-mediated presystemic and systemic metabolism: studies with tizanidine and caffeine. *Eur J Clin Pharmacol 62*, 451–461.

Backman, J. T., Kyrklund, C., Neuvonen, M., & Neuvonen, P. J. (2002). Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther 72*, 685–691.

Bahadur, N., Leathart, J. B. S., Mutch, E., Steimel-Crespi, D., Dunn, S. A., Gilissen, R., et al. (2002). CYP2C8 polymorphisms in Caucasians and their relationship with paclitaxel 6alpha-hydroxylase activity in human liver microsomes. *Biochem Pharmacol 64*, 1579–1589.

Baldwin, R. M., Ohlsson, S., Pedersen, R. S., Mwinyi, J., Ingelman-Sundberg, M., Eliasson, E., et al. (2008). Increased omeprazole metabolism in carriers of the CYP2C19*17 allele; a pharmacokinetic study in healthy volunteers. *Br J Clin Pharmacol 65*, 767–774.

Bauer, T., Bouman, H. J., Van Werkum, J. W., Ford, N. F., Ten Berg, J. M., & Taubert, D. (2011). Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *BMJ 343*, d4588.

Beedanagari, S. R., Taylor, R. T., Bui, P., Wang, F., Nickerson, D. W., & Hankinson, O. (2010). Role of epigenetic mechanisms in differential regulation of the dioxin-inducible human CYP1A1 and CYP1B1 genes. *Mol Pharmacol 78*, 608–616.

Beierle, I., Meibohm, B., & Derendorf, H. (1999). Gender differences in pharmacokinetics and pharmacodynamics. *Int J Clin Pharmacol Ther 37*, 529–547.

Benowitz, N. L., Lessov-Schlaggar, C. N., Swan, G. E., & Jacob, P., III (2006). Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin Pharmacol Ther 79*, 480–488.

Benowitz, N. L., Peng, M., & Jacob, P., III (2003). Effects of cigarette smoking and carbon monoxide on chlorzoxazone and caffeine metabolism. *Clin Pharmacol Ther 74*, 468–474.

Bergmann, T. K., Brasch-Andersen, C., Gréen, H., Mirza, M., Pedersen, R. S., Nielsen, F., et al. (2011a). Impact of CYP2C8*3 on paclitaxel clearance: a population pharmacokinetic and pharmacogenomic study in 93 patients with ovarian cancer. *Pharmacogenomics J 11*, 113–120.

Bergmann, T. K., Gréen, H., Brasch-Andersen, C., Mirza, M. R., Herrstedt, J., Hølund, B., et al. (2011b). Retrospective study of the impact of pharmacogenetic variants on paclitaxel toxicity and survival in patients with ovarian cancer. *Eur J Clin Pharmacol 67*, 693–700.

Berlin, D. S., Sangkuhl, K., Klein, T. E., & Altman, R. B. (2011). PharmGKB summary: cytochrome P450, family 2, subfamily J, polypeptide 2: CYP2J2. *Pharmacogenet Genomics 21*, 308–311.

Bertilsson, L. (2007). Metabolism of antidepressant and neuroleptic drugs by cytochrome p450s: clinical and interethnic aspects. *Clin Pharmacol Ther 82*, 606–609.

Bertilsson, L., Dahl, M. L., Sjöqvist, F., Aberg-Wistedt, A., Humble, M., Johansson, I., et al. (1993). Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. *Lancet 341*, 63.

Bertilsson, L., Henthorn, T. K., Sanz, E., Tybring, G., Säwe, J., & Villén, T. (1989). Importance of genetic factors in the regulation of diazepam metabolism: relationship to S-mephenytoin, but not debrisoquin, hydroxylation phenotype. *Clin Pharmacol Ther 45*, 348–355.

Bertino, J. R., Banerjee, D., & Mishra, P. J. (2007). Pharmacogenomics of microRNA: a miRSNP towards individualized therapy. *Pharmacogenomics 8*, 1625–1627.

Bièche, I., Narjoz, C., Asselah, T., Vacher, S., Marcellin, P., Lidereau, R., et al. (2007). Reverse transcriptase-PCR quantification of mRNA levels from cytochrome (CYP)1, CYP2 and CYP3 families in 22 different human tissues. *Pharmacogenet Genomics 17*, 731–742.

Biggs, J. S., Wan, J., Cutler, N. S., Hakkola, J., Uusimäki, P., Raunio, H., et al. (2007). Transcription factor binding to a putative double E-box motif represses CYP3A4 expression in human lung cells. *Mol Pharmacol 72*, 514–525.

Bijl, M. J., Visser, L. E., Van Schaik, R. H. N., Kors, J. A., Witteman, J. C. M., Hofman, A., et al. (2009). Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. *Clin Pharmacol Ther 85*, 45–50.

Birdwell, K. A., Grady, B., Choi, L., Xu, H., Bian, A., Denny, J. C., et al. (2012). The use of a DNA biobank linked to electronic medical records to characterize pharmacogenomic predictors of tacrolimus dose requirement in kidney transplant recipients. *Pharmacogenet Genomics 22*, 32–42.

Black, J. L., Litzow, M. R., Hogan, W. J., O'Kane, D. J., Walker, D. L., Lesnick, T. G., et al. (2012). Correlation of CYP2B6, CYP2C19, ABCC4 and SOD2 genotype with outcomes in allogeneic blood and marrow transplant patients. *Leuk Res 36*, 59–66.

Blake, M. J., Gaedigk, A., Pearce, R. E., Bomgaars, L. R., Christensen, M. L., Stowe, C., et al. (2007). Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. *Clin Pharmacol Ther 81*, 510–516.

Bock, K. W., Schrenk, D., Forster, A., Griese, E. U., Mörike, K., Brockmeier, D., et al. (1994). The influence of environmental and genetic factors on CYP2D6, CYP1A2 and UDP-glucuronosyltransferases in man using sparteine, caffeine, and paracetamol as probes. *Pharmacogenetics 4*, 209–218.

Bolbrinker, J., Seeberg, S., Schostak, M., Kempkensteffen, C., Baelde, H., De Heer, E., et al. (2012). CYP3A5 genotype–phenotype analysis in the human kidney reveals a strong site-specific expression of CYP3A5 in the proximal tubule in carriers of the CYP3A5*1 allele. *Drug Metab Dispos 40*, 639–641.

Bolt, H. M., Roos, P. H., & Thier, R. (2003). The cytochrome P-450 isoenzyme CYP2E1 in the biological processing of industrial chemicals: consequences for occupational and environmental medicine. *Int Arch Occup Environ Health 76*, 174–185.

Boulenc, X., Djebli, N., Shi, J., Perrin, L., Brian, W., Van Horn, R., et al. (2012). Effects of omeprazole and genetic polymorphism of CYP2C19 on the clopidogrel active metabolite. *Drug Metab Dispos 40*, 187–197.

Brauch, H., Mürdter, T. E., Eichelbaum, M., & Schwab, M. (2009). Pharmacogenomics of tamoxifen therapy. *Clin Chem 55*, 1770–1782.

Brauch, H., Schroth, W., Goetz, M. P., Mürdter, T. E., Winter, S., Ingle, J. N., et al. (2013). Tamoxifen use in postmenopausal breast cancer: CYP2D6 matters. *J Clin Oncol 31*, 176–180.

Bray, J., Sludden, J., Griffin, M. J., Cole, M., Verrill, M., Jamieson, D., et al. (2010). Influence of pharmacogenetics on response and toxicity in breast cancer patients treated with doxorubicin and cyclophosphamide. *Br J Cancer 102*, 1003–1009.

Brøsen, K. (2004). Some aspects of genetic polymorphism in the biotransformation of antidepressants. *Therapie 59*, 5–12.

Browning, S. L., Tarekegn, A., Bekele, E., Bradman, N., & Thomas, M. G. (2010). CYP1A2 is more variable than previously thought: a genomic biography of the gene behind the human drug-metabolizing enzyme. *Pharmacogenet Genomics 20*, 647–664.

Bu, H. -Z. (2006). A literature review of enzyme kinetic parameters for CYP3A4-mediated metabolic reactions of 113 drugs in human liver microsomes: structure–kinetics relationship assessment. *Curr Drug Metab 7*, 231–249.

Buechler, C., & Weiss, T. S. (2011). Does hepatic steatosis affect drug metabolizing enzymes in the liver? *Curr Drug Metab 12*, 24–34.

Bumpus, N. N., & Hollenberg, P. F. (2008). Investigation of the mechanisms underlying the differential effects of the K262R mutation of P450 2B6 on catalytic activity. *Mol Pharmacol 74*, 990–999.

Bumpus, N. N., Kent, U. M., & Hollenberg, P. F. (2006). Metabolism of efavirenz and 8-hydroxyefavirenz by P450 2B6 leads to inactivation by two distinct mechanisms. *J Pharmacol Exp Ther 318*, 345–351.

Bumpus, N. N., Sridar, C., Kent, U. M., & Hollenberg, P. F. (2005). The naturally occurring cytochrome P450 (P450) 2B6 K262R mutant of P450 2B6 exhibits alterations in substrate metabolism and inactivation. *Drug Metab Dispos 33*, 795–802.

Bunten, H., Liang, W. -J., Pounder, D., Seneviratne, C., & Osselton, M. D. (2011). CYP2B6 and OPRM1 gene variations predict methadone-related deaths. *Addict Biol 16*, 142–144.

Burger, D., Van der Heiden, I., La Porte, C., Van der Ende, M., Groeneveld, P., Richter, C., et al. (2006). Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol 61*, 148–154.

Burk, O., Arnold, K. A., Nussler, A. K., Schaeffeler, E., Efimova, E., Avery, B. A., et al. (2005). Antimalarial artemisinin drugs induce cytochrome P450 and MDR1 expression by activation of xenosensors pregnane X receptor and constitutive androstane receptor. *Mol Pharmacol 67*, 1954–1965.

Burk, O., Koch, I., Raucy, J., Hustert, E., Eichelbaum, M., Brockmöller, J., et al. (2004). The induction of cytochrome P450 3A5 (CYP3A5) in the human liver and intestine is mediated by the xenobiotic sensors pregnane X receptor (PXR) and constitutively activated receptor (CAR). *J Biol Chem 279*, 38379–38385.

Burk, O., Tegude, H., Koch, I., Hustert, E., Wolbold, R., Glaeser, H., et al. (2002). Molecular mechanisms of polymorphic CYP3A7 expression in adult human liver and intestine. *J Biol Chem 277*, 24280–24288.

Buters, J. T., Sakai, S., Richter, T., Pineau, T., Alexander, D. L., Savas, U., et al. (1999). Cytochrome P450 CYP1B1 determines susceptibility to 7, 12-dimethylbenz[a] anthracene-induced lymphomas. *Proc Natl Acad Sci U S A 96*, 1977–1982.

Cairns, W., Smith, C. A., McLaren, A. W., & Wolf, C. R. (1996). Characterization of the human cytochrome P4502D6 promoter. A potential role for antagonistic interactions between members of the nuclear receptor family. *J Biol Chem 271*, 25269–25276.

Caraco, Y., Sheller, J., & Wood, A. J. (1997). Pharmacogenetic determinants of codeine induction by rifampin: the impact on codeine's respiratory, psychomotor and miotic effects. *J Pharmacol Exp Ther 281*, 330–336.

Carbonell, N., Verstuyft, C., Massard, J., Letierce, A., Cellier, C., Deforges, L., et al. (2010). CYP2C9*3 loss-of-function allele is associated with acute upper gastrointestinal bleeding related to the use of NSAIDs other than aspirin. *Clin Pharmacol Ther 87*, 693–698.

Caro, A. A., & Cederbaum, A. I. (2004). Oxidative stress, toxicology, and pharmacology of CYP2E1. *Annu Rev Pharmacol Toxicol 44*, 27–42.

Cederbaum, A. I. (2006). CYP2E1–biochemical and toxicological aspects and role in alcohol-induced liver injury. *Mt Sinai J Med 73*, 657–672.

Chang, T. K. H., Chen, J., Pillay, V., Ho, J. -Y., & Bandiera, S. M. (2003). Real-time polymerase chain reaction analysis of CYP1B1 gene expression in human liver. *Toxicol Sci 71*, 11–19.

Chang, T. K., Weber, G. F., Crespi, C. L., & Waxman, D. J. (1993). Differential activation of cyclophosphamide and ifosphamide by cytochromes P-450 2B and 3A in human liver microsomes. *Cancer Res 53*, 5629–5637.

Chavarria-Soley, G., Sticht, H., Aklillu, E., Ingelman-Sundberg, M., Pasutto, F., Reis, A., et al. (2008). Mutations in CYP1B1 cause primary congenital glaucoma by reduction of either activity or abundance of the enzyme. *Hum Mutat 29*, 1147–1153.

Chehal, M. K., & Granville, D. J. (2006). Cytochrome p450 2C (CYP2C) in ischemic heart injury and vascular dysfunction. *Can J Physiol Pharmacol 84*, 15–20.

Chen, Y., & Goldstein, J. A. (2009). The transcriptional regulation of the human CYP2C genes. *Curr Drug Metab 10*, 567–578.

Chen, C., Li, G., Liao, W., Wu, J., Liu, L., Ma, D., et al. (2009). Selective inhibitors of CYP2J2 related to terfenadine exhibit strong activity against human cancers in vitro and in vivo. *J Pharmacol Exp Ther 329*, 908–918.

Choudhary, D., Jansson, I., Sarfarazi, M., & Schenkman, J. B. (2008). Characterization of the biochemical and structural phenotypes of four CYP1B1 mutations observed in individuals with primary congenital glaucoma. *Pharmacogenet Genomics 18*, 665–676.

Christensen, P. M., Gøtzsche, P. C., & Brøsen, K. (1998). The sparteine/debrisoquine (CYP2D6) oxidation polymorphism and the risk of Parkinson's disease: a meta-analysis. *Pharmacogenetics 8*, 473–479.

Coller, J. K., Krebsfaenger, N., Klein, K., Endrizzi, K., Wolbold, R., Lang, T., et al. (2002). The influence of CYP2B6, CYP2C9 and CYP2D6 genotypes on the formation of the potent antioestrogen Z-4-hydroxy-tamoxifen in human liver. *Br J Clin Pharmacol 54*, 157–167.

Collet, J. -P., Hulot, J. -S., Pena, A., Villard, E., Esteve, J. -B., Silvain, J., et al. (2009). Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet 373*, 309–317.

Corchero, J., Granvil, C. P., Akiyama, T. E., Hayhurst, G. P., Pimprale, S., Feigenbaum, L., et al. (2001). The CYP2D6 humanized mouse: effect of the human CYP2D6 transgene and HNF4alpha on the disposition of debrisoquine in the mouse. *Mol Pharmacol 60*, 1260–1267.

Cornelis, M. C., El-Sohemy, A., & Campos, H. (2004). Genetic polymorphism of CYP1A2 increases the risk of myocardial infarction. *J Med Genet 41*, 758–762.

Cornelis, M. C., El-Sohemy, A., Kabagambe, E. K., & Campos, H. (2006). Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA 295*, 1135–1141.

Cornelis, M. C., Monda, K. L., Yu, K., Paynter, N., Azzato, E. M., Bennett, S. N., et al. (2011). Genome-wide meta-analysis identifies regions on 7p21 (AHR) and 15q24 (CYP1A2) as determinants of habitual caffeine consumption. *PLoS Genet 7*, e1002033.

Cotreau, M. M., Von Moltke, L. L., & Greenblatt, D. J. (2005). The influence of age and sex on the clearance of cytochrome P450 3A substrates. *Clin Pharmacokinet 44*, 33–60.

Crane, A. L., Klein, K., Zanger, U. M., & Olson, J. R. (2012). Effect of CYP2B6*6 and CYP2C19*2 genotype on chlorpyrifos metabolism. *Toxicology 293*, 115–122.

Crespi, C. L., & Miller, V. P. (1997). The R144C change in the CYP2C9*2 allele alters interaction of the cytochrome P450 with NADPH:cytochrome P450 oxidoreductase. *Pharmacogenetics 7*, 203–210.

Cresteil, T. (1998). Onset of xenobiotic metabolism in children: toxicological implications. *Food Addit Contam 15 Suppl.*, 45–51.

Crettol, S., Déglon, J. -J., Besson, J., Croquette-Krokkar, M., Gothuey, I., Hämmig, R., et al. (2005). Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther 78*, 593–604.

Crisafulli, C., Fabbri, C., Porcelli, S., Drago, A., Spina, E., De Ronchi, D., et al. (2011). Pharmacogenetics of antidepressants. *Front Pharmacol 2*, 6.

Croom, E. L., Stevens, J. C., Hines, R. N., Wallace, A. D., & Hodgson, E. (2009). Human hepatic CYP2B6 developmental expression: the impact of age and genotype. *Biochem Pharmacol 78*, 184–190.

Cui, L., Dillehay, K., Chen, W., Shen, D., Dong, Z., & Li, W. (2012). Association of the CYP1B1 Leu432Val polymorphism with the risk of prostate cancer: a meta-analysis. *Mol Biol Rep 39*, 7465–7471.

Dai, D., Zeldin, D. C., Blaisdell, J. A., Chanas, B., Coulter, S. J., Ghanayem, B. I., et al. (2001). Polymorphisms in human CYP2C8 decrease metabolism of the anticancer drug paclitaxel and arachidonic acid. *Pharmacogenetics 11*, 597–607.

Daily, E. B., & Aquilante, C. L. (2009). Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. *Pharmacogenomics 10*, 1489–1510.

Daly, A. K. (2006). Significance of the minor cytochrome P450 3A isoforms. *Clin Pharmacokinet 45*, 13–31.

Dannenberg, L. O., & Edenberg, H. J. (2006). Epigenetics of gene expression in human hepatoma cells: expression profiling the response to inhibition of DNA methylation and histone deacetylation. *BMC Genomics 7*, 181.

Dansette, P. M., Rosi, J., Bertho, G., & Mansuy, D. (2011). Cytochromes P450 catalyze both steps of the major pathway of clopidogrel bioactivation, whereas paraoxonase catalyzes the formation of a minor thiol metabolite isomer. *Chem Res Toxicol 25*, 348–356.

Darbar, D., & Roden, D. M. (2006). Pharmacogenetics of antiarrhythmic therapy. *Expert Opin Pharmacother 7*, 1583–1590.

Das, P. C., Cao, Y., Rose, R. L., Cherrington, N., & Hodgson, E. (2008). Enzyme induction and cytotoxicity in human hepatocytes by chlorpyrifos and N, N-diethyl-m-toluamide (DEET). *Drug Metabol Drug Interact 23*, 237–260.

De Jonge, H., De Loor, H., Verbeke, K., Vanrenterghem, Y., & Kuypers, D. R. J. (2011). In vivo CYP3A activity is significantly lower in cyclosporine-treated as compared with tacrolimus-treated renal allograft recipients. *Clin Pharmacol Ther 90*, 414–422.

De Leon, J., Susce, M. T., Johnson, M., Hardin, M., Maw, L., Shao, A., et al. (2009). DNA microarray technology in the clinical environment: the AmpliChip CYP450 test for CYP2D6 and CYP2C19 genotyping. *CNS Spectr 14*, 19–34.

De Morais, S. M., Wilkinson, G. R., Blaisdell, J., Meyer, U. A., Nakamura, K., & Goldstein, J. A. (1994a). Identification of a new genetic defect responsible for the polymorphism of (S)-mephenytoin metabolism in Japanese. *Mol Pharmacol 46*, 594–598.

De Morais, S. M., Wilkinson, G. R., Blaisdell, J., Nakamura, K., Meyer, U. A., & Goldstein, J. A. (1994b). The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. *J Biol Chem 269*, 15419–15422.

Dehal, S. S., & Kupfer, D. (1997). CYP2D6 catalyzes tamoxifen 4-hydroxylation in human liver. *Cancer Res 57*, 3402–3406.

Delozier, T. C., Kissling, G. E., Coulter, S. J., Dai, D., Foley, J. F., Bradbury, J. A., et al. (2007). Detection of human CYP2C8, CYP2C9, and CYP2J2 in cardiovascular tissues. *Drug Metab Dispos 35*, 682–688.

Desta, Z., Kreutz, Y., Nguyen, A. T., Li, L., Skaar, T., Kamdem, L. K., et al. (2011). Plasma letrozole concentrations in postmenopausal women with breast cancer are associated with CYP2A6 genetic variants, body mass index, and age. *Clin Pharmacol Ther 90*, 693–700.

Desta, Z., Saussele, T., Ward, B., Blievernicht, J., Li, L., Klein, K., et al. (2007). Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. *Pharmacogenomics 8*, 547–558.

Desta, Z., Zhao, X., Shin, J. -G., & Flockhart, D. A. (2002). Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet 41*, 913–958.

Dhir, R. N., & Shapiro, B. H. (2003). Interpulse growth hormone secretion in the episodic plasma profile causes the sex reversal of cytochrome P450s in senescent male rats. *Proc Natl Acad Sci U S A 100*, 15224–15228.

Di Iulio, J., Fayet, A., Arab-Alameddine, M., Rotger, M., Lubomirov, R., Cavassini, M., et al. (2009). In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. *Pharmacogenet Genomics 19*, 300–309.

Di, Y. M., Chow, V. D. -W., Yang, L. -P., & Zhou, S. -F. (2009). Structure, function, regulation and polymorphism of human cytochrome P450 2A6. *Curr Drug Metab 10*, 754–800.

Diczfalusy, U., Nylén, H., Elander, P., & Bertilsson, L. (2011). 4β-Hydroxycholesterol, an endogenous marker of CYP3A4/5 activity in humans. *Br J Clin Pharmacol 71*, 183–189.

Ding, X., & Kaminsky, L. S. (2003). Human extrahepatic cytochromes P450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. *Annu Rev Pharmacol Toxicol 43*, 149–173.

Ding, S., Lake, B. G., Friedberg, T., & Wolf, C. R. (1995). Expression and alternative splicing of the cytochrome P-450 CYP2A7. *Biochem J 306*(Pt. 1), 161–166.

Djordjevic, N., Ghotbi, R., Jankovic, S., & Aklillu, E. (2010). Induction of CYP1A2 by heavy coffee consumption is associated with the CYP1A2–163C>A polymorphism. *Eur J Clin Pharmacol 66*, 697–703.

Dobrinas, M., Cornuz, J., Oneda, B., Kohler Serra, M., Puhl, M., & Eap, C. B. (2011). Impact of smoking, smoking cessation, and genetic polymorphisms on CYP1A2 activity and inducibility. *Clin Pharmacol Ther 90*, 117–125.

Dobrinas, M., Cornuz, J., Pedrido, L., & Eap, C. B. (2012). Influence of cytochrome P450 oxidoreductase genetic polymorphisms on CYP1A2 activity and inducibility by smoking. *Pharmacogenet Genomics 22*, 143–151.

Druesne-Pecollo, N., Tehard, B., Mallet, Y., Gerber, M., Norat, T., Hercberg, S., et al. (2009). Alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. *Lancet Oncol 10*, 173–180.

Du, L., Neis, M. M., Ladd, P. A., Lanza, D. L., Yost, G. S., & Keeney, D. S. (2006). Effects of the differentiated keratinocyte phenotype on expression levels of CYP1-4 family genes in human skin cells. *Toxicol Appl Pharmacol 213*, 135–144.

Duniec-Dmuchowski, Z., Ellis, E., Strom, S. C., & Kocarek, T. A. (2007). Regulation of CYP3A4 and CYP2B6 expression by liver X receptor agonists. *Biochem Pharmacol 74*, 1535–1540.

Dutheil, F., Beaune, P., & Loriot, M. -A. (2008). Xenobiotic metabolizing enzymes in the central nervous system: contribution of cytochrome P450 enzymes in normal and pathological human brain. *Biochimie 90*, 426–436.

Dutheil, F., Dauchy, S., Diry, M., Sazdovitch, V., Cloarec, O., Mellottée, L., et al. (2009). Xenobiotic-metabolizing enzymes and transporters in the normal human brain: regional and cellular mapping as a basis for putative roles in cerebral function. *Drug Metab Dispos 37*, 1528–1538.

Dvorak, Z., Modriansky, M., Pichard-Garcia, L., Balaguer, P., Vilarem, M. -J., Ulrichová, J., et al. (2003). Colchicine down-regulates cytochrome P450 2B6, 2C8, 2C9, and 3A4 in human hepatocytes by affecting their glucocorticoid receptor-mediated regulation. *Mol Pharmacol 64*, 160–169.

Eap, C. B., Crettol, S., Rougier, J. -S., Schläpfer, J., Sintra Grilo, L., Déglon, J. -J., et al. (2007). Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. *Clin Pharmacol Ther 81*, 719–728.

Eckhardt, K., Li, S., Ammon, S., Schänzle, G., Mikus, G., & Eichelbaum, M. (1998). Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain 76*, 27–33.

Economopoulos, K. P., & Sergentanis, T. N. (2010). Three polymorphisms in cytochrome P450 1B1 (CYP1B1) gene and breast cancer risk: A meta-analysis. *Breast Cancer Res Treat 122*, 545–551.

Edginton, A. N., & Willmann, S. (2008). Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. *Clin Pharmacokinet 47*, 743–752.

Eichelbaum, M., Spannbrucker, N., Steincke, B., & Dengler, H. J. (1979). Defective N-oxidation of sparteine in man: a new pharmacogenetic defect. *Eur J Clin Pharmacol 16*, 183–187.

Eissing, T., Kuepfer, L., Becker, C., Block, M., Coboeken, K., Gaub, T., et al. (2011). A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. *Front Physiol 2*, 4.

Elbekai, R. H., Korashy, H. M., & El-Kadi, A. O. S. (2004). The effect of liver cirrhosis on the regulation and expression of drug metabolizing enzymes. *Curr Drug Metab 5*, 157–167.

Elens, L., Becker, M. L., Haufroid, V., Hofman, A., Visser, L. E., Uitterlinden, A. G., et al. (2011a). Novel CYP3A4 intron 6 single nucleotide polymorphism is associated with simvastatin-mediated cholesterol reduction in The Rotterdam Study. *Pharmacogenet Genomics 21*, 861–866.

Elens, L., Bouamar, R., Hesselink, D. A., Haufroid, V., Van der Heiden, I. P., Van Gelder, T., et al. (2011b). A new functional CYP3A4 intron 6 polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients. *Clin Chem 57*, 1574–1583.

Elens, L., Van Schaik, R. H., Panin, N., De Meyer, M., Wallemacq, P., Lison, D., et al. (2011c). Effect of a new functional CYP3A4 polymorphism on calcineurin inhibitors' dose requirements and trough blood levels in stable renal transplant patients. *Pharmacogenomics 12*, 1383–1396.

Endrizzi, K., Fischer, J., Klein, K., Schwab, M., Nüssler, A., Neuhaus, P., et al. (2002). Discriminative quantification of cytochrome P4502D6 and 2D7/8 pseudogene expression by TaqMan real-time reverse transcriptase polymerase chain reaction. *Anal Biochem 300*, 121–131.

Engel, G., Hofmann, U., Heidemann, H., Cosme, J., & Eichelbaum, M. (1996). Antipyrine as a probe for human oxidative drug metabolism: identification of the cytochrome P450 enzymes catalyzing 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine formation. *Clin Pharmacol Ther 59*, 613–623.

Estany-Gestal, A., Salgado-Barreira, A., Sánchez-Diz, P., & Figueiras, A. (2011). Influence of CYP2C9 genetic variants on gastrointestinal bleeding associated with nonsteroidal anti-inflammatory drugs: a systematic critical review. *Pharmacogenet Genomics 21*, 357–364.

Faucette, S. R., Hawke, R. L., Lecluyse, E. L., Shord, S. S., Yan, B., Laethem, R. M., et al. (2000). Validation of bupropion hydroxylation as a selective marker of human cytochrome P450 2B6 catalytic activity. *Drug Metab Dispos 28*, 1222–1230.

Faucette, S. R., Sueyoshi, T., Smith, C. M., Negishi, M., Lecluyse, E. L., & Wang, H. (2006). Differential regulation of hepatic CYP2B6 and CYP3A4 genes by constitutive androstane receptor but not pregnane X receptor. *J Pharmacol Exp Ther 317*, 1200–1209.

Faucette, S. R., Wang, H., Hamilton, G. A., Jolley, S. L., Gilbert, D., Lindley, C., et al. (2004). Regulation of CYP2B6 in primary human hepatocytes by prototypical inducers. *Drug Metab Dispos 32*, 348–358.

Faucette, S. R., Zhang, T. -C., Moore, R., Sueyoshi, T., Omiecinski, C. J., LeCluyse, E. L., et al. (2007). Relative activation of human pregnane X receptor versus constitutive androstane receptor defines distinct classes of CYP2B6 and CYP3A4 inducers. *J Pharmacol Exp Ther 320*, 72–80.

Feidt, D. M., Klein, K., Hofmann, U., Riedmaier, S., Knobeloch, D., Thasler, W. E., et al. (2010). Profiling induction of cytochrome p450 enzyme activity by statins using a new liquid chromatography-tandem mass spectrometry cocktail assay in human hepatocytes. *Drug Metab Dispos 38*, 1589–1597.

Ferguson, C. S., & Tyndale, R. F. (2011). Cytochrome P450 enzymes in the brain: emerging evidence of biological significance. *Trends Pharmacol Sci 32*, 708–714.

Finn, R. D., McLaren, A. W., Carrie, D., Henderson, C. J., & Wolf, C. R. (2007). Conditional deletion of cytochrome P450 oxidoreductase in the liver and gastrointestinal tract: a new model for studying the functions of the P450 system. *J Pharmacol Exp Ther 322*, 40–47.

Flück, C. E., & Pandey, A. V. (2011). Clinical and biochemical consequences of p450 oxidoreductase deficiency. *Endocr Dev 20*, 63–79.

Flück, C. E., Pandey, A. V., Huang, N., Agrawal, V., & Miller, W. L. (2008). P450 oxidoreductase deficiency — a new form of congenital adrenal hyperplasia. *Endocr Dev 13*, 67–81.

Flück, C. E., Tajima, T., Pandey, A. V., Arlt, W., Okuhara, K., Verge, C. F., et al. (2004). Mutant P450 oxidoreductase causes disordered steroidogenesis with and without Antley–Bixler syndrome. *Nat Genet 36*, 228–230.

Foti, R. S., Rock, D. A., Wienkers, L. C., & Wahlstrom, J. L. (2010). Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies using in vitro data and in vivo simulation. *Drug Metab Dispos 38*, 981–987.

Frank, D., Jaehde, U., & Fuhr, U. (2007). Evaluation of probe drugs and pharmacokinetic metrics for CYP2D6 phenotyping. *Eur J Clin Pharmacol 63*, 321–333.

Friedman, R. C., Farh, K. K. -H., Burge, C. B., & Bartel, D. P. (2009). Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res 19*, 92–105.

Frueh, F. W., & Gurwitz, D. (2004). From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community. *Pharmacogenomics 5*, 571–579.

Fuhr, U., Jetter, A., & Kirchheiner, J. (2007). Appropriate phenotyping procedures for drug metabolizing enzymes and transporters in humans and their simultaneous use in the "cocktail" approach. *Clin Pharmacol Ther 81*, 270–283.

Fujita, K., Yamamoto, W., Endo, S., Endo, H., Nagashima, F., Ichikawa, W., et al. (2008). CYP2A6 and the plasma level of 5-chloro-2, 4-dihydroxypyridine are determinants of the pharmacokinetic variability of tegafur and 5-fluorouracil, respectively, in Japanese patients with cancer given S-1. *Cancer Sci 99*, 1049–1054.

Fukami, T., Nakajima, M., Yamanaka, H., Fukushima, Y., McLeod, H. L., & Yokoi, T. (2007). A novel duplication type of CYP2A6 gene in African-American population. *Drug Metab Dispos 35*, 515–520.

Furuta, T., Ohashi, K., Kamata, T., Takashima, M., Kosuge, K., Kawasaki, T., et al. (1998). Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med 129*, 1027–1030.

Furuta, T., Shirai, N., Kodaira, M., Sugimoto, M., Nogaki, A., Kuriyama, S., et al. (2007). Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of *H. pylori*. *Clin Pharmacol Ther 81*, 521–528.

Furuta, T., Shirai, N., Sugimoto, M., Ohashi, K., & Ishizaki, T. (2004). Pharmacogenomics of proton pump inhibitors. *Pharmacogenomics 5*, 181–202.

Fux, R., Mörike, K., Pröhmer, A. M. T., Delabar, U., Schwab, M., Schaeffeler, E., et al. (2005). Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clin Pharmacol Ther 78*, 378–387.

Gaedigk, A. (2000). Interethnic differences of drug-metabolizing enzymes. *Int J Clin Pharmacol Ther 38*, 61–68.

Gaedigk, A., Baker, D. W., Totah, R. A., Gaedigk, R., Pearce, R. E., Vyhlidal, C. A., et al. (2006). Variability of CYP2J2 expression in human fetal tissues. *J Pharmacol Exp Ther 319*, 523–532.

Gaedigk, A., Gaedigk, R., & Leeder, J. S. (2005). CYP2D7 splice variants in human liver and brain: does CYP2D7 encode functional protein? *Biochem Biophys Res Commun 336*, 1241–1250.

Gaedigk, A., Jaime, L. K. M., Bertino, J. S., Jr., Bérard, A., Pratt, V. M., Bradfordand, L. D., et al. (2010). Identification of novel CYP2D7-2D6 hybrids: non-functional and functional variants. *Front Pharmacol 1*, 121.

Gaedigk, A., Twist, G. P., & Leeder, J. S. (2012). CYP2D6, SULT1A1 and UGT2B17 copy number variation: quantitative detection by multiplex PCR. *Pharmacogenomics 13*, 91–111.

Gamazon, E. R., Nicolae, D. L., & Cox, N. J. (2011). A study of CNVs as trait-associated polymorphisms and as expression quantitative trait loci. *PLoS Genet 7*, e1001292.

Gamazon, E. R., Zhang, W., Huang, R. S., Dolan, M. E., & Cox, N. J. (2009). A pharmacogene database enhanced by the 1000 Genomes Project. *Pharmacogenet Genomics 19*, 829–832.

Gandhi, M., Aweeka, F., Greenblatt, R. M., & Blaschke, T. F. (2004). Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol 44*, 499–523.

Gao, Y., Liu, D., Wang, H., Zhu, J., & Chen, C. (2010). Functional characterization of five CYP2C8 variants and prediction of CYP2C8 genotype-dependent effects on in vitro and in vivo drug–drug interactions. *Xenobiotica 40*, 467–475.

Garcia-Martin, E., Martínez, C., Tabarés, B., Frías, J., & Agúndez, J. A. G. (2004). Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. *Clin Pharmacol Ther 76*, 119–127.

Gasche, Y., Daali, Y., Fathi, M., Chiappe, A., Cottini, S., Dayer, P., et al. (2004). Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med 351*, 2827–2831.

Gatanaga, H., Hayashida, T., Tsuchiya, K., Yoshino, M., Kuwahara, T., Tsukada, H., et al. (2007). Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. *Clin Infect Dis 45*, 1230–1237.

Gatanaga, H., & Oka, S. (2009). Successful genotype-tailored treatment with small-dose efavirenz. *AIDS 23*, 433–434.

Gay, S. C., Shah, M. B., Talakad, J. C., Maekawa, K., Roberts, A. G., Wilderman, P. R., et al. (2010). Crystal structure of a cytochrome P450 2B6 genetic variant in complex with the inhibitor 4-(4-chlorophenyl)imidazole at 2.0-A resolution. *Mol Pharmacol 77*, 529–538.

Geisler, T., Schaeffeler, E., Dippon, J., Winter, S., Buse, V., Bischofs, C., et al. (2008). CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. *Pharmacogenomics 9*, 1251–1259.

Gelston, E. A., Coller, J. K., Lopatko, O. V., James, H. M., Schmidt, H., White, J. M., et al. (2012). Methadone inhibits CYP2D6 and UGT2B7/2B4 in vivo: a study using codeine in methadone- and buprenorphine-maintained subjects. *Br J Clin Pharmacol 73*, 786–794.

Gervot, L., Rochat, B., Gautier, J. C., Bohnenstengel, F., Kroemer, H., De Berardinis, V., et al. (1999). Human CYP2B6: expression, inducibility and catalytic activities. *Pharmacogenetics 9*, 295–306.

Ghobadi, C., Gregory, A., Crewe, H. K., Rostami-Hodjegan, A., & Lennard, M. S. (2008). CYP2D6 is primarily responsible for the metabolism of clomiphene. *Drug Metab Pharmacokinet 23*, 101–105.

Ghotbi, R., Christensen, M., Roh, H. -K., Ingelman-Sundberg, M., Aklillu, E., & Bertilsson, L. (2007). Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype–phenotype relationship in Swedes and Koreans. *Eur J Clin Pharmacol 63*, 537–546.

Ghotbi, R., Gomez, A., Milani, L., Tybring, G., Syvänen, A. -C., Bertilsson, L., et al. (2009). Allele-specific expression and gene methylation in the control of CYP1A2 mRNA level in human livers. *Pharmacogenomics J 9*, 208–217.

Glaeser, H., Drescher, S., Eichelbaum, M., & Fromm, M. F. (2005). Influence of rifampicin on the expression and function of human intestinal cytochrome P450 enzymes. *Br J Clin Pharmacol 59*, 199–206.

Glubb, D. M., Dholakia, N., & Innocenti, F. (2012). Liver expression quantitative trait loci: a foundation for pharmacogenomic research. *Front Genet 3*, 153.

Gnerre, C., Blättler, S., Kaufmann, M. R., Looser, R., & Meyer, U. A. (2004). Regulation of CYP3A4 by the bile acid receptor FXR: evidence for functional binding sites in the CYP3A4 gene. *Pharmacogenetics 14*, 635–645.

Goetz, M. P., Knox, S. K., Suman, V. J., Rae, J. M., Safgren, S. L., Ames, M. M., et al. (2007). The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat 101*, 113–121.

Goldstein, J. A. (2001). Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Br J Clin Pharmacol 52*, 349–355.

Gomes, A. M., Winter, S., Klein, K., Turpeinen, M., Schaeffeler, E., Schwab, M., et al. (2009). Pharmacogenomics of human liver cytochrome P450 oxidoreductase: multifactorial analysis and impact on microsomal drug oxidation. *Pharmacogenomics 10*, 579–599.

Gómez-Lechón, M. J., Jover, R., & Donato, M. T. (2009). Cytochrome p450 and steatosis. *Curr Drug Metab 10*, 692–699.

Gonzalez, F. J. (2007). The 2006 Bernard B. Brodie Award Lecture. Cyp2e1. *Drug Metab Dispos 35*, 1–8.

Granfors, M. T., Backman, J. T., Laitila, J., & Neuvonen, P. J. (2004). Tizanidine is mainly metabolized by cytochrome p450 1A2 in vitro. *Br J Clin Pharmacol 57*, 349–353.

Griese, E. U., Zanger, U. M., Brudermanns, U., Gaedigk, A., Mikus, G., Mörike, K., et al. (1998). Assessment of the predictive power of genotypes for the in-vivo catalytic function of CYP2D6 in a German population. *Pharmacogenetics 8*, 15–26.

Gu, J., Weng, Y., Zhang, Q. -Y., Cui, H., Behr, M., Wu, L., et al. (2003). Liver-specific deletion of the NADPH-cytochrome P450 reductase gene: impact on plasma cholesterol homeostasis and the function and regulation of microsomal cytochrome P450 and heme oxygenase. *J Biol Chem 278*, 25895–25901.

Guengerich, F. P. (2008). Cytochrome P450 and chemical toxicology. *Chem Res Toxicol 21*, 70–83.

Guengerich, F. P., & Cheng, Q. (2011). Orphans in the human cytochrome P450 superfamily: approaches to discovering functions and relevance in pharmacology. *Pharmacol Rev 63*, 684–699.

Gunes, A., & Dahl, M. -L. (2008). Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms. *Pharmacogenomics 9*, 625–637.

Haas, D. W., Ribaudo, H. J., Kim, R. B., Tierney, C., Wilkinson, G. R., Gulick, R. M., et al. (2004). Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS 18*, 2391–2400.

Haberl, M., Anwald, B., Klein, K., Weil, R., Fuss, C., Gepdiremen, A., et al. (2005). Three haplotypes associated with CYP2A6 phenotypes in Caucasians. *Pharmacogenet Genomics 15*, 609–624.

Han, X. -M., Ouyang, D. -S., Chen, X. -P., Shu, Y., Jiang, C. -H., Tan, Z. -R., et al. (2002). Inducibility of CYP1A2 by omeprazole in vivo related to the genetic polymorphism of CYP1A2. *Br J Clin Pharmacol 54*, 540–543.

Hara, H., & Adachi, T. (2002). Contribution of hepatocyte nuclear factor-4 to down-regulation of CYP2D6 gene expression by nitric oxide. *Mol Pharmacol 61*, 194–200.

Hart, S. N., Wang, S., Nakamoto, K., Wesselman, C., Li, Y., & Zhong, X. (2008). Genetic polymorphisms in cytochrome P450 oxidoreductase influence microsomal P450-catalyzed drug metabolism. *Pharmacogenet Genomics 18*, 11–24.

He, S. -M., Zhou, Z. -W., Li, X. -T., & Zhou, S. -F. (2011). Clinical drugs undergoing polymorphic metabolism by human cytochrome P450 2C9 and the implication in drug development. *Curr Med Chem 18*, 667–713.

Heim, M. H., & Meyer, U. A. (1992). Evolution of a highly polymorphic human cytochrome P450 gene cluster: CYP2D6. *Genomics 14*, 49–58.

Helsby, N. A., & Burns, K. E. (2012). Molecular mechanisms of genetic variation and transcriptional regulation of CYP2C19. *Front Genet 3*, 206.

Helsby, N. A., & Tingle, M. D. (2011). Which CYP2B6 variants have functional consequences for cyclophosphamide bioactivation? *Drug Metab Dispos 40*, 635–637.

Hendrychová, T., Anzenbacherová, E., Hudeček, J., Skopalík, J., Lange, R., Hildebrandt, P., et al. (2011). Flexibility of human cytochrome P450 enzymes: molecular dynamics and spectroscopy reveal important function-related variations. *Biochim Biophys Acta 1814*, 58–68.

Henningsson, A., Marsh, S., Loos, W. J., Karlsson, M. O., Garsa, A., Mross, K., et al. (2005). Association of CYP2C8, CYP3A4, CYP3A5, and ABCB1 polymorphisms with the pharmacokinetics of paclitaxel. *Clin Cancer Res 11*, 8097–8104.

Hesse, L. M., He, P., Krishnaswamy, S., Hao, Q., Hogan, K., Von Moltke, L. L., et al. (2004). Pharmacogenetic determinants of interindividual variability in bupropion hydroxylation by cytochrome P450 2B6 in human liver microsomes. *Pharmacogenetics 14*, 225–238.

Hesselink, D. A., Van Schaik, R. H. N., Van der Heiden, I. P., Van der Werf, M., Gregoor, P. J. H. S., Lindemans, J., et al. (2003). Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther 74*, 245–254.

Hiemke, C., & Härtter, S. (2000). Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther 85*, 11–28.

Higashi, E., Fukami, T., Itoh, M., Kyo, S., Inoue, M., Yokoi, T., et al. (2007). Human CYP2A6 is induced by estrogen via estrogen receptor. *Drug Metab Dispos 35*, 1935–1941.

Hodgson, E., & Rose, R. L. (2007). The importance of cytochrome P450 2B6 in the human metabolism of environmental chemicals. *Pharmacol Ther 113*, 420–428.

Hoffman, S. M., Nelson, D. R., & Keeney, D. S. (2001). Organization, structure and evolution of the CYP2 gene cluster on human chromosome 19. *Pharmacogenetics 11*, 687–698.

Hofmann, M. H., Blievernicht, J. K., Klein, K., Saussele, T., Schaeffeler, E., Schwab, M., et al. (2008). Aberrant splicing caused by single nucleotide polymorphism c.516G>T [Q172H], a marker of CYP2B6*6, is responsible for decreased expression and activity of CYP2B6 in liver. *J Pharmacol Exp Ther 325*, 284–292.

Holmes, M. V., Perel, P., Shah, T., Hingorani, A. D., & Casas, J. P. (2011). CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA 306*, 2704–2714.

Holstein, A., Plaschke, A., Ptak, M., Egberts, E. -H., El-Din, J., Brockmöller, J., et al. (2005). Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. *Br J Clin Pharmacol 60*, 103–106.

Holzhütter, H. -G., Drasdo, D., Preusser, T., Lippert, J., & Henney, A. M. (2012). The virtual liver: a multidisciplinary, multilevel challenge for systems biology. *Wiley Interdiscip Rev Syst Biol Med 4*, 221–235.

Holzinger, E. R., Grady, B., Ritchie, M. D., Ribaudo, H. J., Acosta, E. P., Morse, G. D., et al. (2012). Genome-wide association study of plasma efavirenz pharmacokinetics in AIDS Clinical Trials Group protocols implicates several CYP2B6 variants. *Pharmacogenet Genomics 22*, 858–867.

Honda, M., Muroi, Y., Tamaki, Y., Saigusa, D., Suzuki, N., Tomioka, Y., et al. (2011). Functional characterization of CYP2B6 allelic variants in demethylation of antimalarial artemether. *Drug Metab Dispos 39*, 1860–1865.

Huang, N., Agrawal, V., Giacomini, K. M., & Miller, W. L. (2008a). Genetics of P450 oxidoreductase: sequence variation in 842 individuals of four ethnicities and activities of 15 missense mutations. *Proc Natl Acad Sci U S A 105*, 1733–1738.

Huang, N., Pandey, A. V., Agrawal, V., Reardon, W., Lapunzina, P. D., Mowat, D., et al. (2005). Diversity and function of mutations in p450 oxidoreductase in patients with Antley–Bixler syndrome and disordered steroidogenesis. *Am J Hum Genet 76*, 729–749.

Huang, S. -M., Strong, J. M., Zhang, L., Reynolds, K. S., Nallani, S., Temple, R., et al. (2008b). New era in drug interaction evaluation: US Food and Drug Administration update on CYP enzymes, transporters, and the guidance process. *J Clin Pharmacol 48*, 662–670.

Hulot, J. -S., Bura, A., Villard, E., Azizi, M., Remones, V., Goyenvalle, C., et al. (2006). Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood 108*, 2244–2247.

Hustert, E., Haberl, M., Burk, O., Wolbold, R., He, Y. Q., Klein, K., et al. (2001). The genetic determinants of the CYP3A5 polymorphism. *Pharmacogenetics 11*, 773–779.

Ingelman-Sundberg, M. (2005). Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J 5*, 6–13.

Ingelman-Sundberg, M., & Gomez, A. (2010). The past, present and future of pharmacoepigenomics. *Pharmacogenomics 11*, 625–627.

Innocenti, F., Cooper, G. M., Stanaway, I. B., Gamazon, E. R., Smith, J. D., Mirkov, S., et al. (2011). Identification, replication, and functional fine-mapping of expression quantitative trait loci in primary human liver tissue. *PLoS Genet 7*, e1002078.

Irvin, W. J., Jr., Walko, C. M., Weck, K. E., Ibrahim, J. G., Chiu, W. K., Dees, E. C., et al. (2011). Genotype-guided tamoxifen dosing increases active metabolite exposure in women with reduced CYP2D6 metabolism: a multicenter study. *J Clin Oncol 29*, 3232–3239.

Itoh, M., Nakajima, M., Higashi, E., Yoshida, R., Nagata, K., Yamazoe, Y., et al. (2006). Induction of human CYP2A6 is mediated by the pregnane X receptor with peroxisome proliferator-activated receptor-gamma coactivator 1alpha. *J Pharmacol Exp Ther 319*, 693–702.

Jain, K. K. (2005). Applications of AmpliChip CYP450. *Mol Diagn 9*, 119–127.
Jang, J. -S., Cho, K. -I., Jin, H. -Y., Seo, J. -S., Yang, T. -H., Kim, D. -K., et al. (2012). Meta-analysis of cytochrome P450 2C19 polymorphism and risk of adverse clinical outcomes among coronary artery disease patients of different ethnic groups treated with clopidogrel. *Am J Cardiol 110*, 502–508.
Jansson, I., Stoilov, I., Sarfarazi, M., & Schenkman, J. B. (2001). Effect of two mutations of human CYP1B1, G61E and R469W, on stability and endogenous steroid substrate metabolism. *Pharmacogenetics 11*, 793–801.
Jaquenoud Sirot, E., Knezevic, B., Morena, G. P., Harenberg, S., Oneda, B., Crettol, S., et al. (2009). ABCB1 and cytochrome P450 polymorphisms: clinical pharmacogenetics of clozapine. *J Clin Psychopharmacol 29*, 319–326.
Jennewein, C., Von Knethen, A., Schmid, T., & Brüne, B. (2010). MicroRNA-27b contributes to lipopolysaccharide-mediated peroxisome proliferator-activated receptor gamma (PPARgamma) mRNA destabilization. *J Biol Chem 285*, 11846–11853.
Jiang, Z., Dalton, T. P., Jin, L., Wang, B., Tsuneoka, Y., Shertzer, H. G., et al. (2005). Toward the evaluation of function in genetic variability: characterizing human SNP frequencies and establishing BAC-transgenic mice carrying the human CYP1A1_CYP1A2 locus. *Hum Mutat 25*, 196–206.
Jiang, Z., Dragin, N., Jorge-Nebert, L. F., Martin, M. V., Guengerich, F. P., Aklillu, E., et al. (2006). Search for an association between the human CYP1A2 genotype and CYP1A2 metabolic phenotype. *Pharmacogenet Genomics 16*, 359–367.
Jin, Y., Wang, Y. -H., Miao, J., Li, L., Kovacs, R. J., Marunde, R., et al. (2007). Cytochrome P450 3A5 genotype is associated with verapamil response in healthy subjects. *Clin Pharmacol Ther 82*, 579–585.
Johansson, I., & Ingelman-Sundberg, M. (2008). CNVs of human genes and their implication in pharmacogenetics. *Cytogenet. Genome Res 123*, 195–204.
Johansson, I., Lundqvist, E., Bertilsson, L., Dahl, M. L., Sjöqvist, F., & Ingelman-Sundberg, M. (1993). Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultrarapid metabolism of debrisoquine. *Proc Natl Acad Sci U S A 90*, 11825–11829.
Johnson, M. D., Zuo, H., Lee, K. -H., Trebley, J. P., Rae, J. M., Weatherman, R. V., et al. (2004). Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. *Breast Cancer Res Treat 85*, 151–159.
Johnstone, E., Benowitz, N., Cargill, A., Jacob, R., Hinks, L., Day, I., et al. (2006). Determinants of the rate of nicotine metabolism and effects on smoking behavior. *Clin Pharmacol Ther 80*, 319–330.
Jonas, D. E., & McLeod, H. L. (2009). Genetic and clinical factors relating to warfarin dosing. *Trends Pharmacol Sci 30*, 375–386.
Jorge-Nebert, L. F., Jiang, Z., Chakraborty, R., Watson, J., Jin, L., McGarvey, S. T., et al. (2010). Analysis of human CYP1A1 and CYP1A2 genes and their shared bidirectional promoter in eight world populations. *Hum Mutat 31*, 27–40.
Josephson, F., Allqvist, A., Janabi, M., Sayi, J., Aklillu, E., Jande, M., et al. (2007). CYP3A5 genotype has an impact on the metabolism of the HIV protease inhibitor saquinavir. *Clin Pharmacol Ther 81*, 708–712.
Joshi, M., & Tyndale, R. F. (2006). Regional and cellular distribution of CYP2E1 in monkey brain and its induction by chronic nicotine. *Neuropharmacology 50*, 568–575.
Jover, R., Bort, R., Gómez-Lechón, M. J., & Castell, J. V. (2002). Down-regulation of human CYP3A4 by the inflammatory signal interleukin-6: molecular mechanism and transcription factors involved. *FASEB J 16*, 1799–1801.
Jover, R., Moya, M., & Gómez-Lechón, M. J. (2009). Transcriptional regulation of cytochrome p450 genes by the nuclear receptor hepatocyte nuclear factor 4-alpha. *Curr Drug Metab 10*, 508–519.
Kamdem, L. K., Meineke, I., Gödtel-Armbrust, U., Brockmöller, J., & Wojnowski, L. (2006). Dominant contribution of P450 3A4 to the hepatic carcinogenic activation of aflatoxin B1. *Chem Res Toxicol 19*, 577–586.
Kang, P., Dalvie, D., Smith, E., Zhou, S., Deese, A., & Nieman, J. A. (2008). Bioactivation of flutamide metabolites by human liver microsomes. *Drug Metab Dispos 36*, 1425–1437.
Karbiener, M., Fischer, C., Nowitsch, S., Opriessnig, P., Papak, C., Ailhaud, G., et al. (2009). microRNA miR-27b impairs human adipocyte differentiation and targets PPARgamma. *Biochem Biophys Res Commun 390*, 247–251.
Kaur-Knudsen, D., Bojesen, S. E., & Nordestgaard, B. G. (2009a). Common polymorphisms in CYP2C9, subclinical atherosclerosis and risk of ischemic vascular disease in 52,000 individuals. *Pharmacogenomics J 9*, 327–332.
Kaur-Knudsen, D., Nordestgaard, B. G., Tybjaerg-Hansen, A., & Bojesen, S. E. (2009b). CYP1B1 genotype and risk of cardiovascular disease, pulmonary disease, and cancer in 50,000 individuals. *Pharmacogenet Genomics 19*, 685–694.
Kawakami, H., Ohtsuki, S., Kamiie, J., Suzuki, T., Abe, T., & Terasaki, T. (2011). Simultaneous absolute quantification of 11 cytochrome P450 isoforms in human liver microsomes by liquid chromatography tandem mass spectrometry with in silico target peptide selection. *J Pharm Sci 100*, 341–352.
Kawashima, S., Kobayashi, K., Takama, K., Higuchi, T., Furihata, T., Hosokawa, M., et al. (2006). Involvement of hepatocyte nuclear factor 4alpha in the different expression level between CYP2C9 and CYP2C19 in the human liver. *Drug Metab Dispos 34*, 1012–1018.
Kazui, M., Nishiya, Y., Ishizuka, T., Hagihara, K., Farid, N. A., Okazaki, O., et al. (2010). Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. *Drug Metab Dispos 38*, 92–99.
Kerb, R., Fux, R., Mörike, K., Kremsner, P. G., Gil, J. P., Gleiter, C. H., et al. (2009). Pharmacogenetics of antimalarial drugs: effect on metabolism and transport. *Lancet Infect Dis 9*, 760–774.
Keshava, C., McCanlies, E. C., & Weston, A. (2004). CYP3A4 polymorphisms–potential risk factors for breast and prostate cancer: a HuGE review. *Am J Epidemiol 160*, 825–841.
Kim, S. K., & Novak, R. F. (2007). The role of intracellular signaling in insulin-mediated regulation of drug metabolizing enzyme gene and protein expression. *Pharmacol Ther 113*, 88–120.
Kim, R. B., & O'Shea, D. (1995). Interindividual variability of chlorzoxazone 6-hydroxylation in men and women and its relationship to CYP2E1 genetic polymorphisms. *Clin Pharmacol Ther 57*, 645–655.
Kimura, S., Umeno, M., Skoda, R. C., Meyer, U. A., & Gonzalez, F. J. (1989). The human debrisoquine 4-hydroxylase (CYP2D) locus: sequence and identification of the polymorphic CYP2D6 gene, a related gene, and a pseudogene. *Am J Hum Genet 45*, 889–904.
King, J., & Aberg, J. A. (2008). Clinical impact of patient population differences and genomic variation in efavirenz therapy. *AIDS 22*, 1709–1717.
King, L. M., Ma, J., Srettabunjong, S., Graves, J., Bradbury, J. A., Li, L., et al. (2002). Cloning of CYP2J2 gene and identification of functional polymorphisms. *Mol Pharmacol 61*, 840–852.
Kinirons, M. T., & O'Mahony, M. S. (2004). Drug metabolism and ageing. *Br J Clin Pharmacol 57*, 540–544.
Kirchheiner, J., Klein, C., Meineke, I., Sasse, J., Zanger, U. M., Mürdter, T. E., et al. (2003). Bupropion and 4-OH-bupropion pharmacokinetics in relation to genetic polymorphisms in CYP2B6. *Pharmacogenetics 13*, 619–626.
Kirchheiner, J., Nickchen, K., Bauer, M., Wong, M. -L., Licinio, J., Roots, I., et al. (2004). Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry 9*, 442–473.
Kirchheiner, J., Thomas, S., Bauer, S., Tomalik-Scharte, D., Hering, U., Doroshyenko, O., et al. (2006). Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype. *Clin Pharmacol Ther 80*, 657–667.
Kisselev, P., Schunck, W. -H., Roots, I., & Schwarz, D. (2005). Association of CYP1A1 polymorphisms with differential metabolic activation of 17beta-estradiol and estrone. *Cancer Res 65*, 2972–2978.
Kitada, M. (2003). Genetic polymorphism of cytochrome P450 enzymes in Asian populations: focus on CYP2D6. *Int J Clin Pharmacol Res 23*, 31–35.
Kiyotani, K., Mushiroda, T., Imamura, C. K., Hosono, N., Tsunoda, T., Kubo, M., et al. (2010). Significant effect of polymorphisms in CYP2D6 and ABCC2 on clinical outcomes of adjuvant tamoxifen therapy for breast cancer patients. *J Clin Oncol 28*, 1287–1293.
Kiyotani, K., Mushiroda, T., Imamura, C. K., Tanigawara, Y., Hosono, N., Kubo, M., et al. (2012). Dose-adjustment study of tamoxifen based on CYP2D6 genotypes in Japanese breast cancer patients. *Breast Cancer Res Treat 131*, 137–145.
Klein, T. E., Altman, R. B., Eriksson, N., Gage, B. F., Kimmel, S. E., Lee, M. -T. M., et al. (2009). Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med 360*, 753–764.
Klein, K., Lang, T., Saussele, T., Barbosa-Sicard, E., Schunck, W. -H., Eichelbaum, M., et al. (2005). Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional variants, and possible implications for anti-HIV therapy with efavirenz. *Pharmacogenet Genomics 15*, 861–873.
Klein, K., Thomas, M., Winter, S., Nussler, A. K., Niemi, M., Schwab, M., et al. (2012). PPARA: a novel genetic determinant of CYP3A4 in vitro and in vivo. *Clin Pharmacol Ther 91*, 1044–1052.
Klein, K., Winter, S., Turpeinen, M., Schwab, M., & Zanger, U. M. (2010). Pathway-targeted pharmacogenomics of CYP1A2 in human liver. *Front Pharmacol*, 1.
Klotz, U. (2006). Clinical impact of CYP2C19 polymorphism on the action of proton pump inhibitors: a review of a special problem. *Int J Clin Pharmacol Ther 44*, 297–302.
Klotz, U. (2007). Antiarrhythmics: elimination and dosage considerations in hepatic impairment. *Clin Pharmacokinet 46*, 985–996.
Klotz, U., Schwab, M., & Treiber, G. (2004). CYP2C19 polymorphism and proton pump inhibitors. *Basic Clin Pharmacol Toxicol 95*, 2–8.
Knockaert, L., Fromenty, B., & Robin, M. -A. (2011). Mechanisms of mitochondrial targeting of cytochrome P450 2E1: physiopathological role in liver injury and obesity. *FEBS J 278*, 4252–4260.
Koch, I., Weil, R., Wolbold, R., Brockmöller, J., Hustert, E., Burk, O., et al. (2002). Interindividual variability and tissue-specificity in the expression of cytochrome P450 3A mRNA. *Drug Metab Dispos 30*, 1108–1114.
Komatsu, T., Yamazaki, H., Shimada, N., Nakajima, M., & Yokoi, T. (2000). Roles of cytochromes P450 1A2, 2A6, and 2C8 in 5-fluorouracil formation from tegafur, an anticancer prodrug, in human liver microsomes. *Drug Metab Dispos 28*, 1457–1463.
Koren, G., Cairns, J., Chitayat, D., Gaedigk, A., & Leeder, S. J. (2006). Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet 368*, 704.
Kosaki, K., Tamura, K., Sato, R., Samejima, H., Tanigawara, Y., & Takahashi, T. (2004). A major influence of CYP2C19 genotype on the steady-state concentration of N-desmethylclobazam. *Brain Dev 26*, 530–534.
Koukouritaki, S. B., Manro, J. R., Marsh, S. A., Stevens, J. C., Rettie, A. E., McCarver, D. G., et al. (2004). Developmental expression of human hepatic CYP2C9 and CYP2C19. *J Pharmacol Exp Ther 308*, 965–974.
Kramer, M. A., Rettie, A. E., Rieder, M. J., Cabacungan, E. T., & Hines, R. N. (2008). Novel CYP2C9 promoter variants and assessment of their impact on gene expression. *Mol Pharmacol 73*, 1751–1760.
Kranendonk, M., Marohnic, C. C., Panda, S. P., Duarte, M. P., Oliveira, J. S., Masters, B. S. S., et al. (2008). Impairment of human CYP1A2-mediated xenobiotic metabolism by Antley–Bixler syndrome variants of cytochrome P450 oxidoreductase. *Arch Biochem Biophys 475*, 93–99.
Kreth, K., Kovar, K., Schwab, M., & Zanger, U. M. (2000). Identification of the human cytochromes P450 involved in the oxidative metabolism of "Ecstasy"-related designer drugs. *Biochem Pharmacol 59*, 1563–1571.
Kubota, T., Nakajima-Taniguchi, C., Fukuda, T., Funamoto, M., Maeda, M., Tange, E., et al. (2006). CYP2A6 polymorphisms are associated with nicotine dependence and influence withdrawal symptoms in smoking cessation. *Pharmacogenomics J 6*, 115–119.

Kuehl, P., Zhang, J., Lin, Y., Lamba, J., Assem, M., Schuetz, J., et al. (2001). Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet 27*, 383–391.

Küpfer, A., & Preisig, R. (1984). Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. *Eur J Clin Pharmacol 26*, 753–759.

Kurzawski, M., Gawrońska-Szklarz, B., Wrześniewska, J., Siuda, A., Starzyńska, T., & Droździk, M. (2006). Effect of CYP2C19*17 gene variant on *Helicobacter pylori* eradication in peptic ulcer patients. *Eur J Clin Pharmacol 62*, 877–880.

Lafite, P., Dijols, S., Zeldin, D. C., Dansette, P. M., & Mansuy, D. (2007). Selective, competitive and mechanism-based inhibitors of human cytochrome P450 2J2. *Arch Biochem Biophys 464*, 155–168.

Laganà, A., Forte, S., Giudice, A., Arena, M. R., Puglisi, P. L., Giugno, R., et al. (2009). miRò: a miRNA knowledge base. *Database (Oxford) 2009*, bap008. http://dx.doi.org/10.1093/database/bap008.

Lai, X. -S., Yang, L. -P., Li, X. -T., Liu, J. -P., Zhou, Z. -W., & Zhou, S. -F. (2009). Human CYP2C8: structure, substrate specificity, inhibitor selectivity, inducers and polymorphisms. *Curr Drug Metab 10*, 1009–1047.

Laika, B., Leucht, S., Heres, S., Schneider, H., & Steimer, W. (2010). Pharmacogenetics and olanzapine treatment: CYP1A2*1F and serotonergic polymorphisms influence therapeutic outcome. *Pharmacogenomics J 10*, 20–29.

Lake, A. D., Novak, P., Fisher, C. D., Jackson, J. P., Hardwick, R. N., Billheimer, D. D., et al. (2011). Analysis of global and absorption, distribution, metabolism, and elimination gene expression in the progressive stages of human nonalcoholic fatty liver disease. *Drug Metab Dispos 39*, 1954–1960.

Lamba, J., Lamba, V., & Schuetz, E. (2005). Genetic variants of PXR (NR1I2) and CAR (NR1I3) and their implications in drug metabolism and pharmacogenetics. *Curr Drug Metab 6*, 369–383.

Lamba, J., Lamba, V., Strom, S., Venkataramanan, R., & Schuetz, E. (2008). Novel single nucleotide polymorphisms in the promoter and intron 1 of human pregnane X receptor/NR1I2 and their association with CYP3A4 expression. *Drug Metab Dispos 36*, 169–181.

Lamba, V., Lamba, J., Yasuda, K., Strom, S., Davila, J., Hancock, M. L., et al. (2003). Hepatic CYP2B6 expression: gender and ethnic differences and relationship to CYP2B6 genotype and CAR (constitutive androstane receptor) expression. *J Pharmacol Exp Ther 307*, 906–922.

Lamba, V., Panetta, J. C., Strom, S., & Schuetz, E. G. (2010). Genetic predictors of interindividual variability in hepatic CYP3A4 expression. *J Pharmacol Exp Ther 332*, 1088–1099.

Lang, T., Klein, K., Fischer, J., Nüssler, A. K., Neuhaus, P., Hofmann, U., et al. (2001). Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. *Pharmacogenetics 11*, 399–415.

Lang, T., Klein, K., Richter, T., Zibat, A., Kerb, R., Eichelbaum, M., et al. (2004). Multiple novel nonsynonymous CYP2B6 gene polymorphisms in Caucasians: demonstration of phenotypic null alleles. *J Pharmacol Exp Ther 311*, 34–43.

Langenfeld, E., Zanger, U. M., Jung, K., Meyer, H. E., & Marcus, K. (2009). Mass spectrometry-based absolute quantification of microsomal cytochrome P450 2D6 in human liver. *Proteomics 9*, 2313–2323.

Läpple, F., Von Richter, O., Fromm, M. F., Richter, T., Thon, K. P., Wisser, H., et al. (2003). Differential expression and function of CYP2C isoforms in human intestine and liver. *Pharmacogenetics 13*, 565–575.

Leclerc, J., Tournel, G., Courcot-Ngoubo Ngangue, E., Pottier, N., Lafitte, J. -J., Jaillard, S., et al. (2010). Profiling gene expression of whole cytochrome P450 superfamily in human bronchial and peripheral lung tissues: differential expression in non-small cell lung cancers. *Biochimie 92*, 292–306.

Lee, S. -J. (2013). Clinical application of CYP2C19 pharmacogenetics toward more personalized medicine. *Front Genet 3*(318). http://dx.doi.org/10.3389/fgene.2012.00318.

Lee, S. S., Cha, E. -Y., Jung, H. -J., Shon, J. -H., Kim, E. -Y., Yeo, C. -W., et al. (2008a). Genetic polymorphism of hepatocyte nuclear factor-4alpha influences human cytochrome P450 2D6 activity. *Hepatology 48*, 635–645.

Lee, C. R., Goldstein, J. A., & Pieper, J. A. (2002). Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics 12*, 251–263.

Lee, M. -Y., Mukherjee, N., Pakstis, A. J., Khaliq, S., Mohyuddin, A., Mehdi, S. Q., et al. (2008b). Global patterns of variation in allele and haplotype frequencies and linkage disequilibrium across the CYP2E1 gene. *Pharmacogenomics J 8*, 349–356.

Lee, C. A., Neul, D., Clouser-Roche, A., Dalvie, D., Wester, M. R., Jiang, Y., et al. (2010). Identification of novel substrates for human cytochrome P450 2J2. *Drug Metab Dispos 38*, 347–356.

Leeder, J. S., Gaedigk, R., Marcucci, K. A., Gaedigk, A., Vyhlidal, C. A., Schindel, B. P., et al. (2005). Variability of CYP3A7 expression in human fetal liver. *J Pharmacol Exp Ther 314*, 626–635.

Lehr, T., Yuan, J., Hall, D., Zimdahl-Gelling, H., Schaefer, H. G., Staab, A., et al. (2011). Integration of absorption, distribution, metabolism, and elimination genotyping data into a population pharmacokinetic analysis of nevirapine. *Pharmacogenet Genomics 21*, 721–730.

Leppert, W. (2011). CYP2D6 in the metabolism of opioids for mild to moderate pain. *Pharmacology 87*, 274–285.

Leskelä, S., Jara, C., Leandro-García, L. J., Martínez, A., García-Donas, J., Hernando, S., et al. (2011). Polymorphisms in cytochromes P450 2C8 and 3A5 are associated with paclitaxel neurotoxicity. *Pharmacogenomics J 11*, 121–129.

Levran, O., Peles, E., Hamon, S., Randesi, M., Adelson, M., & Kreek, M. J. (2011). CYP2B6 SNPs are associated with methadone dose required for effective treatment of opioid addiction. *Addict Biol*. http://dx.doi.org/10.1111/j.1369-1600.2011.00349.x.

Lewis, D. F. V., Lake, B. G., & Dickins, M. (2004). Substrates of human cytochromes P450 from families CYP1 and CYP2: analysis of enzyme selectivity and metabolism. *Drug Metabol Drug Interact 20*, 111–142.

Li, X. -Q., Björkman, A., Andersson, T. B., Ridderström, M., & Masimirembwa, C. M. (2002). Amodiaquine clearance and its metabolism to N-desethylamodiaquine is mediated by CYP2C8: a new high affinity and turnover enzyme-specific probe substrate. *J Pharmacol Exp Ther 300*, 399–407.

Li, H., Ferguson, S. S., & Wang, H. (2010). Synergistically enhanced CYP2B6 inducibility between a polymorphic mutation in CYP2B6 promoter and pregnane X receptor activation. *Mol Pharmacol 78*, 704–713.

Li, J., Menard, V., Benish, R. L., Jurevic, R. J., Guillemette, C., Stoneking, M., et al. (2012a). Worldwide variation in human drug-metabolism enzyme genes CYP2B6 and UGT2B7: implications for HIV/AIDS treatment. *Pharmacogenomics 13*, 555–570.

Li, D. N., Seidel, A., Pritchard, M. P., Wolf, C. R., & Friedberg, T. (2000). Polymorphisms in P450 CYP1B1 affect the conversion of estradiol to the potentially carcinogenic metabolite 4-hydroxyestradiol. *Pharmacogenetics 10*, 343–353.

Li, H., Xiao, D., Hu, L., & He, T. (2012b). Association of CYP1A1 polymorphisms with prostate cancer risk: an updated meta-analysis. *Mol Biol Rep 39*, 10273–10284.

Lieber, C. S. (1997). Cytochrome P-4502E1: its physiological and pathological role. *Physiol Rev 77*, 517–544.

Lin, J. H. (2007). Pharmacokinetic and pharmacodynamic variability: a daunting challenge in drug therapy. *Curr Drug Metab 8*, 109–136.

Lin, Y. S., Dowling, A. L. S., Quigley, S. D., Farin, F. M., Zhang, J., Lamba, J., et al. (2002). Co-regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism. *Mol Pharmacol 62*, 162–172.

Liu, Y. -T., Hao, H. -P., Liu, C. -X., Wang, G. -J., & Xie, H. -G. (2007). Drugs as CYP3A probes, inducers, and inhibitors. *Drug Metab Rev 39*, 699–721.

Liu, F. -J., Song, X., Yang, D., Deng, R., & Yan, B. (2008). The far and distal enhancers in the CYP3A4 gene co-ordinate the proximal promoter in responding similarly to the pregnane X receptor but differentially to hepatocyte nuclear factor-4alpha. *Biochem J 409*, 243–250.

Li-Wan-Po, A., Girard, T., Farndon, P., Cooley, C., & Lithgow, J. (2010). Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19*17. *Br J Clin Pharmacol 69*, 222–230.

Lobo, E. D., Bergstrom, R. F., Reddy, S., Quinlan, T., Chappell, J., Hong, Q., et al. (2008). In vitro and in vivo evaluations of cytochrome P450 1A2 interactions with duloxetine. *Clin Pharmacokinet 47*, 191–202.

Löfgren, S., Baldwin, R. M., Carlerös, M., Terelius, Y., Fransson-Steen, R., Mwinyi, J., et al. (2009). Regulation of human CYP2C18 and CYP2C19 in transgenic mice: influence of castration, testosterone, and growth hormone. *Drug Metab Dispos 37*, 1505–1512.

Lu, Y., & Cederbaum, A. I. (2008). CYP2E1 and oxidative liver injury by alcohol. *Free Radic Biol Med 44*, 723–738.

Lu, Y., Won, K. A., Nelson, B. J., Qi, D., Rausch, D. J., & Asinger, R. W. (2008). Characteristics of the amiodarone-warfarin interaction during long-term follow-up. *Am J Health Syst Pharm 65*, 947–952.

Lubomirov, R., Colombo, S., Di Iulio, J., Ledergerber, B., Martinez, R., Cavassini, M., et al. (2011). Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study. *J Infect Dis 203*, 246–257.

Lubomirov, R., Di Iulio, J., Fayet, A., Colombo, S., Martinez, R., Marzolini, C., et al. (2010). ADME pharmacogenetics: investigation of the pharmacokinetics of the antiretroviral agent lopinavir coformulated with ritonavir. *Pharmacogenet Genomics 20*, 217–230.

Lunshof, J. E., & Gurwitz, D. (2012). Pharmacogenomic testing: knowing more, doing better. *Clin Pharmacol Ther 91*, 387–389.

Lutz, M., Schwab, M., Griese, E. -U., Marx, C., Müller-Oerlinghausen, B., Schönhöfer, P. S., et al. (2002). Visual disorders associated with omeprazole and their relation to CYP2C19 polymorphism. *Pharmacogenetics 12*, 73–75.

MacArthur, D. G., Balasubramanian, S., Frankish, A., Huang, N., Morris, J., Walter, K., et al. (2012). A systematic survey of loss-of-function variants in human protein-coding genes. *Science 335*, 823–828.

Madadi, P., Avard, D., & Koren, G. (2012). Pharmacogenetics of opioids for the treatment of acute maternal pain during pregnancy and lactation. *Curr Drug Metab 13*, 721–727.

Madadi, P., Ross, C. J. D., Hayden, M. R., Carleton, B. C., Gaedigk, A., Leeder, J. S., et al. (2009). Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case–control study. *Clin Pharmacol Ther 85*, 31–35.

Madlensky, L., Natarajan, L., Tchu, S., Pu, M., Mortimer, J., Flatt, S. W., et al. (2011). Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. *Clin Pharmacol Ther 89*, 718–725.

Maglich, J. M., Stoltz, C. M., Goodwin, B., Hawkins-Brown, D., Moore, J. T., & Kliewer, S. A. (2002). Nuclear pregnane x receptor and constitutive androstane receptor regulate overlapping but distinct sets of genes involved in xenobiotic detoxification. *Mol Pharmacol 62*, 638–646.

Mahgoub, A., Idle, J. R., Dring, L. G., Lancaster, R., & Smith, R. L. (1977). Polymorphic hydroxylation of Debrisoquine in man. *Lancet 2*, 584–586.

Mahungu, T., Smith, C., Turner, F., Egan, D., Youle, M., Johnson, M., et al. (2009). Cytochrome P450 2B6 516G−>T is associated with plasma concentrations of nevirapine at both 200 mg twice daily and 400 mg once daily in an ethnically diverse population. *HIV Med 10*, 310–317.

Maimbo, M., Kiyotani, K., Mushiroda, T., Masimirembwa, C., & Nakamura, Y. (2011). CYP2B6 genotype is a strong predictor of systemic exposure to efavirenz in HIV-infected Zimbabweans. *Eur J Clin Pharmacol 68*, 267–271.

Malaiyandi, V., Lerman, C., Benowitz, N. L., Jepson, C., Patterson, F., & Tyndale, R. F. (2006). Impact of CYP2A6 genotype on pretreatment smoking behaviour and nicotine levels from and usage of nicotine replacement therapy. *Mol Psychiatry 11*, 400–409.

Manolopoulos, V. G., Ragia, G., & Tavridou, A. (2011). Pharmacogenomics of oral antidiabetic medications: current data and pharmacoepigenomic perspective. *Pharmacogenomics 12*, 1161–1191.

Marohnic, C. C., Panda, S. P., McCammon, K., Rueff, J., Masters, B. S. S., & Kranendonk, M. (2010). Human cytochrome P450 oxidoreductase deficiency caused by the Y181D mutation: molecular consequences and rescue of defect. *Drug Metab Dispos 38*, 332–340.

Marth, G. T., Yu, F., Indap, A. R., Garimella, K., Gravel, S., Leong, W. F., et al. (2011). The functional spectrum of low-frequency coding variation. *Genome Biol 12*, R84.

Martinez-Jiménez, C. P., Gómez-Lechón, M. J., Castell, J. V., & Jover, R. (2005). Transcriptional regulation of the human hepatic CYP3A4: identification of a new distal enhancer region responsive to CCAAT/enhancer-binding protein beta isoforms (liver activating protein and liver inhibitory protein). *Mol Pharmacol 67*, 2088–2101.

Matsubara, T., Yoshinari, K., Aoyama, K., Sugawara, M., Sekiya, Y., Nagata, K., et al. (2008). Role of vitamin D receptor in the lithocholic acid-mediated CYP3A induction in vitro and in vivo. *Drug Metab Dispos 36*, 2058–2063.

Matsumoto, S., Hirama, T., Matsubara, T., Nagata, K., & Yamazoe, Y. (2002). Involvement of CYP2J2 on the intestinal first-pass metabolism of antihistamine drug, astemizole. *Drug Metab Dispos 30*, 1240–1245.

Matsumura, K., Saito, T., Takahashi, Y., Ozeki, T., Kiyotani, K., Fujieda, M., et al. (2004). Identification of a novel polymorphic enhancer of the human CYP3A4 gene. *Mol Pharmacol 65*, 326–334.

McCarver, D. G., Byun, R., Hines, R. N., Hichme, M., & Wegenek, W. (1998). A genetic polymorphism in the regulatory sequences of human CYP2E1: association with increased chlorzoxazone hydroxylation in the presence of obesity and ethanol intake. *Toxicol Appl Pharmacol 152*, 276–281.

Mega, J. L., Close, S. L., Wiviott, S. D., Shen, L., Hockett, R. D., Brandt, J. T., et al. (2009). Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med 360*, 354–362.

Mehlotra, R. K., Bockarie, M. J., & Zimmerman, P. A. (2007). CYP2B6 983T>C polymorphism is prevalent in West Africa but absent in Papua New Guinea: implications for HIV/AIDS treatment. *Br J Clin Pharmacol 64*, 391–395.

Melanson, S. E. F., Stevenson, K., Kim, H., Antin, J. H., Court, M. H., Ho, V. T., et al. (2010). Allelic variations in CYP2B6 and CYP2C19 and survival of patients receiving cyclophosphamide prior to myeloablative hematopoietic stem cell transplantation. *Am J Hematol 85*, 967–971.

Meyer, U. A. (2004). Pharmacogenetics — five decades of therapeutic lessons from genetic diversity. *Nat Rev Genet 5*, 669–676.

Meyer, U. A., & Zanger, U. M. (1997). Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol 37*, 269–296.

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

Miksys, S., Lerman, C., Shields, P. G., Mash, D. C., & Tyndale, R. F. (2003). Smoking, alcoholism and genetic polymorphisms alter CYP2B6 levels in human brain. *Neuropharmacology 45*, 122–132.

Miksys, S., Rao, Y., Hoffmann, E., Mash, D. C., & Tyndale, R. F. (2002). Regional and cellular expression of CYP2D6 in human brain: higher levels in alcoholics. *J Neurochem 82*, 1376–1387.

Mikus, G., Scholz, I. M., & Weiss, J. (2011). Pharmacogenomics of the triazole antifungal agent voriconazole. *Pharmacogenomics 12*, 861–872.

Miller, W. L., Agrawal, V., Sandee, D., Tee, M. K., Huang, N., Choi, J. H., et al. (2011). Consequences of POR mutations and polymorphisms. *Mol Cell Endocrinol 336*, 174–179.

Millonig, G., Wang, Y., Homann, N., Bernhardt, F., Qin, H., Mueller, S., et al. (2011). Ethanol-mediated carcinogenesis in the human esophagus implicates CYP2E1 induction and the generation of carcinogenic DNA-lesions. *Int J Cancer 128*, 533–540.

Mishra, P. J., Humeniuk, R., Mishra, P. J., Longo-Sorbello, G. S. A., Banerjee, D., & Bertino, J. R. (2007). A miR-24 microRNA binding-site polymorphism in dihydrofolate reductase gene leads to methotrexate resistance. *Proc Natl Acad Sci U S A 104*, 13513–13518.

Mohri, T., Nakajima, M., Fukami, T., Takamiya, M., Aoki, Y., & Yokoi, T. (2010). Human CYP2E1 is regulated by miR-378. *Biochem Pharmacol 79*, 1045–1052.

Mori, K., Blackshear, P. E., Lobenhofer, E. K., Parker, J. S., Orzech, D. P., Roycroft, J. H., et al. (2007). Hepatic transcript levels for genes coding for enzymes associated with xenobiotic metabolism are altered with age. *Toxicol Pathol 35*, 242–251.

Mörike, K., Kivistö, K. T., Schaeffeler, E., Jägle, C., Igel, S., Drescher, S., et al. (2008). Propafenone for the prevention of atrial tachyarrhythmias after cardiac surgery: a randomized, double-blind placebo-controlled trial. *Clin Pharmacol Ther 84*, 104–110.

Murai, K., Yamazaki, H., Nakagawa, K., Kawai, R., & Kamataki, T. (2009). Deactivation of anti-cancer drug letrozole to a carbinol metabolite by polymorphic cytochrome P450 2A6 in human liver microsomes. *Xenobiotica 39*, 795–802.

Mürdter, T. E., Kerb, R., Turpeinen, M., Schroth, W., Ganchev, B., Böhmer, G. M., et al. (2011a). Genetic polymorphism of cytochrome P450 2D6 determines oestrogen receptor activity of the major infertility drug clomiphene via its active metabolites. *Hum Mol Genet 21*, 1145–1154.

Mürdter, T. E., Schroth, W., Bacchus-Gerybadze, L., Winter, S., Heinkele, G., Simon, W., et al. (2011b). Activity levels of tamoxifen metabolites at the estrogen receptor and the impact of genetic polymorphisms of phase I and II enzymes on their concentration levels in plasma. *Clin Pharmacol Ther 89*, 708–717.

Murray, G. I., Melvin, W. T., Greenlee, W. F., & Burke, M. D. (2001). Regulation, function, and tissue-specific expression of cytochrome P450 CYP1B1. *Annu Rev Pharmacol Toxicol 41*, 297–316.

Murray, G. I., Taylor, M. C., McFadyen, M. C., McKay, J. A., Greenlee, W. F., Burke, M. D., et al. (1997). Tumor-specific expression of cytochrome P450 CYP1B1. *Cancer Res 57*, 3026–3031.

Muschler, E., Lal, J., Jetter, A., Rattay, A., Zanger, U., Zadoyan, G., et al. (2009). The role of human CYP2C8 and CYP2C9 variants in pioglitazone metabolism in vitro. *Basic Clin Pharmacol Toxicol 105*, 374–379.

Mwenifumbo, J. C., & Tyndale, R. F. (2007). Genetic variability in CYP2A6 and the pharmacokinetics of nicotine. *Pharmacogenomics 8*, 1385–1402.

Mwenifumbo, J. C., & Tyndale, R. F. (2009). Molecular genetics of nicotine metabolism. *Handb Exp Pharmacol*, 235–259.

Mwenifumbo, J. C., Zhou, Q., Benowitz, N. L., Sellers, E. M., & Tyndale, R. F. (2010). New CYP2A6 gene deletion and conversion variants in a population of Black African descent. *Pharmacogenomics 11*, 189–198.

Mwinyi, J., Cavaco, I., Pedersen, R. S., Persson, A., Burkhardt, S., Mkrtchian, S., et al. (2010a). Regulation of CYP2C19 expression by estrogen receptor α: implications for estrogen-dependent inhibition of drug metabolism. *Mol Pharmacol 78*, 886–894.

Mwinyi, J., Cavaco, I., Yurdakok, B., Mkrtchian, S., & Ingelman-Sundberg, M. (2011). The ligands of estrogen receptor α regulate cytochrome P4502C9 (CYP2C9) expression. *J Pharmacol Exp Ther 338*, 302–309.

Mwinyi, J., Nekvindová, J., Cavaco, I., Hofmann, Y., Pedersen, R. S., Landman, E., et al. (2010b). New insights into the regulation of CYP2C9 gene expression: the role of the transcription factor GATA-4. *Drug Metab Dispos 38*, 415–421.

Naik, A., Belič, A., Zanger, U. M., & Rozman, D. (2013). Molecular interactions between NAFLD and xenobiotic metabolism. *Front Genet 4*(2). http://dx.doi.org/10.3389/fgene.2013.00002.

Nakajima, M., Fukami, T., Yamanaka, H., Higashi, E., Sakai, H., Yoshida, R., et al. (2006). Comprehensive evaluation of variability in nicotine metabolism and CYP2A6 polymorphic alleles in four ethnic populations. *Clin Pharmacol Ther 80*, 282–297.

Nakajima, M., Komagata, S., Fujiki, Y., Kanada, Y., Ebi, H., Itoh, K., et al. (2007). Genetic polymorphisms of CYP2B6 affect the pharmacokinetics/pharmacodynamics of cyclophosphamide in Japanese cancer patients. *Pharmacogenet Genomics 17*, 431–445.

Nakajima, M., Yokoi, T., Mizutani, M., Kinoshita, M., Funayama, M., & Kamataki, T. (1999). Genetic polymorphism in the 5′-flanking region of human CYP1A2 gene: effect on the CYP1A2 inducibility in humans. *J Biochem 125*, 803–808.

Nakamura, Y., Ratain, M. J., Cox, N. J., McLeod, H. L., Kroetz, D. L., & Flockhart, D. A. (2012). Re: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the Breast International Group 1–98 trial. *J Natl Cancer Inst 104*, 1264 (author reply 1266–1268).

Napoli, N., Rini, G. B., Serber, D., Giri, T., Yarramaneni, J., Bucchieri, S., et al. (2009). The Val432Leu polymorphism of the CYP1B1 gene is associated with differences in estrogen metabolism and bone density. *Bone 44*, 442–448.

Naraharisetti, S. B., Lin, Y. S., Rieder, M. J., Marciante, K. D., Psaty, B. M., Thummel, K. E., et al. (2010). Human liver expression of CYP2C8: gender, age, and genotype effects. *Drug Metab Dispos 38*, 889–893.

Neafsey, P., Ginsberg, G., Hattis, D., Johns, D. O., Guyton, K. Z., & Sonawane, B. (2009). Genetic polymorphism in CYP2E1: population distribution of CYP2E1 activity. *J Toxicol Environ Health B Crit Rev 12*, 362–388.

Nebert, D. W., & Dalton, T. P. (2006). The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. *Nat Rev Cancer 6*, 947–960.

Nebert, D. W., Dalton, T. P., Okey, A. B., & Gonzalez, F. J. (2004). Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. *J Biol Chem 279*, 23847–23850.

Nebert, D. W., & Karp, C. L. (2008). Endogenous functions of the aryl hydrocarbon receptor (AHR): intersection of cytochrome P450 1 (CYP1)-metabolized eicosanoids and AHR biology. *J Biol Chem 283*, 36061–36065.

Nebert, D. W., & Russell, D. W. (2002). Clinical importance of the cytochromes P450. *Lancet 360*, 1155–1162.

Nelson, D. R. (2004). Cytochrome P450 nomenclature, 2004. *Methods Mol Biol 320*, 1–10.

Nelson, D. R., Zeldin, D. C., Hoffman, S. M. G., Maltais, L. J., Wain, H. M., & Nebert, D. W. (2004). Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. *Pharmacogenetics 14*, 1–18.

Nielsen, K. K., Brøsen, K., Hansen, M. G., & Gram, L. F. (1994). Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. *Clin Pharmacol Ther 55*, 518–527.

Niemi, M., Leathart, J. B., Neuvonen, M., Backman, J. T., Daly, A. K., & Neuvonen, P. J. (2003). Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. *Clin Pharmacol Ther 74*, 380–387.

Niwa, T., Murayama, N., & Yamazaki, H. (2008). Heterotropic cooperativity in oxidation mediated by cytochrome p450. *Curr Drug Metab 9*, 453–462.

Node, K., Huo, Y., Ruan, X., Yang, B., Spiecker, M., Ley, K., et al. (1999). Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. *Science 285*, 1276–1279.

Nyakutira, C., Röshammar, D., Chigutsa, E., Chonzi, P., Ashton, M., Nhachi, C., et al. (2008). High prevalence of the CYP2B6 516G−>T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur J Clin Pharmacol 64*, 357–365.

Ogilvie, B. W., Zhang, D., Li, W., Rodrigues, A. D., Gipson, A. E., Holsapple, J., et al. (2006). Glucuronidation converts gemfibrozil to a potent, metabolism-dependent inhibitor of CYP2C8: implications for drug–drug interactions. *Drug Metab Dispos 34*, 191–197.

Ohlsson Rosenborg, S., Mwinyi, J., Andersson, M., Baldwin, R. M., Pedersen, R. S., Sim, S. C., et al. (2008). Kinetics of omeprazole and escitalopram in relation to the CYP2C19*17 allele in healthy subjects. *Eur J Clin Pharmacol 64*, 1175–1179.

Ohtsuki, S., Schaefer, O., Kawakami, H., Inoue, T., Liehner, S., Sato, A., et al. (2012). Simultaneous absolute protein quantification of transporters, cytochrome P450s and UDP-glucuronosyltransferases as a novel approach for the characterization of individual human liver: comparison with mRNA levels and activities. *Drug Metab Dispos 40*, 83–92.

Oneda, B., Crettol, S., Jaquenoud Sirot, E., Bochud, M., Ansermot, N., & Eap, C. B. (2009). The P450 oxidoreductase genotype is associated with CYP3A activity in vivo as measured by the midazolam phenotyping test. *Pharmacogenet Genomics 19*, 877–883.

Oneta, C. M., Lieber, C. S., Li, J., Rüttimann, S., Schmid, B., Lattmann, J., et al. (2002). Dynamics of cytochrome P4502E1 activity in man: induction by ethanol and disappearance during withdrawal phase. *J Hepatol 36*, 47–52.

Onica, T., Nichols, K., Larin, M., Ng, L., Maslen, A., Dvorak, Z., et al. (2008). Dexamethasone-mediated up-regulation of human CYP2A6 involves the glucocorticoid receptor and increased binding of hepatic nuclear factor 4 alpha to the proximal promoter. *Mol Pharmacol 73*, 451–460.

Onizuka, M., Kunii, N., Toyosaki, M., Machida, S., Ohgiya, D., Ogawa, Y., et al. (2011). Cytochrome P450 genetic polymorphisms influence the serum concentration of calcineurin inhibitors in allogeneic hematopoietic SCT recipients. *Bone Marrow Transplant 46*, 1113–1117.

Otto, D. M. E., Henderson, C. J., Carrie, D., Davey, M., Gundersen, T. E., Blomhoff, R., et al. (2003). Identification of novel roles of the cytochrome p450 system in early embryogenesis: effects on vasculogenesis and retinoic acid homeostasis. *Mol Cell Biol 23*, 6103–6116.

Ou, Z., Wada, T., Gramignoli, R., Li, S., Strom, S. C., Huang, M., et al. (2011). MicroRNA hsa-miR-613 targets the human LXRα gene and mediates a feedback loop of LXRα autoregulation. *Mol Endocrinol 25*, 584–596.

Ou-Yang, D. S., Huang, S. L., Wang, W., Xie, H. G., Xu, Z. H., Shu, Y., et al. (2000). Phenotypic polymorphism and gender-related differences of CYP1A2 activity in a Chinese population. *Br J Clin Pharmacol 49*, 145–151.

Ozdemir, V., Kalow, W., Tang, B. K., Paterson, A. D., Walker, S. E., Endrenyi, L., et al. (2000). Evaluation of the genetic component of variability in CYP3A4 activity: a repeated drug administration method. *Pharmacogenetics 10*, 373–388.

Paine, M. F., Hart, H. L., Ludington, S. S., Haining, R. L., Rettie, A. E., & Zeldin, D. C. (2006). The human intestinal cytochrome P450 "pie". *Drug Metab Dispos 34*, 880–886.

Palatini, P., Ceolotto, G., Ragazzo, F., Dorigatti, F., Saladini, F., Papparella, I., et al. (2009). CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension. *J Hypertens 27*, 1594–1601.

Palma, B. B., Silva, E., Sousa, M., Vosmeer, C. R., Lastdrager, J., Rueff, J., et al. (2010). Functional characterization of eight human cytochrome P450 1A2 gene variants by recombinant protein expression. *Pharmacogenomics J 10*, 478–488.

Pan, Y. -Z., Gao, W., & Yu, A. -M. (2009). MicroRNAs regulate CYP3A4 expression via direct and indirect targeting. *Drug Metab Dispos 37*, 2112–2117.

Pang, G. S. Y., Wang, J., Wang, Z., & Lee, C. G. L. (2009). Predicting potentially functional SNPs in drug-response genes. *Pharmacogenomics 10*, 639–653.

Parikh, S., Ouedraogo, J. -B., Goldstein, J. A., Rosenthal, P. J., & Kroetz, D. L. (2007). Amodiaquine metabolism is impaired by common polymorphisms in CYP2C8: implications for malaria treatment in Africa. *Clin Pharmacol Ther 82*, 197–203.

Pascussi, J. -M., Gerbal-Chaloin, S., Duret, C., Daujat-Chavanieu, M., Vilarem, M. -J., & Maurel, P. (2008). The tangle of nuclear receptors that controls xenobiotic metabolism and transport: crosstalk and consequences. *Annu Rev Pharmacol Toxicol 48*, 1–32.

Patsopoulos, N. A., Ntzani, E. E., Zintzaras, E., & Ioannidis, J. P. A. (2005). CYP2D6 polymorphisms and the risk of tardive dyskinesia in schizophrenia: a meta-analysis. *Pharmacogenet Genomics 15*, 151–158.

Pavek, P., & Dvorak, Z. (2008). Xenobiotic-induced transcriptional regulation of xenobiotic metabolizing enzymes of the cytochrome P450 superfamily in human extrahepatic tissues. *Curr Drug Metab 9*, 129–143.

Pedersen, R. S., Damkier, P., & Brosen, K. (2006). The effects of human CYP2C8 genotype and fluvoxamine on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol 62*, 682–689.

Pelkonen, O., Rautio, A., Raunio, H., & Pasanen, M. (2000). CYP2A6: a human coumarin 7-hydroxylase. *Toxicology 144*, 139–147.

Penno, M. B., Dvorchik, B. H., & Vesell, E. S. (1981). Genetic variation in rates of antipyrine metabolite formation: a study in uninduced twins. *Proc Natl Acad Sci U S A 78*, 5193–5196.

Penzak, S. R., Kabuye, G., Mugyenyi, P., Mbamanya, F., Natarajan, V., Alfaro, R. M., et al. (2007). Cytochrome P450 2B6 (CYP2B6) G516T influences nevirapine plasma concentrations in HIV-infected patients in Uganda. *HIV Med 8*, 86–91.

Perera, M. A. (2010). The missing linkage: what pharmacogenetic associations are left to find in CYP3A? *Expert Opin Drug Metab Toxicol 6*, 17–28.

Perera, M. A., Thirumaran, R. K., Cox, N. J., Hanauer, S., Das, S., Brimer-Cline, C., et al. (2009). Prediction of CYP3A4 enzyme activity using haplotype tag SNPs in African Americans. *Pharmacogenomics J 9*, 49–60.

Pharoah, P. D. P., Abraham, J., & Caldas, C. (2012). Re: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the Breast International Group 1–98 trial and Re: CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. *J Natl Cancer Inst 104*, 1263–1264 (author reply 1266–1268).

Pilotto, A., Seripa, D., Franceschi, M., Scarcelli, C., Colaizzo, D., Grandone, E., et al. (2007). Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms. *Gastroenterology 133*, 465–471.

Pirmohamed, M. (2009). The applications of pharmacogenetics to prescribing: what is currently practicable? *Clin Med 9*, 493–495.

Qiu, H., Mathäs, M., Nestler, S., Bengel, C., Nem, D., Gödtel-Armbrust, U., et al. (2010). The unique complexity of the CYP3A4 upstream region suggests a nongenetic explanation of its expression variability. *Pharmacogenet Genomics 20*, 167–178.

Raccor, B. S., Claessens, A. J., Dinh, J. C., Park, J. R., Hawkins, D. S., Thomas, S. S., et al. (2012). Potential contribution of cytochrome P450 2B6 to hepatic 4-hydroxycyclophosphamide formation in vitro and in vivo. *Drug Metab Dispos 40*, 54–63.

Rae, J. M., Drury, S., Hayes, D. F., Stearns, V., Thibert, J. N., Haynes, B. P., et al. (2012). CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. *J Natl Cancer Inst 104*, 452–460.

Rahmioglu, N., Heaton, J., Clement, G., Gill, R., Surdulescu, G., Zlobecka, K., et al. (2012). Genome-wide association study reveals a complex genetic architecture underpinning-induced CYP3A4 enzyme activity. *Eur J Drug Metab Pharmacokinet* [Electronic publication ahead of print].

Raimundo, S., Toscano, C., Klein, K., Fischer, J., Griese, E. -U., Eichelbaum, M., et al. (2004). A novel intronic mutation, 2988G>A, with high predictivity for impaired function of cytochrome P450 2D6 in white subjects. *Clin Pharmacol Ther 76*, 128–138.

Rakhmanina, N. Y., & Van den Anker, J. N. (2010). Efavirenz in the therapy of HIV infection. *Expert Opin Drug Metab Toxicol 6*, 95–103.

Rakhshandehroo, M., Hooiveld, G., Müller, M., & Kersten, S. (2009). Comparative analysis of gene regulation by the transcription factor PPARalpha between mouse and human. *PLoS One 4*, e6796.

Rasmussen, B. B., Brix, T. H., Kyvik, K. O., & Brøsen, K. (2002). The interindividual differences in the 3-demthylation of caffeine alias CYP1A2 is determined by both genetic and environmental factors. *Pharmacogenetics 12*, 473–478.

Rau, T., Wuttke, H., Michels, L. M., Werner, U., Bergmann, K., Kreft, M., et al. (2009). Impact of the CYP2D6 genotype on the clinical effects of metoprolol: a prospective longitudinal study. *Clin Pharmacol Ther 85*, 269–272.

Raunio, H., Hakkola, J., & Pelkonen, O. (2005). Regulation of CYP3A genes in the human respiratory tract. *Chem Biol Interact 151*, 53–62.

Raunio, H., & Rahnasto-Rilla, M. (2012). CYP2A6: genetics, structure, regulation, and function. *Drug Metabol Drug Interact 27*, 73–88.

Raunio, H., Rautio, A., Gullstén, H., & Pelkonen, O. (2001). Polymorphisms of CYP2A6 and its practical consequences. *Br J Clin Pharmacol 52*, 357–363.

Rebbeck, T. R., Jaffe, J. M., Walker, A. H., Wein, A. J., & Malkowicz, S. B. (1998). Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4. *J Natl Cancer Inst 90*, 1225–1229.

Rebsamen, M. C., Desmeules, J., Daali, Y., Chiappe, A., Diemand, A., Rey, C., et al. (2009). The AmpliChip CYP450 test: cytochrome P450 2D6 genotype assessment and phenotype prediction. *Pharmacogenomics J 9*, 34–41.

Regan, M. M., Leyland-Jones, B., Bouzyk, M., Pagani, O., Tang, W., Kammler, R., et al. (2012). CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1–98 trial. *J Natl Cancer Inst 104*, 441–451.

Relling, M. V., Lin, J. S., Ayers, G. D., & Evans, W. E. (1992). Racial and gender differences in N-acetyltransferase, xanthine oxidase, and CYP1A2 activities. *Clin Pharmacol Ther 52*, 643–658.

Rettie, A. E., & Jones, J. P. (2005). Clinical and toxicological relevance of CYP2C9: drug–drug interactions and pharmacogenetics. *Annu Rev Pharmacol Toxicol 45*, 477–494.

Ribaudo, H. J., Haas, D. W., Tierney, C., Kim, R. B., Wilkinson, G. R., Gulick, R. M., et al. (2006). Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis 42*, 401–407.

Ribaudo, H. J., Liu, H., Schwab, M., Schaeffeler, E., Eichelbaum, M., Motsinger-Reif, A. A., et al. (2010). Effect of CYP2B6, ABCB1, and CYP3A5 polymorphisms on efavirenz pharmacokinetics and treatment response: an AIDS Clinical Trials Group study. *J Infect Dis 202*, 717–722.

Rieder, M. J., Reiner, A. P., Gage, B. F., Nickerson, D. A., Eby, C. S., McLeod, H. L., et al. (2005). Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med 352*, 2285–2293.

Rieger, J. K., Bodan, D. A., & Zanger, U. M. (2011). MIRNA-DISTILLER: a stand-alone application to compile microRNA data from databases. *Front Genet 2*, 39.

Roberts, A. G., Yang, J., Halpert, J. R., Nelson, S. D., Thummel, K. T., & Atkins, W. M. (2011). The structural basis for homotropic and heterotropic cooperativity of midazolam metabolism by human cytochrome P450 3A4. *Biochemistry 50*, 10804–10818.

Rocha, V., Porcher, R., Fernandes, J. F., Filion, A., Bittencourt, H., Silva, W., Jr., et al. (2009). Association of drug metabolism gene polymorphisms with toxicities, graft-versus-host disease and survival after HLA-identical sibling hematopoietic stem cell transplantation for patients with leukemia. *Leukemia 23*, 545–556.

Rodriguez-Antona, C., Bort, R., Jover, R., Tindberg, N., Ingelman-Sundberg, M., Gómez-Lechón, M. J., et al. (2003). Transcriptional regulation of human CYP3A4 basal expression by CCAAT enhancer-binding protein alpha and hepatocyte nuclear factor-3 gamma. *Mol Pharmacol 63*, 1180–1189.

Rodriguez-Antona, C., Gomez, A., Karlgren, M., Sim, S. C., & Ingelman-Sundberg, M. (2010). Molecular genetics and epigenetics of the cytochrome P450 gene family and its relevance for cancer risk and treatment. *Hum Genet 127*, 1–17.

Rodríguez-Antona, C., Niemi, M., Backman, J. T., Kajosaari, L. I., Neuvonen, P. J., Robledo, M., et al. (2008). Characterization of novel CYP2C8 haplotypes and their contribution to paclitaxel and repaglinide metabolism. *Pharmacogenomics J 8*, 268–277.

Rodríguez-Antona, C., Sayi, J. G., Gustafsson, L. L., Bertilsson, L., & Ingelman-Sundberg, M. (2005). Phenotype–genotype variability in the human CYP3A locus as assessed by the probe drug quinine and analyses of variant CYP3A4 alleles. *Biochem Biophys Res Commun 338*, 299–305.

Rosemary, J., & Adithan, C. (2007). The pharmacogenetics of CYP2C9 and CYP2C19: ethnic variation and clinical significance. *Curr Clin Pharmacol 2*, 93–109.

Rossini, A., De Almeida Simão, T., Albano, R. M., & Pinto, L. F. R. (2008). CYP2A6 polymorphisms and risk for tobacco-related cancers. *Pharmacogenomics 9*, 1737–1752.

Rostami-Hodjegan, A., & Tucker, G. T. (2007). Simulation and prediction of in vivo drug metabolism in human populations from in vitro data. *Nat Rev Drug Discov 6*, 140–148.

Rotger, M., Tegude, H., Colombo, S., Cavassini, M., Furrer, H., Décosterd, L., et al. (2007). Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther 81*, 557–566.
Rowland, P., Blaney, F. E., Smyth, M. G., Jones, J. J., Leydon, V. R., Oxbrow, A. K., et al. (2006). Crystal structure of human cytochrome P450 2D6. *J Biol Chem 281*, 7614–7622.
Roy, J. -N., Lajoie, J., Zijenah, L. S., Barama, A., Poirier, C., Ward, B. J., et al. (2005). CYP3A5 genetic polymorphisms in different ethnic populations. *Drug Metab Dispos 33*, 884–887.
Sachse, C., Brockmöller, J., Bauer, S., & Roots, I. (1997). Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. *Am J Hum Genet 60*, 284–295.
Sachse, C., Brockmöller, J., Bauer, S., & Roots, I. (1999). Functional significance of a C–>A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. *Br J Clin Pharmacol 47*, 445–449.
Sadee, W. (2012). The relevance of "missing heritability" in pharmacogenomics. *Clin Pharmacol Ther 92*, 428–430.
Sadee, W., Wang, D., Papp, A. C., Pinsonneault, J. K., Smith, R. M., Moyer, R. A., et al. (2011). Pharmacogenomics of the RNA world: structural RNA polymorphisms in drug therapy. *Clin Pharmacol Ther 89*, 355–365.
Sakuyama, K., Sasaki, T., Ujiie, S., Obata, K., Mizugaki, M., Ishikawa, M., et al. (2008). Functional characterization of 17 CYP2D6 allelic variants (CYP2D6.2, 10, 14A-B, 18, 27, 36, 39, 47–51, 53–55, and 57). *Drug Metab Dispos 36*, 2460–2467.
Sandee, D., Morrissey, K., Agrawal, V., Tam, H. K., Kramer, M. A., Tracy, T. S., et al. (2010). Effects of genetic variants of human P450 oxidoreductase on catalysis by CYP2D6 in vitro. *Pharmacogenet Genomics 20*, 677–686.
Sansen, S., Yano, J. K., Reynald, R. L., Schoch, G. A., Griffin, K. J., Stout, C. D., et al. (2007). Adaptations for the oxidation of polycyclic aromatic hydrocarbons exhibited by the structure of human P450 1A2. *J Biol Chem 282*, 14348–14355.
Saussele, T., Burk, O., Blievernicht, J. K., Klein, K., Nussler, A., Nussler, N., et al. (2007). Selective induction of human hepatic cytochromes P450 2B6 and 3A4 by metamizole. *Clin Pharmacol Ther 82*, 265–274.
Schadt, E. E., Molony, C., Chudin, E., Hao, K., Yang, X., Lum, P. Y., et al. (2008). Mapping the genetic architecture of gene expression in human liver. *PLoS Biol 6*, e107.
Schaeffeler, E., Schwab, M., Eichelbaum, M., & Zanger, U. M. (2003). CYP2D6 genotyping strategy based on gene copy number determination by TaqMan real-time PCR. *Hum Mutat 22*, 476–485.
Schirmer, M., Rosenberger, A., Klein, K., Kulle, B., Toliat, M. R., Nürnberg, P., et al. (2007). Sex-dependent genetic markers of CYP3A4 expression and activity in human liver microsomes. *Pharmacogenomics 8*, 443–453.
Schmeier, S., Schaefer, U., MacPherson, C. R., & Bajic, V. B. (2011). dPORE-miRNA: polymorphic regulation of microRNA genes. *PLoS One 6*, e16657.
Schmidt, R., Baumann, F., Hanschmann, H., Geissler, F., & Preiss, R. (2001). Gender difference in ifosfamide metabolism by human liver microsomes. *Eur J Drug Metab Pharmacokinet 26*, 193–200.
Schröder, A., Wollnik, J., Wrzodek, C., Dräger, A., Bonin, M., Burk, O., et al. (2011). Inferring statin-induced gene regulatory relationships in primary human hepatocytes. *Bioinformatics 27*, 2473–2477.
Schröder, A., Klein, K., Winter, S., Schwab, M., Bonin, M., Zell, A., et al. (2013). Genomics of ADME gene expression: mapping expression quantitative trait loci relevant for absorption, distribution, metabolism and excretion of drugs in human liver. *Pharmacogenomics J 13*, 12–20.
Schroth, W., Antoniadou, L., Fritz, P., Schwab, M., Muerdter, T., Zanger, U. M., et al. (2007). Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol 25*, 5187–5193.
Schroth, W., Goetz, M. P., Hamann, U., Fasching, P. A., Schmidt, M., Winter, S., et al. (2009). Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA 302*, 1429–1436.
Schults, M. A., Timmermans, L., Godschalk, R. W., Theys, J., Wouters, B. G., Van Schooten, F. J., et al. (2010). Diminished carcinogen detoxification is a novel mechanism for hypoxia-inducible factor 1-mediated genetic instability. *J Biol Chem 285*, 14558–14564.
Schwab, M., Klotz, U., Hofmann, U., Schaeffeler, E., Leodolter, A., Malfertheiner, P., et al. (2005). Esomeprazole-induced healing of gastroesophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. *Clin Pharmacol Ther 78*, 627–634.
Schwab, M., & Schaeffeler, E. (2011). Warfarin pharmacogenetics meets clinical use. *Blood 118*, 2938–2939.
Schwab, M., Schaeffeler, E., Klotz, U., & Treiber, G. (2004). CYP2C19 polymorphism is a major predictor of treatment failure in white patients by use of lansoprazole-based quadruple therapy for eradication of *Helicobacter pylori*. *Clin Pharmacol Ther 76*, 201–209.
Schwartz, J. B. (2007). The current state of knowledge on age, sex, and their interactions on clinical pharmacology. *Clin Pharmacol Ther 82*, 87–96.
Scordo, M. G., Dahl, M. -L., Spina, E., Cordici, F., & Arena, M. G. (2006). No association between CYP2D6 polymorphism and Alzheimer's disease in an Italian population. *Pharmacol Res 53*, 162–165.
Scott, E. E., & Halpert, J. R. (2005). Structures of cytochrome P450 3A4. *Trends Biochem Sci 30*, 5–7.
Scott, S. A., Jaremko, M., Lubitz, S. A., Kornreich, R., Halperin, J. L., & Desnick, R. J. (2009). CYP2C9*8 is prevalent among African-Americans: implications for pharmacogenetic dosing. *Pharmacogenomics 10*, 1243–1255.
Sergentanis, T. N., & Economopoulos, K. P. (2009). Four polymorphisms in cytochrome P450 1A1 (CYP1A1) gene and breast cancer risk: a meta-analysis. *Breast Cancer Res Treat 122*, 459–469.
Shah, M. B., Pascual, J., Zhang, Q., Stout, C. D., & Halpert, J. R. (2011). Structures of cytochrome P450 2B6 bound to 4-benzylpyridine and 4-(4-nitrobenzyl)pyridine: insight into inhibitor binding and rearrangement of active site side chains. *Mol Pharmacol 80*, 1047–1055.
Shaik, A. P., Jamil, K., & Das, P. (2009). CYP1A1 polymorphisms and risk of prostate cancer: a meta-analysis. *Urol J 6*, 78–86.
Shen, A. L., O'Leary, K. A., & Kasper, C. B. (2002). Association of multiple developmental defects and embryonic lethality with loss of microsomal NADPH-cytochrome P450 oxidoreductase. *J Biol Chem 277*, 6536–6541.
Shi, X., Zhou, S., Wang, Z., Zhou, Z., & Wang, Z. (2008). CYP1A1 and GSTM1 polymorphisms and lung cancer risk in Chinese populations: a meta-analysis. *Lung Cancer 59*, 155–163.
Shimada, T., Yamazaki, H., & Guengerich, F. P. (1996). Ethnic-related differences in coumarin 7-hydroxylation activities catalyzed by cytochrome P4502A6 in liver microsomes of Japanese and Caucasian populations. *Xenobiotica 26*, 395–403.
Shimada, T., Yamazaki, H., Mimura, M., Inui, Y., & Guengerich, F. P. (1994). Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther 270*, 414–423.
Shimamoto, J., Ieiri, I., Urae, A., Kimura, M., Irie, S., Kubota, T., et al. (2000). Lack of differences in diclofenac (a substrate for CYP2C9) pharmacokinetics in healthy volunteers with respect to the single CYP2C9*3 allele. *Eur J Clin Pharmacol 56*, 65–68.
Sibbing, D., Koch, W., Gebhard, D., Schuster, T., Braun, S., Stegherr, J., et al. (2010). Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation 121*, 512–518.
Siegle, I., Fritz, P., Eckhardt, K., Zanger, U. M., & Eichelbaum, M. (2001). Cellular localization and regional distribution of CYP2D6 mRNA and protein expression in human brain. *Pharmacogenetics 11*, 237–245.
Sim, S. C., Edwards, R. J., Boobis, A. R., & Ingelman-Sundberg, M. (2005). CYP3A7 protein expression is high in a fraction of adult human livers and partially associated with the CYP3A7*1C allele. *Pharmacogenet Genomics 15*, 625–631.
Sim, S. C., Miller, W. L., Zhong, X. -B., Arlt, W., Ogata, T., Ding, X., et al. (2009). Nomenclature for alleles of the cytochrome P450 oxidoreductase gene. *Pharmacogenet Genomics 19*, 565–566.
Sim, S. C., Risinger, C., Dahl, M. -L., Aklillu, E., Christensen, M., Bertilsson, L., et al. (2006). A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther 79*, 103–113.
Simon, T., Verstuyft, C., Mary-Krause, M., Quteineh, L., Drouet, E., Méneveau, N., et al. (2009). Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med 360*, 363–375.
Slaviero, K. A., Clarke, S. J., & Rivory, L. P. (2003). Inflammatory response: an unrecognised source of variability in the pharmacokinetics and pharmacodynamics of cancer chemotherapy. *Lancet Oncol 4*, 224–232.
Sofi, F., Giusti, B., Marcucci, R., Gori, A. M., Abbate, R., & Gensini, G. F. (2011). Cytochrome P450 2C19*2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. *Pharmacogenomics J 11*, 199–206.
Spiecker, M., Darius, H., Hankeln, T., Soufi, M., Sattler, A. M., Schaefer, J. R., et al. (2004). Risk of coronary artery disease associated with polymorphism of the cytochrome P450 epoxygenase CYP2J2. *Circulation 110*, 2132–2136.
Spurdle, A. B., Goodwin, B., Hodgson, E., Hopper, J. L., Chen, X., Purdie, D. M., et al. (2002). The CYP3A4*1B polymorphism has no functional significance and is not associated with risk of breast or ovarian cancer. *Pharmacogenetics 12*, 355–366.
Staatz, C. E., Goodman, L. K., & Tett, S. E. (2010a). Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part I. *Clin Pharmacokinet 49*, 141–175.
Staatz, C. E., Goodman, L. K., & Tett, S. E. (2010b). Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part II. *Clin Pharmacokinet 49*, 207–221.
Stamer, U. M., Zhang, L., & Stüber, F. (2010). Personalized therapy in pain management: where do we stand? *Pharmacogenomics 11*, 843–864.
Stanton, V., Jr. (2012). Re: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the Breast International Group 1–98 trial. *J Natl Cancer Inst 104*, 1265–1266 (author reply 1266–1268).
Steimer, W., Zöpf, K., Von Amelunxen, S., Pfeiffer, H., Bachofer, J., Popp, J., et al. (2005). Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. *Clin Chem 51*, 376–385.
Stevens, J. C. (2006). New perspectives on the impact of cytochrome P450 3A expression for pediatric pharmacology. *Drug Discov Today 11*, 440–445.
Stevens, J. C., Marsh, S. A., Zaya, M. J., Regina, K. J., Divakaran, K., Le, M., et al. (2008). Developmental changes in human liver CYP2D6 expression. *Drug Metab Dispos 36*, 1587–1593.
Stiborová, M., Martínek, V., Rýdlová, H., Koblas, T., & Hodek, P. (2005). Expression of cytochrome P450 1A1 and its contribution to oxidation of a potential human carcinogen 1-phenylazo-2-naphthol (Sudan I) in human livers. *Cancer Lett 220*, 145–154.
Stingl, J. C., Brockmöller, J., & Viviani, R. (2012). Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. *Mol Psychiatry*. http://dx.doi.org/10.1038/mp.2012.42 [Electronic publication ahead of print].
Su, T., Bao, Z., Zhang, Q. Y., Smith, T. J., Hong, J. Y., & Ding, X. (2000). Human cytochrome P450 CYP2A13: predominant expression in the respiratory tract and its high efficiency metabolic activation of a tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Cancer Res 60*, 5074–5079.

Sueyoshi, T., Kawamoto, T., Zelko, I., Honkakoski, P., & Negishi, M. (1999). The repressed nuclear receptor CAR responds to phenobarbital in activating the human CYP2B6 gene. *J Biol Chem 274*, 6043–6046.

Sulem, P., Gudbjartsson, D. F., Geller, F., Prokopenko, I., Feenstra, B., Aben, K. K. H., et al. (2011). Sequence variants at CYP1A1-CYP1A2 and AHR associate with coffee consumption. *Hum Mol Genet 20*, 2071–2077.

Surendiran, A., Pradhan, S. C., Agrawal, A., Subrahmanyam, D. K. S., Rajan, S., Anichavezhi, D., et al. (2011). Influence of CYP2C9 gene polymorphisms on response to glibenclamide in type 2 diabetes mellitus patients. *Eur J Clin Pharmacol 67*, 797–801.

Tai, E. S., Demissie, S., Cupples, L. A., Corella, D., Wilson, P. W., Schaefer, E. J., et al. (2002). Association between the PPARA L162V polymorphism and plasma lipid levels: the Framingham Offspring Study. *Arterioscler Thromb Vasc Biol 22*, 805–810.

Takagi, S., Nakajima, M., Kida, K., Yamaura, Y., Fukami, T., & Yokoi, T. (2010). MicroRNAs regulate human hepatocyte nuclear factor 4alpha, modulating the expression of metabolic enzymes and cell cycle. *J Biol Chem 285*, 4415–4422.

Takagi, S., Nakajima, M., Mohri, T., & Yokoi, T. (2008). Post-transcriptional regulation of human pregnane X receptor by micro-RNA affects the expression of cytochrome P450 3A4. *J Biol Chem 283*, 9674–9680.

Takahashi, T., Lasker, J. M., Rosman, A. S., & Lieber, C. S. (1993). Induction of cytochrome P-4502E1 in the human liver by ethanol is caused by a corresponding increase in encoding messenger RNA. *Hepatology 17*, 236–245.

Takanashi, K., Tainaka, H., Kobayashi, K., Yasumori, T., Hosakawa, M., & Chiba, K. (2000). CYP2C9 Ile359 and Leu359 variants: enzyme kinetic study with seven substrates. *Pharmacogenetics 10*, 95–104.

Talakad, J. C., Kumar, S., & Halpert, J. R. (2009). Decreased susceptibility of the cytochrome P450 2B6 variant K262R to inhibition by several clinically important drugs. *Drug Metab Dispos 37*, 644–650.

Tan, W., Wu, J., Tang, H., & Lin, D. (2001). Expression of cytochrome P4502E1 in human liver: relationship between genotype and phenotype in Chinese. *Sci China C Life Sci 44*, 356–364.

Tee, M. K., Huang, N., Damm, I., & Miller, W. L. (2011). Transcriptional regulation of the human P450 oxidoreductase gene: hormonal regulation and influence of promoter polymorphisms. *Mol Endocrinol 25*, 715–731.

Tegude, H., Schnabel, A., Zanger, U. M., Klein, K., Eichelbaum, M., & Burk, O. (2007). Molecular mechanism of basal CYP3A4 regulation by hepatocyte nuclear factor 4alpha: evidence for direct regulation in the intestine. *Drug Metab Dispos 35*, 946–954.

Teichert, M., Eijgelsheim, M., Rivadeneira, F., Uitterlinden, A. G., Van Schaik, R. H. N., Hofman, A., et al. (2009). A genome-wide association study of acenocoumarol maintenance dosage. *Hum Mol Genet 18*, 3758–3768.

Teichert, M., Eijgelsheim, M., Uitterlinden, A. G., Buhre, P. N., Hofman, A., De Smet, P. A. G. M., et al. (2011). Dependency of phenprocoumon dosage on polymorphisms in the VKORC1, CYP2C9, and CYP4F2 genes. *Pharmacogenet Genomics 21*, 26–34.

Telenti, A., & Zanger, U. M. (2008). Pharmacogenetics of anti-HIV drugs. *Annu Rev Pharmacol Toxicol 48*, 227–256.

Thangavel, C., Boopathi, E., & Shapiro, B. H. (2011). Intrinsic sexually dimorphic expression of the principal human CYP3A4 correlated with suboptimal activation of GH/glucocorticoid-dependent transcriptional pathways in men. *Endocrinology 152*, 4813–4824.

Thelen, K., & Dressman, J. B. (2009). Cytochrome P450-mediated metabolism in the human gut wall. *J Pharm Pharmacol 61*, 541–558.

Thompson, E. E., Kuttab-Boulos, H., Yang, L., Roe, B. A., & Di Rienzo, A. (2006). Sequence diversity and haplotype structure at the human CYP3A cluster. *Pharmacogenomics J 6*, 105–114.

Thorgeirsson, T. E., Gudbjartsson, D. F., Surakka, I., Vink, J. M., Amin, N., Geller, F., et al. (2010). Sequence variants at CHRNB3-CHRNA6 and CYP2A6 affect smoking behavior. *Nat Genet 42*, 448–453.

Timsit, Y. E., & Negishi, M. (2007). CAR and PXR: the xenobiotic-sensing receptors. *Steroids 72*, 231–246.

Tirona, R. G., Lee, W., Leake, B. F., Lan, L. -B., Cline, C. B., Lamba, V., et al. (2003). The orphan nuclear receptor HNF4alpha determines PXR- and CAR-mediated xenobiotic induction of CYP3A4. *Nat Med 9*, 220–224.

Tomalik-Scharte, D., Fuhr, U., Hellmich, M., Frank, D., Doroshyenko, O., Jetter, A., et al. (2011). Effect of the CYP2C8 genotype on the pharmacokinetics and pharmacodynamics of repaglinide. *Drug Metab Dispos 39*, 927–932.

Tomalik-Scharte, D., Maiter, D., Kirchheiner, J., Ivison, H. E., Fuhr, U., & Arlt, W. (2010). Impaired hepatic drug and steroid metabolism in congenital adrenal hyperplasia due to P450 oxidoreductase deficiency. *Eur J Endocrinol 163*, 919–924.

Tornio, A., Niemi, M., Neuvonen, P. J., & Backman, J. T. (2008). Trimethoprim and the CYP2C8*3 allele have opposite effects on the pharmacokinetics of pioglitazone. *Drug Metab Dispos 36*, 73–80.

Toscano, C., Klein, K., Blievernicht, J., Schaeffeler, E., Saussele, T., Raimundo, S., et al. (2006). Impaired expression of CYP2D6 in intermediate metabolizers carrying the *41 allele caused by the intronic SNP 2988G>A: evidence for modulation of splicing events. *Pharmacogenet Genomics 16*, 755–766.

Trafalis, D. T., Panteli, E. S., Grivas, A., Tsigris, C., & Karamanakos, P. N. (2010). CYP2E1 and risk of chemically mediated cancers. *Expert Opin Drug Metab Toxicol 6*, 307–319.

Tsuchiya, Y., Nakajima, M., Takagi, S., Taniya, T., & Yokoi, T. (2006). MicroRNA regulates the expression of human cytochrome P450 1B1. *Cancer Res 66*, 9090–9098.

Turpeinen, M., Hofmann, U., Klein, K., Mürdter, T., Schwab, M., & Zanger, U. M. (2009). A predominate role of CYP1A2 for the metabolism of nabumetone to the active metabolite, 6-methoxy-2-naphthylacetic acid, in human liver microsomes. *Drug Metab Dispos 37*, 1017–1024.

Turpeinen, M., & Zanger, U. M. (2012). Cytochrome P450 2B6: function, genetics, and clinical relevance. *Drug Metabol Drug Interact*, 1–13.

Ueda, R., Iketaki, H., Nagata, K., Kimura, S., Gonzalez, F. J., Kusano, K., et al. (2006). A common regulatory region functions bidirectionally in transcriptional activation of the human CYP1A1 and CYP1A2 genes. *Mol Pharmacol 69*, 1924–1930.

Van der Weide, J., Steijns, L. S., & Van Weelden, M. J. (2003). The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. *Pharmacogenetics 13*, 169–172.

Vasiliou, V., & Gonzalez, F. J. (2008). Role of CYP1B1 in glaucoma. *Annu Rev Pharmacol Toxicol 48*, 333–358.

Vieira, I., Sonnier, M., & Cresteil, T. (1996). Developmental expression of CYP2E1 in the human liver. Hypermethylation control of gene expression during the neonatal period. *Eur J Biochem 238*, 476–483.

Villeneuve, J. -P., & Pichette, V. (2004). Cytochrome P450 and liver diseases. *Curr Drug Metab 5*, 273–282.

Von Richter, O., Burk, O., Fromm, M. F., Thon, K. P., Eichelbaum, M., & Kivistö, K. T. (2004a). Cytochrome P450 3A4 and P-glycoprotein expression in human small intestinal enterocytes and hepatocytes: a comparative analysis in paired tissue specimens. *Clin Pharmacol Ther 75*, 172–183.

Von Richter, O., Pitarque, M., Rodríguez-Antona, C., Testa, A., Mantovani, R., Oscarson, M., et al. (2004b). Polymorphic NF-Y dependent regulation of human nicotine C-oxidase (CYP2A6). *Pharmacogenetics 14*, 369–379.

Wallemacq, P., Armstrong, V. W., Brunet, M., Haufroid, V., Holt, D. W., Johnston, A., et al. (2009). Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. *Ther Drug Monit 31*, 139–152.

Walsky, R. L., & Obach, R. S. (2004). Validated assays for human cytochrome P450 activities. *Drug Metab Dispos 32*, 647–660.

Wandel, C., Witte, J. S., Hall, J. M., Stein, C. M., Wood, A. J., & Wilkinson, G. R. (2000). CYP3A activity in African American and European American men: population differences and functional effect of the CYP3A4*1B5′-promoter region polymorphism. *Clin Pharmacol Ther 68*, 82–91.

Wang, X., Abdelrahman, D. R., Zharikova, O. L., Patrikeeva, S. L., Hankins, G. D. V., Ahmed, M. S., et al. (2010a). Bupropion metabolism by human placenta. *Biochem Pharmacol 79*, 1684–1690.

Wang, H., Faucette, S., Sueyoshi, T., Moore, R., Ferguson, S., Negishi, M., et al. (2003). A novel distal enhancer module regulated by pregnane X receptor/constitutive androstane receptor is essential for the maximal induction of CYP2B6 gene expression. *J Biol Chem 278*, 14146–14152.

Wang, D., Guo, Y., Wrighton, S. A., Cooke, G. E., & Sadee, W. (2011). Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. *Pharmacogenomics J 11*, 274–286.

Wang, P., Mao, Y., Razo, J., Zhou, X., Wong, S. T. C., Patel, S., et al. (2010c). Using genetic and clinical factors to predict tacrolimus dose in renal transplant recipients. *Pharmacogenomics 11*, 1389–1402.

Wang, Y., Millonig, G., Nair, J., Patsenker, E., Stickel, F., Mueller, S., et al. (2009). Ethanol-induced cytochrome P4502E1 causes carcinogenic etheno-DNA lesions in alcoholic liver disease. *Hepatology 50*, 453–461.

Wang, Y., Yang, H., Li, L., Wang, H., Zhang, C., Yin, G., et al. (2010b). Association between CYP2E1 genetic polymorphisms and lung cancer risk: a meta-analysis. *Eur J Cancer 46*, 758–764.

Wang, H., Zhang, Z., Han, S., Lu, Y., Feng, F., & Yuan, J. (2012). CYP1A2 rs762551 polymorphism contributes to cancer susceptibility: a meta-analysis from 19 case–control studies. *BMC Cancer 12*, 528.

Ward, B. A., Gorski, J. C., Jones, D. R., Hall, S. D., Flockhart, D. A., & Desta, Z. (2003). The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. *J Pharmacol Exp Ther 306*, 287–300.

Wassenaar, C. A., Dong, Q., Wei, Q., Amos, C. I., Spitz, M. R., & Tyndale, R. F. (2011). Relationship between CYP2A6 and CHRNA5-CHRNA3-CHRNB4 variation and smoking behaviors and lung cancer risk. *J Natl Cancer Inst 103*, 1342–1346.

Watanabe, T., Sakuyama, K., Sasaki, T., Ishii, Y., Ishikawa, M., Hirasawa, N., et al. (2010). Functional characterization of 26 CYP2B6 allelic variants (CYP2B6.2-CYP2B6.28, except CYP2B6.22). *Pharmacogenet Genomics 20*, 459–462.

Waxman, D. J., & Holloway, M. G. (2009). Sex differences in the expression of hepatic drug metabolizing enzymes. *Mol Pharmacol 76*, 215–228.

Wei, R., Yang, F., Urban, T. J., Li, L., Chalasani, N., Flockhart, D. A., et al. (2012). Impact of the interaction between 3′-UTR SNPs and microRNA on the expression of human xenobiotic metabolism enzyme and transporter genes. *Front Genet 3*, 248.

Wennerholm, A., Dandara, C., Sayi, J., Svensson, J. -O., Abdi, Y. A., Ingelman-Sundberg, M., et al. (2002). The African-specific CYP2D617 allele encodes an enzyme with changed substrate specificity. *Clin Pharmacol Ther 71*, 77–88.

Westlind-Johnsson, A., Malmebo, S., Johansson, A., Otter, C., Andersson, T. B., Johansson, I., et al. (2003). Comparative analysis of CYP3A expression in human liver suggests only a minor role for CYP3A5 in drug metabolism. *Drug Metab Dispos 31*, 755–761.

Widschwendter, M., Siegmund, K. D., Müller, H. M., Figl, H., Marth, C., Müller-Holzner, E., et al. (2004). Association of breast cancer DNA methylation profiles with hormone receptor status and response to tamoxifen. *Cancer Res 64*, 3807–3813.

Williams, P. A., Cosme, J., Ward, A., Angove, H. C., Matak Vinković, D., & Jhoti, H. (2003). Crystal structure of human cytochrome P450 2C9 with bound warfarin. *Nature 424*, 464–468.

Williams, J. A., Ring, B. J., Cantrell, V. E., Jones, D. R., Eckstein, J., Ruterbories, K., et al. (2002). Comparative metabolic capabilities of CYP3A4, CYP3A5, and CYP3A7. *Drug Metab Dispos 30*, 883–891.

Willmann, S., Edginton, A. N., Coboeken, K., Ahr, G., & Lippert, J. (2009). Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. *Clin Pharmacol Ther 86*, 634–643.

Woelderink, A., Ibarreta, D., Hopkins, M. M., & Rodriguez-Cerezo, E. (2006). The current clinical practice of pharmacogenetic testing in Europe: TPMT and HER2 as case studies. *Pharmacogenomics J 6*, 3–7.
Wolbold, R., Klein, K., Burk, O., Nüssler, A. K., Neuhaus, P., Eichelbaum, M., et al. (2003). Sex is a major determinant of CYP3A4 expression in human liver. *Hepatology 38*, 978–988.
Wray, J. A., Sugden, M. C., Zeldin, D. C., Greenwood, G. K., Samsuddin, S., Miller-Degraff, L., et al. (2009). The epoxygenases CYP2J2 activates the nuclear receptor PPARalpha in vitro and in vivo. *PLoS One 4*, e7421.
Wrighton, S. A., Stevens, J. C., Becker, G. W., & VandenBranden, M. (1993). Isolation and characterization of human liver cytochrome P450 2C19: correlation between 2C19 and S-mephenytoin 4′-hydroxylation. *Arch Biochem Biophys 306*, 240–245.
Wu, S., Moomaw, C. R., Tomer, K. B., Falck, J. R., & Zeldin, D. C. (1996). Molecular cloning and expression of CYP2J2, a human cytochrome P450 arachidonic acid epoxygenase highly expressed in heart. *J Biol Chem 271*, 3460–3468.
Wyen, C., Hendra, H., Siccardi, M., Platten, M., Jaeger, H., Harrer, T., et al. (2011). Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. *J Antimicrob Chemother 66*, 2092–2098.
Xiao, F., Zuo, Z., Cai, G., Kang, S., Gao, X., & Li, T. (2009). miRecords: an integrated resource for microRNA–target interactions. *Nucleic Acids Res 37*, D105–D110.
Xie, H., Griskevicius, L., Ståhle, L., Hassan, Z., Yasar, U., Rane, A., et al. (2006). Pharmacogenetics of cyclophosphamide in patients with hematological malignancies. *Eur J Pharm Sci 27*, 54–61.
Xie, H. -J., Yasar, U., Lundgren, S., Griskevicius, L., Terelius, Y., Hassan, M., et al. (2003). Role of polymorphic human CYP2B6 in cyclophosphamide bioactivation. *Pharmacogenomics J 3*, 53–61.
Xiong, Y., Wang, M., Fang, K., Xing, Q., Feng, G., Shen, L., et al. (2011). A systematic genetic polymorphism analysis of the CYP2C9 gene in four different geographical Han populations in mainland China. *Genomics 97*, 277–281.
Xu, H., Murray, M., & McLachlan, A. J. (2009). Influence of genetic polymorphisms on the pharmacokinetics and pharmaco-dynamics of sulfonylurea drugs. *Curr Drug Metab 10*, 643–658.
Xu, X., Zhang, X. A., & Wang, D. W. (2011). The roles of CYP450 epoxygenases and metabolites, epoxyeicosatrienoic acids, in cardiovascular and malignant diseases. *Adv Drug Deliv Rev 63*, 597–609.
Yamanaka, H., Nakajima, M., Fukami, T., Sakai, H., Nakamura, A., Katoh, M., et al. (2005). CYP2A6 AND CYP2B6 are involved in nornicotine formation from nicotine in humans: interindividual differences in these contributions. *Drug Metab Dispos 33*, 1811–1818.
Yamazaki, H., Inoue, K., Hashimoto, M., & Shimada, T. (1999). Roles of CYP2A6 and CYP2B6 in nicotine C-oxidation by human liver microsomes. *Arch Toxicol 73*, 65–70.
Yamazaki, H., Okayama, A., Imai, N., Guengerich, F. P., & Shimizu, M. (2006). Inter-individual variation of cytochrome P4502J2 expression and catalytic activities in liver microsomes from Japanese and Caucasian populations. *Xenobiotica 36*, 1201–1209.
Yang, J. -C., & Lin, C. -J. (2010). CYP2C19 genotypes in the pharmacokinetics/pharmacodynamics of proton pump inhibitor-based therapy of *Helicobacter pylori* infection. *Expert Opin Drug Metab Toxicol 6*, 29–41.
Yang, X., Zhang, B., Molony, C., Chudin, E., Hao, K., Zhu, J., et al. (2010). Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver. *Genome Res 2010*, 1020–1036.
Yao, S., Barlow, W. E., Albain, K. S., Choi, J. -Y., Zhao, H., Livingston, R. B., et al. (2010a). Gene polymorphisms in cyclophosphamide metabolism pathway, treatment-related toxicity, and disease-free survival in SWOG 8897 clinical trial for breast cancer. *Clin Cancer Res 16*, 6169–6176.
Yao, L., Yu, X., & Yu, L. (2010b). Lack of significant association between CYP1A1 T3801C polymorphism and breast cancer risk: a meta-analysis involving 25,087 subjects. *Breast Cancer Res Treat 122*, 503–507.
Yeo, C. -W., Lee, S. -J., Lee, S. S., Bae, S. K., Kim, E. -Y., Shon, J. -H., et al. (2011). Discovery of a novel allelic variant of CYP2C8, CYP2C8*11, in Asian populations and its clinical effect on the rosiglitazone disposition in vivo. *Drug Metab Dispos 39*, 711–716.
Yimer, G., Amogne, W., Habtewold, A., Makonnen, E., Ueda, N., Suda, A., et al. (2012). High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-based HAART-induced liver injury in the treatment of naïve HIV patients from Ethiopia: a prospective cohort study. *Pharmacogenomics J 12*, 499–506.
Yoshinari, K., Ueda, R., Kusano, K., Yoshimura, T., Nagata, K., & Yamazoe, Y. (2008). Omeprazole transactivates human CYP1A1 and CYP1A2 expression through the common regulatory region containing multiple xenobiotic-responsive elements. *Biochem Pharmacol 76*, 139–145.
Yoshinari, K., Yoda, N., Toriyabe, T., & Yamazoe, Y. (2010). Constitutive androstane receptor transcriptionally activates human CYP1A1 and CYP1A2 genes through a common regulatory element in the 5′-flanking region. *Biochem Pharmacol 79*, 261–269.
Yu, A. -M., Granvil, C. P., Haining, R. L., Krausz, K. W., Corchero, J., Küpfer, A., et al. (2003a). The relative contribution of monoamine oxidase and cytochrome p450 isozymes to the metabolic deamination of the trace amine tryptamine. *J Pharmacol Exp Ther 304*, 539–546.
Yu, A. -M., Idle, J. R., Byrd, L. G., Krausz, K. W., Küpfer, A., & Gonzalez, F. J. (2003b). Regeneration of serotonin from 5-methoxytryptamine by polymorphic human CYP2D6. *Pharmacogenetics 13*, 173–181.
Yu, K. S., Yim, D. S., Cho, J. Y., Park, S. S., Park, J. Y., Lee, K. H., et al. (2001). Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther 69*, 266–273.
Yuan, J., Guo, S., Hall, D., Cammett, A. M., Jayadev, S., Distel, M., et al. (2011). Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. *AIDS 25*, 1271–1280.
Zabalza, M., Subirana, I., Sala, J., Lluis-Ganella, C., Lucas, G., Tomás, M., et al. (2011). Meta-analyses of the association between cytochrome CYP2C19 loss- and gain-of-function polymorphisms and cardiovascular outcomes in patients with coronary artery disease treated with clopidogrel. *Heart 98*, 100–108.
Zanger, U. (2008). The *CYP2D* Subfamily. In C. Ioannides (Ed.), *Cytochromes P450: role in the metabolism and toxicity of drugs and other xenobiotics* (pp. 241–275). : Royal Society of Chemistry.
Zanger, U. M., Fischer, J., Raimundo, S., Stüven, T., Evert, B. O., Schwab, M., et al. (2001). Comprehensive analysis of the genetic factors determining expression and function of hepatic CYP2D6. *Pharmacogenetics 11*, 573–585.
Zanger, U. M., & Hofmann, M. H. (2008). Polymorphic cytochromes P450 CYP2B6 and CYP2D6: recent advances on single nucleotide polymorphisms affecting splicing. *Acta Chim Slov 55*, 38.
Zanger, U. M., Klein, K., Saussele, T., Blievernicht, J., Hofmann, M. H., & Schwab, M. (2007). Polymorphic CYP2B6: molecular mechanisms and emerging clinical significance. *Pharmacogenomics 8*, 743–759.
Zanger, U. M., Raimundo, S., & Eichelbaum, M. (2004). Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch Pharmacol 369*, 23–37.
Zanger, U. M., Turpeinen, M., Klein, K., & Schwab, M. (2008). Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. *Anal Bioanal Chem 392*, 1093–1108.
Zhai, G., Teumer, A., Stolk, L., Perry, J. R. B., Vandenput, L., Coviello, A. D., et al. (2011). Eight common genetic variants associated with serum DHEAS levels suggest a key role in ageing mechanisms. *PLoS Genet 7*, e1002025.
Zhang, Y., Klein, K., Sugathan, A., Nassery, N., Dombkowski, A., Zanger, U. M., et al. (2011). Transcriptional profiling of human liver identifies sex-biased genes associated with polygenic dyslipidemia and coronary artery disease. *PLoS One 6*, e23506.
Zhou, H., Josephy, P. D., Kim, D., & Guengerich, F. P. (2004). Functional characterization of four allelic variants of human cytochrome P450 1A2. *Arch Biochem Biophys 422*, 23–30.
Zhou, S. -F., Wang, B., Yang, L. -P., & Liu, J. -P. (2009). Structure, function, regulation and polymorphism and the clinical significance of human cytochrome P450 1A2. *Drug Metab Rev 42*, 268–354.
Zuern, C. S., Schwab, M., Gawaz, M., & Geisler, T. (2010). Platelet pharmacogenomics. *J Thromb Haemost 8*, 1147–1158.
Zukunft, J., Lang, T., Richter, T., Hirsch-Ernst, K. I., Nussler, A. K., Klein, K., et al. (2005). A natural CYP2B6 TATA box polymorphism (−82T–>C) leading to enhanced transcription and relocation of the transcriptional start site. *Mol Pharmacol 67*, 1772–1782.