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Toxicology Letters 120 (2001) 259–268

Toxicology Letters

www.elsevier.com/locate/toxlet

Genetic variability in susceptibility and response to toxicants

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Abstract

Xenobiotic metabolism is carried out by phase I and phase II enzymes which are to a large extent polymorphic. The majority of cytochrome P450 (CYP) enzymes involved in xenobiotic metabolism are polymorphic and inducible, resulting in abolished, quantitatively or qualitatively altered or enhanced drug metabolising activity. Stable duplication, multiduplication or amplification of active genes have been described. In mouse models it is apparent that inactivation of specific enzymes active in xenobiotic metabolism can affect the risk for cancer development in relation to specific xenobiotic exposure, whereas the situation in humans is far more complex. The polymorphism of CYP enzymes is expected to influence individual sensitivity and toxicity for different environmental agents, although there is as yet no real consensus in the literature about specific firm relationships in this regard. The incidence of serious and fatal adverse drug reactions (ADRs) has been found to be very high among hospitalised patients, the cost of ADRs to society is large and they are responsible for 5–10% of all hospital admissions. It is likely that predictive genotyping could avoid 10–20% of ADRs. In the present contribution an overview is presented regarding our present knowledge about the polymorphism of phase I enzymes, with emphasis on xenobiotic metabolising CYPs and the importance for metabolic activation of xenobiotics.

Keywords: Genetic polymorphism; Ultrarapid metabolism; Poor metabolisers; Drug adducts; Genotyping; Idiosyncratic drug toxicity; Molecular epidemiology

1. Introduction

Interindividual variability in xenobiotic metabolism and drug response is extensive. The drug level in plasma can vary by more than 1000-fold between two individuals having the same weight and with the same drug dosage. The causes for this variation are of genetic, physiological, pathophysiological and environmental origin. Genetic variability is known for drug absorption, drug metabolism and for drug interactions with receptors. This forms the basis for slow and rapid drug absorption, poor, efficient or ultrarapid drug metabolism and poor or efficient receptor interactions. Environmental influence includes induction and inhibition of drug transport and metabolism. Inhibition caused by, for example drug interactions, is an important factor for the outcome of the drug plasma levels reached. Ageing is known to result in a reduced capacity for drug metabolism as well as in a lower response to inducers of drug metabolising enzymes. In the past decade, genetic factors for this variability

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0378-4274/01/$ - see front matter
PII: S0378-4274(01)00278-8

have received much emphasis. One could envision that genetic factors could account for about 20–40% of interindividual differences in drug metabolism and response, but for certain drugs or classes of drugs, genetic factors will be of the utmost importance for the outcome of drug therapy.

One can estimate that there are about 50 000 different genes in the human genome. Earlier calculations of up to 140 000 genes were considered to be erroneous when the complete sequences of chromosomes 21 and 22 became available, containing a surprisingly low number of genes. With a total of 3.12 billion nucleotides and the occurrence of Single Nucleotide Polymorphisms (SNPs) consisting of either base pair substitutions, nucleotide insertions or base deletions between two different individuals at a frequency of 1/1250 bp, one can estimate the total number of SNPs to be about 2.5 million. In total, the number of SNPs in the population might be much larger due to the occurrence of rare mutations and could approach 15–30 million.

The number of SNPs reported is increasing rapidly. In March 2000, only about 100 000 SNPs were present in the databases but by 29 September 2000, as many as 1 463 574 SNPs had been described (http://www.ncbi.nlm.nih.gov/SNP/). Of these, it is clear that the majority do not have any function and are located mainly between the genes, intergenic SNPs (iSNPs). One can estimate that the number of iSNPs accounts for 2 million. Another class of SNPs are the perigenic SNPs (pSNPs) located in non-coding gene regions such as the upstream regulatory regions, in introns, as well as consisting of silent mutations. Between 200 000 and 500 000 pSNPs might be present in the genome. In the coding regions, the cSNPs cause alterations in amino acids and an estimate of the number of these is between 50 000 and 100 000. Thus, the entire phenotype would be dependent on the individual composition of these, giving a theoretical possibility of, assuming two base variations on each SNP, $2^{100\,000}$ different individuals, equal to more than $10^{30\,000}$ different humans. Knowledge of all these cSNPs would be of the utmost importance for understanding the genetic basis for disease as well as for the differential response to drug treatment.

2. Adverse drug reactions

Adverse drug reactions are a more important problem in drug treatment and drug development than previously thought. A meta-analysis revealed that serious adverse drug reactions occur among 6.7% of all hospitalised patients and that 0.32% of all hospitalised patients develop fatal adverse reactions, causing more than 100 000 deaths annually in the US (Lazarou et al., 1998). Even though this study was criticised for having many old studies among those causing the majority of deaths, subsequent follow up by the same authors, including studies in non-US countries, revealed a similar figure (Lazarou, 1998). ADRs cause up to 5.5% of all hospital admissions (Einarson, 1993), a figure recently supported by a UK study where 7.5% of all admissions were due to ADRs (Green et al., 2000). In Sweden it is evident that adverse drug reactions cause up to 12% of all admissions to internal medicine clinics (Mjörndal et al., 1999). The cost of ADRs, including on average 2 days of prolonged hospitalisation and reduced productivity, has been estimated to be 100 billion US$ annually in the US (Marshall, 1997). An important application of pharmacogenetics and genotyping for drug metabolising enzymes is the prediction of adverse drug reactions and optimisation of drug treatment with respect to efficacy, thus avoiding treatment of subjects who, based on their genetic constitution, will not respond to the drug. It would be my estimation that perhaps 10–20% of adverse drug reactions and associated deaths could be prevented by using predictive genotyping. In this overview I emphasise what is known regarding the genetic polymorphism of phase I enzymes, in particular P450s, and the functional consequences with emphasis on xenobiotic metabolism.

3. Polymorphic phase I enzymes

In Table 1, an overview of the polymorphic phase I enzymes of functional importance for the metabolism of xenobiotics is given. Besides P450s, polymorphisms in aldehyde dehydrogenase, alcohol dehydrogenase, dihydropyrimidine dehydro-

Table 1
Functional importance of polymorphism in phase I enzymes

Enzymes	Importance for metabolism	Polymorphism, significance
P450s		
CYP1A1	Carcinogens	Unproven
CYP1A2	Drugs and carcinogens	Induction polymorphism
CYP1B1	Carcinogens, oestrogens (?)	Rare null alleles, many variants of uncertain significance
CYP2A6	Nicotine, drugs, carcinogens	Important functional polymorphism
CYP2B6	Drugs	Polymorphically expressed
CYP2C8	Some drugs	
CYP2C9	Drugs	Very significant
CYP2C19	Drugs	Very significant
CYP2D6	Drugs	Very significant
CYP2E1	Carcinogens, some drugs	Not shown hitherto
CYP3A4	Drugs, carcinogens	Rare functional variants
CYP3A5	Drugs	Polymorphically expressed
Aldehyde dehydrogenases		
ALDH1A1	Retinal	Acetaldehyde metabolism
ALDH1B1	Aliphatic aldehydes	Significant
ALDH2	Acetaldehyde	Very significant for acetaldehyde metabolism and alcoholism
ALDH3A1	Fatty and aromatic aldehydes	Remains to be investigated
ALDH3A2	Fatty and aromatic aldehydes	Sjögren–Larsson syndrome
Alcohol dehydrogenases		
ADH1	Ethanol	Ethanol metabolism
ADH3	Ethanol; formaldehyde	Ethanol metabolism
Dihydropyrimidine dehydrogenase	5-Fluorouracil	Significant for 5-FU treatment
NQO1 (DT-diaphorase)	Antitumor quinones	Significant for activity

genase and DT-diaphorase are significant for the rate at which a specific individual is able to metabolise various xenobiotics. DT-diaphorase has been implicated as important in the activation of chemotherapeutic prodrugs and for the detoxication of certain potentially carcinogenic xenobiotics. It has a functional polymorphism in C609T causing a Pro187Serine substitution leading to reduced enzyme activity (Siegel et al., 1999; Misra et al., 2000). Its presence has been related to the incidence of cancers such as colorectal cancer, basal cell carcinomas prostaticadenocarcinoma or benign prostatic hyperplasia and myeloid leukemia. The enzyme is not inducible in subjects homozygous for 609T and this might be related to an increased risk for benzene toxicity among such individuals (Moran et al., 1999).

Individuals with a deficiency in the enzyme dihydropyrimidine dehydrogenase (DPD) may experience severe toxicity when treated with 5-fluorouracil (5-FU). Reduced DPD activity is associated with neurological abnormalities in paediatric patients. Some mutant variants have been identified (Ridge et al., 1998; Collie-Duguid et al., 2000), but there is still no way by which genotyping can predict all the phenotypes in an appropriate manner. Further research is needed in this area. Therapeutic outcome during cancer treatment with the DPD substrate 5-fluorouracil is, to a great extent, dependent on drug dosage where the individual's capacity for metabolism is taken into account and hence therapeutic drug monitoring would facilitate drug therapy considerably (Iyer, 1999).

The polymorphism of alcohol dehydrogenases is most relevant for the metabolism of ethanol and subjects, mainly in Asia, are found with variants causing high activity (Jörnvall et al., 2000). Concerning aldehyde dehydrogenases, 16 different genes have been identified in the human genome (Vasiliou and Pappa, 2000). Polymorphism in ALDH2 is important in determining differences in the capacity for metabolism of acetaldehyde, for decreasing the risk for alcoholism and possibly for increasing the risk for ethanol-related cancers. Polymorphisms in several of the other *ALDH* genes are associated with metabolic diseases with neurological manifestations and

ALDH3A2 deficiency leads to Sjögren-Larsson syndrome. Several other polymorphic variants have yet to be characterised and their roles in xenobiotic metabolism remain to be elucidated.

4. P450 enzymes

Sequencing of the human genome has revealed 58 different human P450 (CYP) genes according to David R. Nelson's estimation (http://drnelson.utmem.edu/cytochromeP450.html). The genes in CYP families 1–3 are listed in Table 1. These are the CYP enzymes active in the metabolism of drugs and other xenobiotics. The majority of these genes are polymorphic and, in addition, a large number of pseudogenes are present. In fact, it appears that only CYP1A1 and CYP2E1 are relatively well preserved and in essence no functionally important mutations are present within these genes.

The reason for this conservation might be the endogenous importance of the corresponding enzymes. CYP2E1 is a gluconeogenetic enzyme and converts acetone to acetol which is subsequently converted to gluconeogenetic precursors. It is most plausible that a selection pressure has occurred because of its important role during conditions of extensive starvation. Indeed, the blood acetone levels are severely increased in CYP2E1 null mice as compared to the corresponding wild type mice (Bondoc et al., 1999). In the case of CYP1A1, its physiological role is unknown. The Ah-receptor has, however, an important role in the cell cycle and it could be hypothesised that CYP1A1 might be an important mediator in some cell types. Concerning CYP2J2, CYP2R1, CYP2S1, CYP2U1 and CYP2W1, no polymorphisms have yet been described but are likely to appear in the literature in the near future.

Thus, interindividual distribution of many of these P450 forms varies strikingly and their extensive polymorphism is likely, to a great extent, the result of dietary adaptation of different populations in the world. In addition, of course, genetic drift is an important factor for the interethnic differences seen. No important endogenous substrates have been described for any of the polymorphic P450s and their primary function is in the metabolism of dietary components.

In order to help scientists in the field, a web page has been created which contains continuously updated information regarding the polymorphic forms of CYPs (http://www.imm.ki.se/CYPalleles/). The aim of this page is to provide scientists with a useful nomenclature for all enzyme variants with links to relevant literature describing the properties of the polymorphic enzymes. An important factor is also to bring scientists up to date with the most recent knowledge allowing them to check whether allelic variants they have found have been described before. Presently a current update of the genetic polymorphisms of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, CYP5A1 and CYP8A1 is presented. The field of polymorphic CYPs is quite complex and more than 80 different allelic forms of e.g. *CYP2D6* have now been described. A list of the most relevant variant forms of the CYPs of highest importance for the metabolism of drugs and other xenobiotics, as well as their allele frequencies in Caucasians and Oriental populations, is given in Table 2. As can be noted, most allelic forms are distributed with pronounced interethnic differences.

5. Consequences of mutations in the *CYP*-genes

Mutations in the *CYP* genes can cause enzyme products with abolished, reduced, altered or increased enzyme activity. Alleles causing abolished enzyme activity often have the whole gene deleted, but there are also defective alleles present with mutations causing altered splicing, stop codons, abolished transcriptional start sites or deleterious amino acid changes. Mutations in substrate recognition sites (SRS) can cause the synthesis of enzymes with an altered substrate specificity as exemplified by *CYP2D6*17*, found entirely in black African populations, and by *CYP2C9*3*. Furthermore, mutations in the folding region can cause altered protein folding and differences in substrate specificity, as seen with *CYP2D6*10* (Fukuda et al., 2000).

Table 2
Human P450s in gene families 1–3

1A1	Conserved, role in cell cycle?	2E1	Conserved, role in gluconeogenesis
1A2	Induction polymorphism	2F1	
1B1	Polymorphic	2F1P	Pseudogene
2A6	Polymorphic	2G1	Pseudogene
2A7	Not functional	2G2	Pseudogene
2A13	Olfactory mucosa	2J2	
2A18	Pseudogene	2R1	
2B6	Polymorphic	2S1	
2B7	Pseudogene	2T2	Pseudogene
2C8	Polymorphic	2T3	Pseudogene
2C9	Polymorphic	2U1	Functional?
2C18	Polymorphic	2W1	
2C19	Polymorphic	3A4	Polymorphic
2D6	Polymorphic	3A5	Polymorphic
2D7	Pseudogene	3A7	Fetal expression
2D8	Pseudogene	3A43	Functional?

The functional consequences of the polymorphisms of the *P450* genes are given in Table 1. It is evident that the polymorphisms of CYP2B6, CYP2C9, CYP2C19, CYP2D6 are the most important in the metabolism of drugs and determine, to a great extent, therapeutic success when using drugs which are specific substrates for these enzymes. With respect to the polymorphism of CYP1A2 and CYP2A6, these are of greater relative importance when the metabolism of carcinogens and other environmentally relevant chemicals are taken into consideration. CYP1A2 is induced by smoking and, interestingly, a polymorphism in the regulatory intron 1 has been found to be strongly related to the inducibility of this enzyme among smokers (Sachse et al., 1999). Also, additional polymorphisms upstream might be of importance for CYP1A2 expression (Nakajima et al., 1999). It would be of interest to study the functional basis for this polymorphism in greater detail and its implications for metabolic activation of precarcinogens.

CYP2A6 metabolises certain drugs like methoxyflurane, halothane, losigamone, letrozole, valproic acid and disulfiram and activates a number of precarcinogens, including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*-nitrosodiethylamine, 1,3-butadiene and 2,6-dichlorobenzonitrile. It is also the major enzyme responsible for nicotine metabolism. Nicotine is *C*-oxidised to cotinine followed by cotinine 3′-hydroxylation (see Oscarson, 2001, for a review). At present five functionally different forms of the gene have been described, which cause abolished or reduced enzyme activity (see below). The frequency of variant alleles in the Caucasian population is low, whereas *CYP2A6*4*, having a gene deletion, is common among Orientals. The polymorphism might be of importance for determining smoking behaviour and for susceptibility for various cancer forms, although this has to be investigated in greater detail.

When studying the effect of the mutations on CYP function one must bear in mind that folding of the enzyme can be different for two very similar polymorphic variants and that mutations might influence each other in this respect. Thus, when studying the function of the *CYP2D6*17* allele, it was evident that the carriers of this variant had reduced capacity for metabolism of CYP2D6 substrates (Masimirembwa et al., 1996). However, introduction of the unique mutation T107I into CYP2D6 wild-type cDNA had no effect on the properties of the enzyme in vitro (Oscarson et al., 1997). It was found that only when the R296C mutation was present together with the T107I mutation, did the enzyme exhibit altered properties for the drug substrates codeine and bufuralol, and a fivefold higher K_m was apparent. We have also recently obtained similar

results for CYP1B1. In total we have found five different functional mutations in the gene causing amino acid changes which yield, in theory, 32 different haplotypes. Of these, at least seven different haplotypes are distributed in, for example, the Ethiopian population, and only two of these cause altered function of the enzyme in the metabolism of estradiol (Aklilu et al., unpublished observations). This emphasises the fact that in, for example, molecular epidemiological studies, there can be great uncertainty when studying the influence of just one functional mutation in a gene, without taking the complete haplotype into consideration.

Another very important aspect when studying polymorphic CYPs is that the genotyping technique used for determination of the mutations at the genomic level is appropriate and correct. In the case of the CYP2A6 gene, some studies have been published which have considered a relationship between the frequency of defective variants of the CYP2A6 gene and smoking behaviour (Pianezza et al., 1998; London et al., 1999). However, a very high frequency of the CYP2A6*2 and CYP2A6*3 alleles was found in these studies. Re-examination of the genotyping technique used by these authors revealed that the PCR-based genotyping did not amplify specifically the CYP2A6 gene in the first step, as originally thought, due to a CYP2A7 gene conversion event just downstream of exon 9 where the reverse primer for the CYP2A6 gene was supposed to bind (Oscarson et al., 1999). Therefore, in the second mutation specific PCR reaction, the pseudogene *CYP2A7* was amplified instead, giving an erroneously high frequency of the *CYP2A6*2* and *CYP2A6*3* alleles. In fact, the *CYP2A6*3* allele has hitherto not been found in any subject investigated. Overall, the variant *CYP2A6* alleles are quite rare among Caucasians, whereas *CYP2A6*4*, which is a null allele, is quite common among Orientals (Table 2).

5.1. In vivo importance

Pharmacogenetic and toxicogenetic studies rely very much on validation of the importance of the variant alleles in functional assays carried out both in vivo and in vitro. In my opinion, mutations to be studied must, in the first place, create alterations in the gene products that are likely to affect function. Silent mutations or mutations in non-coding regions of dubious effects on expression should not primarily be investigated. Although such mutations might be linked to others of greater functional significance, there are always exceptions to such linkages and the study is then conducted using the wrong target, sometimes wasting time and money.

5.2. Ultrarapid metabolizers

In contrast to PMs, ultrarapid metabolisers (UMs) carry two or more active genes on the same allele (Johansson et al., 1993; Lundqvist et al., 1999). The gene effect is striking and clearance of nortrityline or debrisoquine is proportional to the number of *CYP2D6* gene copies (Dalen et al., 1998, 1999). Alleles with stably duplicated genes have now also been found for glutathione transferase M1 (*GSTM1*) (McLellan et al., 1997) and *CYP2A6* (Rao et al., 2000). Stable gene duplication thus seems to be a general phenomenon among the genes encoding drug metabolising enzymes.

Gene duplication does not occur unless it is beneficial for the organism. This raises the question about the origin of *CYP2D6* duplication, multiduplication and gene amplification, yielding alleles with 2, 3, 4, 5 or 13 gene copies. A focus for *CYP2D6* gene duplications has been in Ethiopia and Saudi Arabia, where 20–30% of the population have this genotype. In contrast, very few subjects with gene duplications are seen in Asia or Northern Europe. In the Mediterranean area, about 10% of the population carry *CYP2D6* gene duplications, most likely the result of Muslim migration through Gibraltar about 700 AD. The distribution of the duplicated *CYP2D6* genes worldwide indicates that the gene duplication event occurred relatively recently, about 2000–5000 years ago.

6. CYP polymorphism and cancer

It is attractive to speculate that polymorphism in the CYP genes would influence an individual's capacity to convert different precarcinogenic compounds into their ultimate carcinogens and thus be a major factor of importance for the individual's susceptibility for developing chemically-induced cancer. Indeed, studies in knockout mice indicate that susceptibility for lymphomas is drastically reduced in *CYP1B1* null mice treated with dimethylbenzanthracene (Buters et al., 1999) and that the risk for papillomas is increased in mice lacking glutathione *S*-transferase P1 and P2 treated with DMBA and TPA (Henderson et al., 1998). However, a similar simple relationship in humans has not been described yet. Of course, the mice that are compared are genetically identical and housed in an identical environment with identical diet. The situation in humans is far more complex. The genetic background is very heterogeneous and different environmental factors are of great relevance for the disease in question and are usually very difficult to compensate for. This makes it much more difficult to study the influence of specific polymorphic genes on cancer risk and other diseases.

The most important CYPs for the activation of precarcinogens are CYP1A1, CYP1A2, CYP1B1, CYP2E1 and CYP3A4. However, at present there does not seem to be any functional polymorphism of obvious importance for any of the corresponding genes. Lack of CYP1B1 is rarely seen and is then manifest in the occurrence of glaucoma. A slight influence of the polymorphism of CYP1A1, although of no apparent functional importance for the gene product, has been seen on the occurrence of lung cancer, as reviewed by Houlston (2000). With respect to CYP1B1, seven functionally different haplotypes have been identified to date (see above) and in the near future it will be clarified whether any of these is significantly associated with the incidence of cancer. There have been reports that high CYP1A2 activity is a risk for colon cancer and, as mentioned, a functional mutation in intron 1 affecting inducibility of the enzyme has been identified (Sachse et al., 1999). However, it remains to be established whether this polymorphism influences cancer risk.

The polymorphism of CYP2A6 is relevant for the metabolism of nicotine and might be important for the activation of some carcinogens. However, the enzyme is expressed entirely in the liver and further studies are required in order to show whether the CYP2A6 polymorphism is important for smoking behaviour or cancer risk. With respect to the *CYP2E1* gene, although polymorphic in non-coding regions, functional variants with mutations creating amino acid substitutions are very rare and an association study with cancer incidence would require several thousands of cases and controls in order to achieve statistical significance. Recently, several polymorphic functional variants of CYP3A4 have been identified, present particularly in Oriental populations (Table 3). These are, however, very rare and their functional importance for carcinogen activation, e.g. of aflatoxin, is still unclear.

Analysis of the risk for cancer and metabolic polymorphism, as reported by Vineis et al. (1999), showed that very small alterations in risk for lung cancer and breast cancer can be seen in subjects who are polymorphic for drug metabolising enzymes when meta-analyses were performed, taking several different studies into account. It is evident that the relationship between any polymorphic locus and disease is best studied using very large numbers of well defined and matched subjects. In the past decade however, such studies have usually not involved more than 70–250 cases and controls and relevant answers have not been obtained until 15–20 different studies have been added together. After it was possible to conduct meta-analyses, sometimes only after 10–12 years of research, it was evident that the specific research area has been controversial and inconclusive. A large study from the beginning would be able to avoid such a non-productive scientific outcome.

In conclusion, the area of CYP polymorphism and risk for cancer has not yet led to the point where we can identify, with certainty, any specific relationship between a risk allele of a CYP and cancer development. Investigation of the polymorphism and function of the recently discovered extrahepatic CYPs is an urgent matter for research. The research area thus needs further de-

velopment with emphasis on CYP allelic variants and haplotypes of established functional significance. In contrast, CYP polymorphisms appear to be of considerable significance for therapeutic outcome during treatment with several different common drugs and predictive genotyping might prevent a substantial number of adverse drug reactions causing severe toxicity with, in some cases, fatal outcomes.

Acknowledgements

The work in the author's laboratory is financed by the Swedish Medical Research Council, The Swedish Cancer Society and by AstraZeneca. I am indebted to my lab colleagues for their contributions to the work described in this review.

Table 3
Major human polymorphic cytochrome P450 enzymes[a]

Enzyme	Major variant alleles	Mutation	Consequence	Allele frequency (%)	
				Caucasians	Orientals
CYP2A6	*CYP2A6*2*	L160H	Inactive enzyme	1–3	0
	*CYP2A6*3*	2A6/2A7	Not known	0	0
	*CYP2A6*4*	Gene deletion	No enzyme	1	15
	*CYP2A6*5*	G479L	Defect. enzyme	0	1
CYP2C9	*CYP2C9*2*	R144C	Reduced affinity for P450 reductase	8–13	0
	*CYP2C9*3*	I359L	Altered substr. spec.	7–9	2–3
CYP2C19	*CYP2C19*2*	Aber. splice site	Inactive enzyme	13	23–32
	*CYP2C19*3*	Stop codon	Inactive enzyme	0	6–10
CYP2D6	*CYP2D6*2xn*	Gene dupl.	Increased activity	1–5	0–2
	*CYP2D6*4*	Splicing defect	Inactive enzyme	12–21	1
	*CYP2D6*5*	Gene deletion	No enzyme	4–6	6
	*CYP2D6*10*	P34S, S486T	Unstable enzyme	1–2	50
	*CYP2D6*17*	T107I, R296C, S486T	Reduced affinity for substrates	0	(in Blacks, 34% allele frequency)
CYP2E1	*CYP2E1*2*	R76H	Less enzyme expressed	0	1
	*CYP2E1*3*	V389I	No effects	<1	0
	*CYP2E1*4*	V179I	No effects	<1	n.d.
CYP3A4	*CYP3A4*2*	S222P	Higher K_m for subst.	3	0
	*CYP3A4*3*	M445T	Unknown	0	<1
	*CYP3A4*4*	I118V	Decreased	0	<1
	*CYP3A4*5*	P218R	Decreased	0	<1
	*CYP3A4*6*	831 insA	Decreased	0	<1

[a] See http://www.imm.ki.se/CYPalleles for details and literature references. Allele frequencies are from Ingelman-Sundberg et al. (1999), Oscarson (2001) and references therein; abbreviations: aber., aberrant; dupl., duplication; n.d., not done; spec., specific; substr., substrate.

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