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REVIEW

Genetic polymorphisms of cytochrome *P*450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity

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ABSTRACT
CYP2D6 is of great importance for the metabolism of clinically used drugs and about 20–25% of those are metabolised by this enzyme. In addition, the enzyme utilises hydroxytryptamines as endogenous substrates. The polymorphism of the enzyme results in poor, intermediate, efficient or ultrarapid metabolisers (UMs) of CYP2D6 drugs. It is plausible that the UM genotype, where more than one active gene on one allele occurs, is the outcome of selective dietary selection in certain populations in North East Africa. The UM phenotype affects 5.5% of the population in Western Europe. A hypothesis for the evolutionary basis behind selection for *CYP2D6* gene duplications is presented in relation to selection for *Cyp6* variants in insecticide resistant *Drosophila* strains. The polymorphism of CYP2D6 significantly affects the pharmacokinetics of about 50% of the drugs in clinical use, which are CYP2D6 substrates. The consequences of the polymorphism at ordinary drug doses can be either adverse drug reactions or no drug response. Examples are presented where CYP2D6 polymorphism affects the efficacy and costs of drug treatment. Predictive *CYP2D6* genotyping is estimated by the author to be beneficial for treatment of about 30–40% of CYP2D6 drug substrates, that is, for about 7–10% of all drugs clinically used, although prospective clinical studies are necessary to evaluate the exact benefit of drug selection and dosage based on the *CYP2D6* genotype.
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BACKGROUND

Pharmacogenetics dealing with inherited differences in drug targets, and drug disposition in the form of drug receptors and drug transporters is rapidly developing.[1–5] At present, our knowledge is most advanced with respect to the influence of polymorphically distributed genes encoding drug metabolising enzymes, although the knowledge about drug receptors and transporters is rapidly growing. The greatest importance on the interindividual differences in drug response at present is exerted by the differences in capacity for drug metabolism caused by genetic polymorphism or by inhibition or induction of drug metabolism. Besides, drug–drug interactions, pathophysiological factors and environmental factors, the genetics of the drug metabolising enzymes plays a critical role for understanding interindividual differences in drug response and

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adverse drug reactions. The highest impact among drug metabolising enzymes is exerted by the cytochromes *P*450s, the major phase I enzymes.[6,7] Among those, CYP2C9, CYP2C19 and CYP2D6 are highly polymorphic and accounts together for about 40% of hepatic human phase I metabolism. In addition, the polymorphisms of CYP1A2, CYP2A6, CYP2B6 and CYP2C8 also contribute to interindividual differences in drug metabolism. CYP2D6 is perhaps the most extensively studied polymorphically expressed drug metabolising enzyme in humans; its polymorphism has a high clinical importance and was the first among the polymorphic P450s to be characterized at the molecular level. Today, more than 48 different drug substrates for this enzyme have been identified (Table 1) and CYP2D6 is responsible for about 25% of the metabolism of known drugs. This might however be a slight overestimation since in the past drugs that are metabolised by this enzyme, due to its polymorphic expression, has specifically been looked for. In the present review, the current knowledge and consequences of the molecular genetics of CYP2D6 is described as well as the knowledge of the impact on drug treatment.

Table 1 Major substrates and inhibitors for CYP2D6

Major classes of drugs as substrates	Ondansetron
Antidepressants	Otycodone
Tricyclic antidepressants	Perhexiline
Serotonin reuptake inhibitors	Perphenaxine
Neuroleptics	Phenacetin
Beta-blockers	Phenformin
Antiarrhytmics	Propafenone
	Propranolol
Specific drugs as substrates	Quinidine
Alprenol	Risiperidone
Amiflamine	Thioridazine
Aprindine	Timolol
Atenolol	Tomoxetine
Bufuralol	Tropisetron
Bupranolol	Zuclopenthixol
Chlorpropamide	
Clomipramine	
Clozapine	*Inhibitors, drugs*
Codeine	Chinidin
Debrisoquine	Fluoxetin
Desimipramine	Levomepromazine
Desmethylcitalopram	Lobelin
Dextromethorphan	Methadone
Dihydrocodeine	Paroxetine
Encainide	Quinidine
Ethylmorphine	Trifluperidol
Flecainide	
Flunarizine	
Fluperlapine	*Inhibitors, alkaloids*[a]
Guanoxan	Ajmalicine
Haloperidol	Ajmalicine
Hydrocodone	Berberine
Imipramine	Coniine
Indoramin	Ergotamine
Maprotiline	Gramine
Methoxyamphetamine	Harmaline
Methoxyphenamine	Laudanosine
Metiamide	Sempervirine
Metoprolol	Vincamine
Mexiletine	Vinblastine
Nortriptyline	

[a]Several of these alkaloids have not been evaluated as substrates. See[56] for a complete list of substrates and inhibitors.

General Characteristics of CYP2D6

CYP2D6 is a polypeptide of 497 amino acids. The enzyme accounts for only a small percentage of all hepatic P450s, but its role in drug metabolism is extensively higher than its relative content (see Zanger *et al*[8]). The different models of the enzyme based on the three-dimensional structure of cytochrome *P*450 BM-3 or CYP2C5, and results from site directed mutagenesis differ much from each other. Despite the success of well-diffracting crystals of the mammalian CYP2B4, CYP2C5, CYP2C9, and CYP3A4, no one has yet being able to obtain good CYP2D6 crystals. It is believed that such crystals are necessary in order to get a template for models that are of enough resolution and accuracy in order to, for example, predict drugs that will be substrates for this enzyme. Such a model would be of severe importance for drug industry because a drug design avoiding compounds being high-affinity substrates for CYP2D6 is central for a successful product on the market.

CYP2D6 substrates are lipophilic bases with a protonable nitrogen atom. The hydroxylation reaction takes place at a distance of 5 or 7 Å from the nitrogen atom. Site directed mutagenesis experiments indicate that Asp301 is the negatively charged amino acid responsible for binding to the substrate nitrogen.[8] In addition, also Ser304, Thr309 and Val370 appear to be involved in substrate binding[9] although further models are required for confirmation.

CYP2D6 has a very high affinity for alkaloids (see Table 1).[10] The enzyme expression is, in contrast to other hepatic xenobiotic metabolising cytochrome *P*450s, not regulated by any known environmental agent and is not inducible by known hormones. Since no phenotype has been described among subjects lacking CYP2D6 or having up to 13 active gene copies, one might conclude that the enzyme has no major endogenous function. A role for metabolism of some neurotransmittors has been suggested. Indeed, recent evidence for CYP2D6 being a specific 5-methoxyindolethylamine *O*-demethylase has been presented,[11] and also 5-methoxytryptamine[12] has been shown to be a substrate. Besides such substrates, it is likely that the enzyme has a major role for metabolism of food constituents, in particular alkaloids (see below).

The action of CYP2D6 on substrates of potential activity in the brain would imply a functional phenotype on subjects, that is, poor metabolisers (PMs) lacking the enzyme. In fact, two studies have indicated a significant relationship between behaviour using psychological tests and the presence of CYP2D6.[13,14] The question arises whether such an activity is essential. Interestingly, Pai *et al*[15] have recently provided evidence that a common variant of the pseudogene *CYP2D7P* could be expressed in an active

form in human brain yielding a functional enzyme product being active in the metabolism of, for example, codeine. Whether this represents a product of true functional importance remains to be elucidated, although the finding as such is of interest.

CYP2D6 Polymorphism—Historical Aspects

The polymorphism of CYP2D6 was independently discovered in three different laboratories. Folke Sjöqvists laboratory showed that the metabolism of nortriptyline and desimipramine, later shown to be CYP2D6 substrates, exhibited a tremendous interindividual variation in plasma levels at the same dosage and two phenotypes were identified.[16] Subsequent studies by the Sjöqvist group using twins revealed that the difference was genetic in nature. Bob Smith and co-workers in London studied the metabolism of two antihypersensitive drugs bethanidine and debrisoquine, which were in use for hypertension. When Bob Smith in May 1975 took 40 mg of debrisoquine, he became dizzy, faint and suffered from severe hypotension. A subsequent study with 10 mg debrisoquine in 94 subjects identified the two phenotypes.[17] Michel Eichelbaum in Bonn studied the antiarrhytmic effects of sparteine and two subjects complained about unpleasant side effects like blurred vision, diploida, dizziness and headache. Analysis of the plasma levels revealed that they had 4–5 times higher levels than the others and the two phenotypes were published in 1978 and 1979.[18,19]

The genetic basis behind the debrisoquine polymorphism was elucidated 10–15 years later. In a collaborative study between Urs Meyers and Frank Gonzalez' Laboratories, polyclonal rat CYP2D antibodies developed in Basel were used as tools to clone the human CYP2D6 cDNA from a human liver λgt 11 cDNA library and the expressed cDNA had the expected bufuralol hydroxylase activity.[20] Using RFLP, Meyers lab could confirm altered RFLP patterns in PMs for debrisoquine,[21] whereas the complete identification of the *CYP2D6*3* and *CYP2D6*4* alleles was published in 1990.[22]

In the late 1980s we identified in fruitful collaboration with Leif Bertilsson and Folke Sjöqvist an RFLP pattern in Chinese active in CYP2D6 metabolism, indicative for PMs in Caucasians[23] and later characterized the most common partially defect *CYP2D6* allele in Orientals, *CYP2D6*10*.[24] As a French group opposed our size identification of the Chinese *Xba*I fragments and we re-screened several different DNA samples by *Xba*I RFLP using a lower density of the agarose gel and found some samples which we thought had uncleaved DNA (see Ingelman-Sundberg[25] for further details). However, examination of their origin revealed that they came from individuals very rapid for debrisoquine metabolism and subjects with up to 12 extra *CYP2D6* gene copies were identified. This turned out to be the first description of a stably amplified active gene in humans[26] and the term ultrarapid metabolisers (UMs) was defined.[27] Subsequent investigations of the frequencies in different populations revealed 30% in Ethiopians,[28] 10% in Spaniards and 10% of the populations in Italy and Turkey, whereas UMs are uncommon (1–2%) in Northern Europe and essentially absent in Asia (see[6] for references). In Ethiopians we found no individual homozygous for defect *CYP2D6* genes but alleles containing 2, 3, 4 as well as 5 *CYP2D6* gene copies.[28] A similar situation was also seen among Saudi Arabians.[29] Evaluation of the number of subjects carrying *CYP2D6* gene duplications in Western Europe reveals that 5.5% of the Europeans carry more than two active *CYP2D6* gene copies and are UMs (Table 2).

CYP2D6 Genetic Polymorphism

The *CYP2D6* gene is localized on chromosome 22q13.1. The locus contains two neighbouring pseudogenes, *CYP2D7* and *CYP2D8*.[30] The evolution of the human *CYP2D* locus has involved elimination of three genes and inactivation of two (*CYP2D7P* and *CYP2D8P*) and partial inactivation of one (*CYP2D6*). At present, more than 46 known different major polymorphic *CYP2D6* alleles are known. The presence of the highly similar closely located pseudogenes carrying detrimental mutations have through, for example, unequal crossover reactions led to the formation of many of the variant *CYP2D6* alleles, which most commonly encode defective gene products. The 'activity' in the *CYP2D* locus is high as compared to, for example, the *CYP2C* locus and as a result many variant alleles have been formed in a relatively short period of time. The most common variant alleles distributed in different ethnic groups are listed in Table 3 and all variant alleles are presented at the home page of the human CYP allele nomenclature committee (http://www.imm.ki.se/cypalleles/cyp2d6.htm). The variant *CYP2D6* alleles can be classified into categories, which cause abolished, decreased, normal, increased or qualitatively altered cataxlytic activity. Among the most important variant ones are *CYP2D6*2, CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*17* and *CYP2D6*41*.

Table 2 An estimation of the number of ultrarapid CYP2D6 metabolisers in Western Europe carrying two or more active *CYP2D6* genes on one allele. The overall percentage in the population is 5.45%

	Million inhabitants	*Frequency UMs*	*Million UMs*
Austria	8	0.04	0.32
Belgium	10	0.03	0.3
Denmark	5	0.01	0.05
England	60	0.03	1.8
Finland	5	0.01	0.05
France	60	0.04	2.4
Germany	82	0.04	3.28
Greece	10	0.1	1
Holland	15	0.03	0.45
Italy	57	0.1	5.7
Norway	5	0.01	0.05
Portugal	10	0.1	1
Spain	40	0.1	4
Sweden	9	0.01	0.09
Total	376		20.49

Table 3 Major human polymorphic variant *CYP2D6* alleles and their global distribution. For a complete list, see http://www.imm.ki.se/cypalleles/cyp2d6.htm

Major variant alleles	*Mutation*	*Consequence*	*Allele frequencies (%)*			
			Caucasians	*Asians*	*Black Africans*	*Ethiopians and Saudi Arabians*
*CYP2D6*2xn*	Gene duplication/ multiduplication	Increased enzyme activity	1–5	0–2	2	10–16
*CYP2D6*4*	Defective splicing	Inactive enzyme	12–21	1	2	1–4
*CYP2D6*5*	Gene deletion	No enzyme	2–7	6	4	1–3
*CYP2D6*10*	P34S, S486T	Unstable enzyme	1–2	51	6	3–9
*CYP2D6*17*	T107I, R296C, S486T	Altered affinity for substrates	0	0	20–35	3–9

For further allele frequencies in different populations, see Bradford.[52]

The most common allele in Asians (allele frequency of >50%) and thus perhaps the most common *CYP2D6* allele in the world is *CYP2D6*10*.[24] The CYP2D6.10 enzyme has a deleterious P34S mutation abolishing the important PPGP sequence necessary for folding of P450 and is therefore very unstable,[24] but it has also a reduced affinity for the substrates.[31] Among Blacks *CYP2D6*17* first described in 1996[32] is the major variant *CYP2D6* allele. It encodes in addition to the two missense mutations seen in *CYP2D6*2* also T107I, which apparently makes an altered active site structure. This creates an altered substrate specificity,[33] which is evident *in vitro*[33] but also when subjects of the *CYP2D6*17* genotype are phenotyped *in vivo*.[34,35] In general, the activity of the CYP2D6.17 enzyme is lower than the wild-type enzyme.

*CYP2D6*41* is a variant of *CYP2D6*2* having −1584 C instead of G. It is less expressed than the corresponding *CYP2D6*2* allele (see Zanger *et al*[36]). It is plausible that –1584G>C is in linkage disequilibrium with another SNP that causes deficient splicing of the mRNA, although this has to be explicitly shown. The effect *in vivo* of *CYP2D6*41* is however rather pronounced and subjects homozygous for this allele are phenotypically like individuals of the intermediary phenotype (IM) with one deficient *CYP2D6* allele.[36]

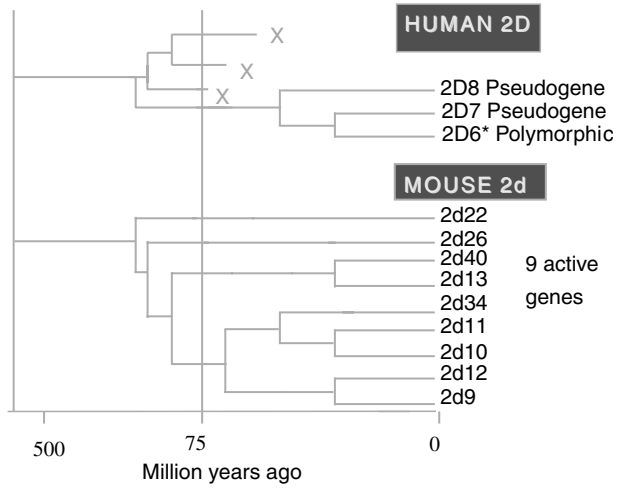

Figure 1 Evolution of genes within the human *CYP2D* and mouse *Cyp2d* loci, according to alignments of gene sequences using ClustalW 1.8.

Evolution of the *CYP2D* Loci

There is a drastic difference between rodents and humans in the number of active *CYP2D* genes. Whereas the mouse has nine different active *Cyp2d* genes,[37] the human carries only one, which indeed is absent from 7% of the Caucasian population (Figure 1). The CYP2D6 enzyme is known to have a very high affinity for plant toxins like alkaloids.[10] It is reasonable to assume that the mouse has retained the genes active because of a need for a dietary detoxification potential, whereas the more restricted food taken by humans in the past including the intellectual capability to transfer information regarding suitable food between generations, has resulted in the loss of a selection pressure as to keep the genes active.

The *CYP2D6* gene is not inducible in common sense through increased gene expression of expression of gene product. In *Drosophila*, selective selection occurs of strains living in, for example, the area of the Senita Cactus secreting toxic isoquinoline alkaloids and only the *Drosophila mettleri* but no *Drosophila melanogaster* strain is surviving in this area because their ability to induce CYP6 and CYP28.[38] An interesting genetic selection also occurs in *Drosophila* being resistant to insecticides. From 1930 to 1960, insecticide resistant stains have rapidly evolved. Interestingly, the molecular genetic basis appears to be selection for an insertion of a transposome (accord element) in the 5′-regulatory region of the *Cyp6b* gene causing 40- to 100-fold higher expression of the gene product.[39] Another mechanism for acquirement of insecticide resistance in *Drosophila* is exemplified by selection for three key mutations in CYP6A2, that is, R335S, L336V and V476L, making the enzyme active towards the metabolism of DDT.[40] An illustration of three different mechanisms for adaptive response towards substrate stress is shown in Figure 2.

Similarly, we have proposed that such a selection has occurred for alleles carrying multiple active *CYP2D6* genes in North East Africa. The basis for this selection would be the capability of the CYP2D6 enzyme to detoxify alkaloids, thereby increasing the availability of potential food among

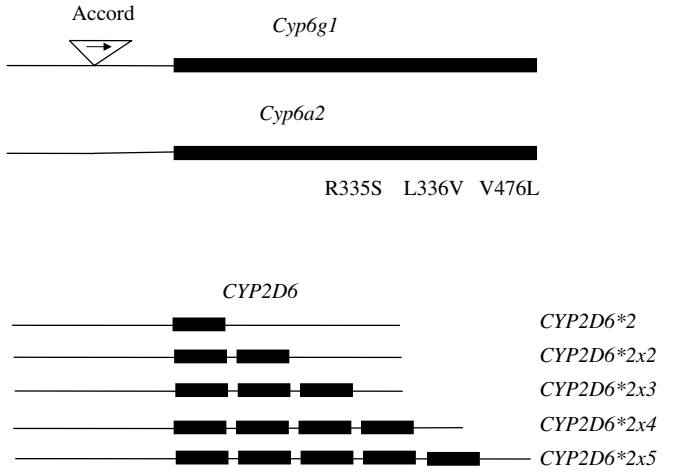

Figure 2 Illustration of mechanisms for *CYP* gene modifications due to selection. In insecticide resistant *Drosophila* strains a transposome (Accord) is inserted, which most probably causes up to 100-fold higher gene expression of *Cyp6g1*.[39] Also, selective mutations in *Cyp6a2* occurs in resistant strains that changes the CYP6A2 enzyme from being inactive to active in the metabolism of DDT.[40] In addition, selection of *CYP2D6* alleles is proposed to have occurred as a pressure event for increasing the capability of alkaloid metabolism and increase the food availability in North East Africa. For further explanations, see text.

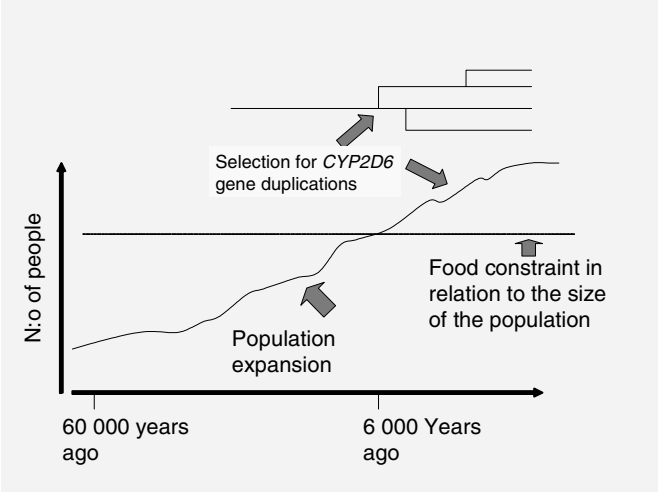

Figure 3 Proposed mechanism for dietary selection of alleles carrying multiple active *CYP2D6* gene copies in populations in North East Africa, an event that is believed to have happened about 5000–10 000 years ago.

carriers of multiple *CYP2D6* gene copies. This would be very beneficial for survival under periods of starvation when only a fraction of the population in this region reaches maturity. Examination of the rate of debrisoquine metabolism in Ethiopians living in Ethiopia as compared to Ethiopians living in Sweden revealed that native Ethiopians of the same genotype were slower in their metabolism as compared to Ethiopians in Sweden, whereas no significant differences were found in the rate of CYP2C19 dependent catalytic reactions as measured with *S*-mephenytoin.[41] This can be interpreted in the manner that constituents in the Ethiopian food, presumably alkaloids, inhibit the CYP2D6 activity and that such components could indeed be a trigger for genetic selection. We propose that the Ethiopian population expanded about 10 000–20 000 years ago to such an extent that food exhibited an important constraint. During periods of starvation, a selection pressure has occurred favouring survival of subjects being able to detoxify plant toxins at a higher extent, increasing the number of plants being able to provide useful food (Figure 3). This created expansion of subpopulations carrying multiple active *CYP2D6* gene copies and also without inactive *CYP2D6* genes. Since by the far the most common variants of *CYP2D6* gene duplicated and multiduplicated are *CYP2D6*2* and *CYP2D6*41*, both creating two amino-acid substitutions as compared to *CYP2D6*1*, it can be speculated that the substrate specificity of this form of the enzyme is beneficial for the metabolism of certain plant products. The subsequent migrations of subjects from North East Africa to the Mediterranean area resulted in the high frequency of UMs in Southern Europe (cf Table 2).

CLINICAL IMPLICATIONS

General Aspects

Estimates reveal that between 20 and 25% of all drugs in clinical use are metabolised at least in part by CYP2D6.[5] Subjects with multiple gene copies will metabolise drugs more rapidly and therapeutic plasma levels will not be achieved at ordinary drug dosages. Individuals lacking functional *CYP2D6* genes metabolise selective CYP2D6 substrates at a lower rate, and the risk for adverse drug reactions is higher. The *CYP2D6* genotype has been successfully shown to predict the clearance of, for example, the antidepressants desipramine, fluvoxamine, mexiletine, mianserin, nortryptiline, and paroxetine as well as the clearance of the neuroleptics perphenazine and zuclopenthixol and the competitive muscarinic receptor antagonist tolterodine (see Ingelman-Sundberg *et al*[42] and Table 4). Adverse effects due to elevated drug plasma levels occur more frequently in PMs in cases where the drug clearance is dependent on CYP2D6 (see Ingelman-Sundberg[5] and Ingelman-Sundberg *et al*[42]). A lack of CYP2D6 enzyme results in reduced effectiveness of drug therapy in instances where prodrugs requiring activation by CYP2D6 are used. This is seen for the analgesic effect of tramadol and codeine.

CYP2D6 Polymorphism and Cancer Treatment

Tamoxifen is metabolised into its active metabolite endoxifen by *N*-demethylation and 4-hydroxylation, reactions that are carried out by CYP2D6.[43] A smaller therapeutic effect has been observed in PMs for CYP2D6 and predictive pheno/genotyping could be relevant before entering the treatment. The effect of antiemetic drugs like the 5-hydroxytryptamine type 3 receptor antagonists tropisetron and ondasetron was found to be highly related to the CYP2D6 phenotype. Lower plasma levels and higher

frequency and intensity of vomiting were seen in subjects carrying more active gene copies of *CYP2D6*.[44]

CYP2D6 Polymorphism in Psychiatry

Important findings have been described with respect to the role of CYP2D6 polymorphism for the clinical outcome of psychoactive drugs. The interesting meta-analysis by Kirchheiner *et al*[45] reveals that the dosage of about 50% of the commonly used antipsychotics is dependent on the *CYP2D6* genotype (Table 4). In a study of 100 consecutive psychiatric inpatients genotyped for CYP2D6 on admission, the number of adverse effects in patients treated with CYP2D6 substrates were highest in PMs and higher in IMs than in EMs or UMs.[46] The costs of treating patients of the UM or PM phenotype were found to be 4000–6000 USD higher per year than those of the IM or EM phenotype and the duration of treatment was longer among PMs.[46]

With respect to treatment of schizophrenia with perphenazine, thioridazine or haloperidol, significant oversedation has been found to be linked to the *CYP2D6* genotype in three different studies. Increased frequency of Parkinsonism was seen in two studies as reviewed by Dahl,[47] whereas no significant relationship has been seen to tardive dyskinesia, acute dystonia, or akathisia. The relationship to Parkinsonism has also been documented in several other studies. For example, in an investigation where 77 patients prescribed on CYP2D6-dependent antipsychotic drugs and 55 patents prescribed on non-CYP2D6 dependent antipsychotic drugs was studied, it was revealed that PMs were four times more likely to start with antiparkinsonian medication.[48] Drugs against parkinsonian side effects were given twice more frequently in PMs among 241 psychiatric patients.[49]

In a thorough study it was found that haloperidol clearance ($n = 172$) correlated with the number of active *CYP2D6* genes. Ratings for pseudoparkinsonism were higher in PMs and a trend towards lower therapeutic efficacy with increasing number of active *CYP2D6* genes was seen. Also, genotyping was as good predictor of ADRs as measurements of drug concentrations.[50]

The meta-analysis by Kirchheiner *et al*[45] reveals that the dosage of about 50% of antidepressants used is much dependent on the CYP2D6 genotype and being most important for imipramine, nortriptyline, maprotiline and others, whereas the metabolism of SSRIs is mainly dependent on the *CYP2C19* genotype. Side effects among PMs have often been registered. In addition, nonresponders of antidepressant therapy is a serious problem and has been found to be associated with the CYP2D6 genotype in a pilot study.[51] Subjects being UMs were highly overrepresented in the non-responder group as compared to the control population. Since 40–50 million people in Europe carry multiple *CYP2D6* genes on the same allele, this finding might indicate an explanation for common lack of response to antidepressants in the European population. This is likely to affect people living in the Mediterranean area where the frequency of *CYP2D6* gene duplications is much higher than in Northern Europe. Further prospective studies in this area appear highly important.

Table 4 Approximate dose adjustments according to the CYP2D6 phenotype as based on the meta-analysis by Kirchheiner *et al*.[45] Recommended dosages in relation to recommended one are presented for the poor metaboliser (PM), intermediate metaboliser (IM), efficient metaboliser (EM) and ultrarapid metaboliser (UM) phenotypes

	PM	*IM*	*EM*	*UM*
Antidepressants				
Imipramine	30	75	130	180
Doxepin	35	77	120	170
Maprotiline	35	77	120	170
Trimipramine	37	83	125	175
Desipramine	40	76	117	165
Nortriptyline	48	90	115	155
Clomipramine	60	85	112	145
Paroxetine	65	90	108	143
Venlafaxine	68	85	105	130
Amitriptyline	70	90	105	135
Mianserin	70	87	110	135
Antipsychotics				
Perphenazine	30	80	130	170
Thioridazine	37	82	127	165
Olanzapine	50	100	120	155
Zuclopenthixol	55	85	115	142
Aripiprazole	60	85	112	130
Flupentixol	68	80	117	135
Haloperidol	67	90	108	126

For the antidepressants mirtazapine, moclobemide, fluoxetine, maprotiline, bupropion, nefazodone, citalopram and sertraline as well as the antipsychotics perazine, risperidone, pimozide, clozapine, levomepromazine, olanzapine no significant dose adjustments based on CYP2D6 was recommended.

CYP2D6 and Cardiovascular Disorders

Monohydroxylation of the antianginal agent perhexiline is almost exclusively catalysed by CYP2D6 with activities being about 100-fold lower in CYP2D6 poor metabolizers than in extensive metabolizers.[53] Perhexiline has a concentration-related hepatotoxicity and peripheral neuropathy and determination of the *CYP2D6* genotype will predict dose requirements and reduce the risk of perhexiline concentration-related toxicity.[54] In a retrospective study, Wuttke *et al*[55] identified 24 patients treated with metoprolol who had experienced pronounced adverse effects. Genotyping revealed a five-fold higher frequency of PMs in this group (38%) as compared to the control population.

CYP2D6 in Molecular Epidemiology

The CYP2D6 phenotype and genotype has been investigated with respect to the risk of suffering from different diseases. Investigators have evaluated hypotheses whether the PM phenotype predispose for diseases besides melanoma, lung-, breast-, anogenital-, basal cell- aerodigestive tract-, oral-, prostate-, pancreatic- and bladder-cancer, also with parkinsonism, Alzheimers disease, optic neuropathy, tremor, hair

colour, neuroleptic malignant syndrome, smoking behaviour, opiate dependence, tardive dyskinesia, tremor, haematological neoplasias, and Lewy body disease, etc, but no established relation has hitherto been found. In light of the absence of any significant procarcinogen for this enzyme and the polygenic nature of the genetic component of the other diseases investigated as well as the high number of SNPs with high penetrance on phenotype in the human genome, these studies are at the present time being considered of less importance to our understanding of the molecular background to such important and multifactorial diseases and abnormal conditions. In general, it can be concluded that most such studies have suffered from poor quality and it is important to emphasise the quality criteria for genetic association studies eligible for publication according to *Nature Genetics* 1999; 22:1–2,

1. The genetic variant studied should be embedded in a plausible biological context.
2. Phenotype homogeneity and genotype accuracy should have high quality.
3. High statistical quality with large cohorts and compliance with The Bradford-Hill criteria (*Proc R Soc Med* 9: 295–300, 1965).
4. Confirmation of the association should be done in an independent population, preferentially family studies are of value in this respect.

CONCLUSIONS

CYP2D6 constitutes a surprisingly important enzyme for drug metabolism despite its low hepatic abundance. It might be considered as the enzyme where the polymorphism is of the greatest importance for the metabolism of drugs of all enzymes in phase I and phase II metabolism. Its complicated polymorphic genetics with more than 80 different allelic variants known makes it necessary to determine several 100 different SNPs in the human genome in order to be able to foresee the CYP2D6 phenotype at a high accuracy. The enzyme appears also to be one of the most important polymorphic drug metabolising enzyme in causing adverse drug reactions. It is then understandable that drug industry nowadays to a great extent screen drug candidates early in development as possible CYP2D6 substrates and drop such candidates where they have alternatives exhibiting reasonable equipotent pharmacology and other properties. This selection might in the long run lead to a less prominent role of this enzyme in the future for drug metabolism.

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DUALITY OF INTEREST

None declared.

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