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PharmGKB summary: very important pharmacogene information for CYP2B6

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Very important pharmacogene – *CYP2B6* Overview

CYP2B6 is a member of the cytochrome P450 family of important pharmacogenes and makes up approximately 2–10% of the total hepatic CYP content [1]. *CYP2B6* is also expressed in the brain, and may be an important factor in the metabolism of drugs acting on the central nervous system (CNS) and neurological side effects of drug treatments [2]. CYP2B6 is responsible for the metabolism of 4% of the top 200 drugs [3] and is highly inducible by several drugs and other xenobiotics [4]. There is high interindividual variation in *CYP2B6* mRNA expression, ranging from 20 to 250-fold, which may be attributed to differential transcriptisonal regulation and inherited genetic variation [4–6]. A large number of variants have been reported (see the CYP allele nomenclature committee website http://www.cypalleles.ki.se/cyp2b6.htm), including many that are present at high frequencies and several that show linkage resulting in multiple haplotypes. These haplotypes are often observed at highly different frequencies in different racial and ethnic groups (reviewed in [7]). *CYP2B6* has been shown to undergo significant alternative splicing [6]. Although multiple splice variants of *CYP2B6* have been reported, the functional relevance of most of these needs further investigation. One of the splice variants, SV1, has been shown to be linked to an important variant (see below for more details) [6,8]. Like other CYPs, *CYP2B6* has a high level of homology with a pseudogene, *CYP2B7P1*, which can interfere with genotyping if assays are not specific enough [3].

Transcription of *CYP2B6* is regulated by the nuclear receptors PXR and CAR, coded for by the genes *NR1I2* and *NR1I3*, respectively. They activate transcription by binding at the proximal response element (PREM located at −1.7 kb upstream of the transcription start site) and the distal response element (XREM located at −8.5 kb of the transcription start site)

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[9,10] in the CYP2B6 promoter. Cross-regulation between *CYP2B6* and *CYP3A4*, *UGT1A1* and hepatic drug transporters that are also regulated by these common transcription factors has been suggested [1]. Many of the drugs that are metabolized by CYP2B6 are also inducers of the gene (through PXR and CAR), including cyclophosphamide, phenobarbital, rifampicin, phenytoin, artimesin, carbamazepine, efavirenz, and nevirapine [7] (see http://www.pharmgkb.org/search/annotatedGene/cyp2b6/index.jsp for a larger list of substrates, inhibitors, and inducers of CYP2B6). Although sex has also been shown to influence CYP2B6 expression, there have been conflicting reports in the literature, which may in turn be because of confounding factors such as race and environment (discussed in Ref. [3]).

As CYP2B6 is the major enzyme involved in the metabolism of efavirenz and nevirapine, its pharmacogenomics has become relevant for the treatment of HIV. Efavirenz has a narrow therapeutic window with severe CNS side effects associated with its high plasma concentrations and treatment failure associated with low concentrations. The variants CYP2B6:516G > T and CYP2B6:983T > C, as well as the haplotype CYP2B6*6 have been associated with adverse effects of efavirenz treatment (discussed below in more detail). Clinical significance of CYP2B6 variants has also been implicated in cyclophosphamide chemotherapy [11,12] and in smoking cessation in response to bupropion [13–16].

Important haplotypes and variants CYP2B6*6

CYP2B6*6 haplotype is characterized by the presence of two nonsynonymous variants CYP2B6:516G > T and CYP2B6:785A > G with or without additional promoter variants (CYP2B6*6A:516G > T and 785A > G; CYP2B6* 6B:516G > T, 785A > G, −1456T > C, and −750T > C, and CYP2B6*6C:516G > T, 785A > G, and −750T > C). The functional consequences of CYP2B6*6 are generally attributed to the coding sequence variants common to all three haplotypes.

Initial studies of CYP2B6*6 were limited by small sample sizes; however, a large in-vitro study showed that this haplotype is associated with lower CYP2B6 protein expression and activity for bupropion and efavirenz in liver microsomes [17]. Other studies with cyclophosphamide and 7-ethoxy-4-trifluoro-methylcoumarin, however, have shown increased activity [11,18,19]. A study of leukemia patients undergoing hematopoietic stem cell transplantation and treatment with cyclophosphamide showed an association of CYP2B6*6 with increased liver toxicity, suggesting that this variant was more active at processing cyclophosphamide to its active metabolites [12]. One in-vivo study of Japanese HIV patients showed increased plasma efavirenz in CYP2B6*6 homozygotes, suggesting lower activity of this variant [20]. Thus, different substrates seem to be processed differently by this variant. A recent study has indicated that CYP2B6:516G > T, which is also associated with aberrant splicing of CYP2B6, may be the causal variant for severely decreased expression and function associated with the CYP2B6*6 haplotype [8] (see below for more details).

CYP2B6:516G > T (rs3745274, CYP2B6:Gln172His)

The CYP2B6:516G > T variant was first reported to be associated with a slight but not significant reduction in hepatic CYP2B6 protein expression and activity [5]. It is present in several haplotypes including the important haplotype, CYP2B6*6. This variant occurs more frequently in Black and African Americans as compared with Caucasians [21]. Recent studies have shown an impact of this variant on CYP2B6-mediated metabolism of nonnucleoside reverse transcriptase inhibitors [22], although some studies with smaller sample sizes have failed to show an effect [23,24]. The 516T allele has been associated with higher plasma exposure to efavirenz and may contribute towards efavirenz-associated CNS

side effects [21,25]. The TT genotype of CYP2B6:516G > T was recently found to be associated with efavirenz pharmacokinetics and psychiatric side effects [25,26]. Conversely, the homozygous G genotype was associated with subtherapeutic plasma concentrations of efavirenz [22,27]. Recent studies have indicated that efavirenz dose modification for haplotypes including the 516G > T genotype may reduce side effects in adults [28] and prevent subtherapeutic concentrations in children [27]. In a recent study, the composite CYP2B6:516G > T/983T > C genotype was significantly associated with plasma levels and clearance for efavirenz but not for nevirapine [29]. Larger prospective studies are, however, needed to validate the value of this association. The 516G > T variant has been associated with aberrant splicing in CYP2B6 (as described below) [8].

CYP2B6:785A > G (rs2279343, CYP2B6:Lys262Arg)

This variant is found alone as the CYP2B6*4 allele and also in combination as part of several other haplotypes including the important CYP2B6*6 haplotype. It is found at high frequencies in all major ethnic groups ranging from 15% in Asians to almost 50% in Black and African Americans [30,31]. This variant has been associated with higher CYP2B6 protein expression in COS-1 cells and demethylation activity with 4-trifluoromethylcoumarin when expressed as part of *4, *6, and *7 alleles [18]. When expressed in yeast, however, there was no effect on bupropion metabolism but it was expressed at higher levels [32]. Wang *et al.* [32] also observed that when expressed in combination with other variants such as the CYP2B6*16 allele (consisting of both Ile328Thr and Lys262Arg), in yeast or HEK-293 cells, the Lys262Arg variant partially rescued the very low expression of CYP2B6 protein seen with the Ile328Thr (983T>C) variant alone. This variant has also been associated with cyclophosphamide toxicity in a study of leukemia patients receiving hematopoietic stem cell transplantation [12].

CYP2B6:983T > C (rs28399499, CYP2B6:Ile328Thr)

The CYP2B6:983T > C variant was reported in a large screen of CYP gene polymorphisms by Solus *et al.* [33] and is the defining SNP of the *18 allele. It occurs with an allele frequency of 4–9% in Black or African Americans and was not observed in Asians and Caucasians [30,31,34]. It was shown at a low frequency (1.1%) in Hispanic Americans in one study [34]. This variant was found in linkage with intronic variants 17897C > T, 18273G > A, 18627G > A, and Lys262Arg in the CYP2B6*16 haplotype [32]. Expression of CYP2B6*18 in COS-1 cells resulted in no detectable protein (Klein *et al.* [30]). Klein *et al.* [30] suggested that Ile328 resides within an α-helix and the change in hydrophobicity from hydrophobic isoleucine to the polar but uncharged threonine may disrupt helix formation. Wang *et al.* found no change in the catalytic activity of this variant with the substrate bupropion, but observed much lower expression of 983T > C allele, 15–30% as compared to wild type. Wang *et al.* [32] also showed that when expressed in combination with the Lys262Arg (785A > G) variant, as in CYP2B6*16, the expression was higher as compared with 983T > C alone. This residue is highly conserved across alignments with other P450s [30]. The presence of this allele is associated with high plasma drug concentrations in patients treated with efavirenz [31,35] and nevirapine [35].

CYP2B6:1459C > T (rs3211371, CYP2B6:Arg487Cys)

The CYP2B6:1459C > T variant was first identified by Lang *et al.* [5] in 2001. Found at allele frequencies of 9–14% in Caucasians and 2–9% in Black or African Americans [7], this variant has been reported to reduce CYP2B6 protein expression in the human liver [5] and brain [36]. Human liver microsomes with the TT genotype had lower protein expression and reduced mephenytoin metabolism ($n = 92$) [5]. Other studies have had conflicting results but were limited by small numbers and lack of homozygotes [6,13]. Preliminary genotyping of a

small sample set ($n = 24$) suggested that individuals with the CC genotype had higher brain CYP2B6 than those with the CT or TT genotypes. Higher brain CYP2B6 activity in smokers and alcoholics may cause altered sensitivity to centrally acting drugs, increased susceptibility to neurotoxins and carcinogenic xenobiotics, and contribute to central tolerance to nicotine [36].

In vivo, 1459C > T was not associated with plasma concentrations of efavirenz or nevirapine [35] or bupropion [14]. In-vivo studies of CYP2B6 and bupropion are, however, confounded by the interactions of CYP2B6 and nicotine and the potential differences between brain and liver CYP2B6 expression and activity. In a smoking cessation study with bupropion, individuals with the DRD2-Taq1 A2/A2 genotype showed higher odds of abstinence only when they possessed the CYP2B6 1459 T/T or C/T genotypes [15]. Some of the bupropion–DRD2 variant effect may be because of the fact that smokers with the CYP2B6 variant may be more vulnerable to abstinence symptoms and relapse. However, it was also noted that bupropion may attenuate these effects, especially among females [16].

CYP2B6:1459C > T has also been reported to have a small but significant effect on clearance of thiotepa or tepa [37].

Splice variant CYP2B6:SV1

As many as five splice variants have been reported for CYP2B6 [6]. The SV1 splice variant lacks exons 4, 5, and 6 and is approximately 500 bp long (the full cDNA is approximately 1500 bp long) [6]. Association of 516G > T SNP with occurrence of CYP2B6 SV1 was first suggested by Lamba *et al.* [6] and has been more recently validated by Hoffman *et al.* [8]. The aberrant splicing of CYP2B6 is associated with the 516G > T variant and has been linked to severely decreased CYP2B6 expression and function in the liver [8].

Conclusion

CYP2B6 is an important pharmacogene involved in the metabolism of many drugs for a variety of clinical conditions. Although several important variants and haplotypes have been identified, the drug–gene interactions for *CYP2B6* still need further investigation to develop predictive dosing regimens based on genotype.

Additional information, including detailed mapping information for CYP2B6 variants, samples genotyped for these variants, and lists of linked drugs and diseases, is presented at http://www.pharmgkb.org/search/annotatedGene/cyp2b6/index.jsp.

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