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Cytochrome P450 2D6

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The cytochrome P450 2D6 (CYP2D6) is an enzyme of great historical importance for pharmacogenetics and is now thought to be involved in the metabolism of up to 25% of the drugs that are in common use in the clinic [1]. Several years before the gene was cloned, researchers observed that Caucasian population responded in a bimodal pattern to certain drugs such as debrisoquine and sparteine [2,3], with most patients exhibiting ‘normal’ pharmacokinetics, whereas others seemed to have great difficulty in metabolizing debrisoquine or sparteine. Debrisoquine and sparteine became examples of so-called probe drugs, and were used to phenotype patients [4]. This finding led researchers to conclude that there were common polymorphisms in an as yet unidentified metabolic gene that contributed to the variable pharmacokinetics of these drugs. The protein responsible for the altered metabolism was later purified from human liver microsomes by Distlerath *et al.* [5]. The gene encoding this protein was initially localized to chromosome 22 by Eichelbaum *et al.* [6]. The cDNA was cloned by Gonzalez *et al.* [7,8] from human liver cDNA libraries using an antibody against the rat ortholog. The deduced human protein revealed 73% sequence similarity with the rat protein and by the use of human–rodent somatic cell hybrids the gene was localized to human chromosome 22 [8], confirming the earlier study [6]. This gene came to be called *CYP2D6*, and is part of the cytochrome P450 gene family – a group of enzymes that is responsible for phase I metabolism and elimination of numerous endogenous substrates and a diverse array of drugs. Among the drug-metabolizing cytochrome P450s, CYP2D6 is the only noninducible enzyme, which results in a large contribution of genetic variation to the interindividual variation in enzyme activity [1]. *CYP2D6* is highly polymorphic, with over 90 known allelic variants [9]. A selection of these variants and haplotypes is described in this summary, and the full list of all named alleles can be found at: <http://www.cypalleles.ki.se/cyp2d6.htm>.

Cytochrome P450 2D6 metabolizer classes

CYP2D6 became an object of intense research after its identification as the gene responsible for the altered activity observed with debrisoquine and other drugs. It soon became apparent that there were many different polymorphisms in all parts of the world that impacted *CYP2D6* activity [10]. There were alleles that led to a complete loss of *CYP2D6* activity, which were common in the initially studied Caucasian populations [11]; however, studies in populations of other ethnic origins revealed reduced function and even hyperfunctional *CYP2D6* alleles [8,12]. A system of assigned patients into four categories based on their ability to metabolize *CYP2D6* substrates began to emerge. They are, listed in the order of highest functioning to lowest: ultrarapid metabolizers (UM), extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM) [13,14]. An individual's highest functioning *CYP2D6* allele predicts his/her phenotypic activity [13,14] (e.g. EM allele and PM allele results in an EM phenotype, UM allele and EM allele results in UM phenotype, IM allele and PM allele results in IM phenotype, etc.). EMs possess at least one fully functional *CYP2D6* allele, and are thought of as phenotypically normal. IMs (two reduced function or one reduced and one non-functional allele) and PMs (two non-functional alleles) are not able to metabolize *CYP2D6* substrates as well as their EM counterparts, and may be at increased risk for adverse effects resulting from higher plasma levels of the parent drug, or lack of efficacy resulting from an inability to form an active metabolite [13]. UM possess multiple functional copies of a single *CYP2D6* gene [15]. The *CYP2D6* copy number has been found to be from 2 to 13 [15]. Each functional copy of *CYP2D6* that is present increases the rate of metabolism of *CYP2D6* substrates significantly [15]. *CYP2D6* allele distributions exhibit significant interethnic differences. According to a review by Ingelman-Sundberg *et al.* [1], PMs are mainly found in Europe, and UMs are mainly found in North Africa and Oceania. Owing to the high Asian prevalence of the *CYP2D6**10 allele, IMs are located to a great extent in Asia [1,16].

Cytochrome P450 2D6 substrates and therapeutic implications

CYP2D6 polymorphisms have implications across many different therapeutic areas, as a diverse array of clinically used drugs are metabolized by *CYP2D6* [13] (see Drugs/Substrates section for references at the full VIP summary: <http://www.pharmgkb.org/search/annotatedGene/cyp2d6/index.jsp>). The impact that a *CYP2D6* polymorphism has on therapy with any of the aforementioned drugs is related to the resulting metabolizer status that the polymorphism(s) cause in the individual receiving therapy, as well as whether the parent drug is active or if it requires *CYP2D6* to metabolize it into an active metabolite. If the parent drug is active, then UMs may suffer from a lack of efficacy whereas IMs and PMs may suffer from complications resulting from higher than desired plasma concentrations of the drug [15]. If the parent drug must be converted to an active metabolite to relieve symptoms, then IMs and PMs may be deficient in the formation of the metabolite, and therefore not receive symptomatic relief [15].

Phenocopying and autophenocopying

Therapy with CYP2D6 substrates can be complex, not only because of genetic variation, but also owing to drug–drug interactions. Many drugs are CYP2D6 inhibitors (such as the statins), and taking an inhibitory drug along with a CYP2D6 substrate can alter the apparent phenotype of the patient. This phenomenon is known as phenocopying [13]. When this situation occurs, an EM can appear to be an IM or a PM because most of the available enzyme is being inhibited by a confounding drug. A related phenotype that can occur with chronic dosing of a CYP2D6 drug is called autophenocopying, in which a CYP2D6 substrate can inhibit its own metabolism over time as the concentration of the drug approaches steady state [13]. The pharmacokinetic profile of a single dose and of repeated dosing for drugs that exhibit phenocopying can therefore differ markedly [13].

CYP2D6 important variants and haplotypes

Traditionally, allele frequency is reported with respect to an individual single nucleotide polymorphism (SNP), and haplotypes are constructed from a collection of those polymorphic sites. However, in the *CYP2D6* literature, allele frequencies are usually reported in terms of haplotypes. We have therefore included the *CYP2D6* allele frequency table in the haplotype section of this summary. *CYP2D6* genotyping has traditionally been done according to an algorithm that appears in Gaedigk *et al.* [17] in which several SNPs are tested for, and if none are found, then the algorithm defaults to either *CYP2D6**1 or *CYP2D6**2. We have classified the SNPs that are used to differentiate the haplotypes that we have summarized, and, when possible, indicated whether that SNP has any role in the altered function. As most of the *CYP2D6* literature is focused on determining an individual's metabolic status, in the full *CYP2D6* VIP report at www.pharmgkb.org we have chosen the haplotypes that most commonly result in altered *CYP2D6* function, although many more exist. The *CYP2D6* variant page should therefore serve mainly as a guide in determining the *CYP2D6* haplotype, which should in turn serve as a guide in determining the metabolizer status and allele frequency. For the full PharmGKB *CYP2D6* haplotype and variant list, including mapping information, see <http://www.pharmgkb.org/search/annotatedGene/cyp2d6/variant.jsp> and <http://www.pharmgkb.org/search/annotatedGene/cyp2d6/haplotype.jsp>.

2549 Del A (rs4986774)

CYP2D6 2549 del A (also known as 2637 del A in the literature) causes a frameshift mutation that results in a truncated, nonfunctional protein. *CYP2D6* 2549 del A was first cloned from a genomic library of a PM by Kagimoto *et al.* [18], and is the diagnostic SNP for the *CYP2D6**3 haplotype [17]. *CYP2D6* 2549 del A is essentially found only in Caucasian populations [19].

1846G > A (rs3892097)

CYP2D6 1846G > A (also known as 1934G > A in the literature) is diagnostic for the nonfunctional *CYP2D6**4 haplotype [17]. *CYP2D6* 1846G > A causes a splicing defect that results in a nonfunctional protein [18]. This variant is responsible for the majority of the

PMs found in Caucasian populations [19], and is also found at much lower frequencies in other populations, such as Koreans [20].

100C > T (rs1065852)

CYP2D6 100C > T (also known as 188C > T in the literature) is part of both the nonfunctional *CYP2D6**4 haplotype and the reduced function *CYP2D6**10 haplotype. As *CYP2D6* 100C > T is present in both a nonfunctional and a reduced function haplotype, it is not likely to be the causative SNP for the lack of function observed with *CYP2D6**4. According to Gaedigk *et al.* [17], the presence of *CYP2D6* 100C > T (188C > T by their nomenclature), and the absence of *CYP2D6* 1846G > A (1934G > A) is diagnostic of *CYP2D6**10.

In-vitro studies in both COS-1 [18] and V79 [21] cells have shown that cells transfected with *CYP2D6* 100C > T alone exhibit reduced function, suggesting that this mutation contributes to the reduced function of the *CYP2D6**10 allele. Association studies have examined the role of this variant in contributing to generalized tonic clonic seizures seen in epilepsy (no association found) [22] and tardive dyskinesia in Chinese schizophrenic patients (weakly positive) [23].

1707 Del T (rs5030655)

CYP2D6 1707 del T (also known as 1795 del T in the literature) causes a frameshift mutation that results in a truncated, nonfunctional version of *CYP2D6*. *CYP2D6* 1707 del T is diagnostic for the nonfunctional haplotype *CYP2D6**6 [17], which makes up a small portion of PMs in Caucasian populations. A cDNA expressing this variant was first cloned by Evert *et al.* [24], and others have identified this mutation among a subset of PMs [25].

1023C > T (rs28371706)

CYP2D6 1023C > T (also known as 1111C > T in the literature) was first identified when screening for reduced function alleles in a Zimbabwean population [26]. It was identified as being part of the reduced function haplotype *CYP2D6**17. According to the genotyping algorithm of Gaedigk *et al.* [17], the presence of *CYP2D6* 1023C > T (1111C > T) and 2850C > T (2938C > T) is diagnostic for *CYP2D6**17.

A subsequent study examined the role of *CYP2D6* 1023C > T and two other SNPs found in *CYP2D6**17 to see which of the SNPs was causative of the reduced function observed with the haplotype [27]. The authors found that the *CYP2D6* 1023C > T single mutation exhibited normal function in transfected COS-1 cells, but when made in combination with another mutation led to an increased K_m (decreased affinity) for bufuralol. Interestingly, when the substrate was codeine, *CYP2D6* 1023C > T alone was sufficient to cause an increase in the K_m of *CYP2D6* for codeine, suggesting that this mutation exhibits substrate-specific effects, and may contribute to the reduction in function of *CYP2D6**17.

1659G > A (rs61736512) and 3183G > A (rs59421388)

CYP2D6 1659G > A (also known as 1747G > A in the literature) and *CYP2D6* 3183G > A (also known as 3271G > A in the literature) were first identified by Marez *et al.* [19] in a screening of a large European population. Although they are very rare in Europeans, both were later identified as part of the reduced functioning haplotype *CYP2D6**29, which is found at an estimated allele frequency of 20% in African Tanzanians [28]. Functional characterization of both variants in COS-1 cells showed a slightly reduced activity as measured by bufuralol hydroxylation, but this activity was reduced further when the *CYP2D6**29 mutations were made in combination [28].

2988G > A (rs28371725)

CYP2D6 2988G > A is an intronic polymorphism that has been shown to be associated with aberrant splicing of *CYP2D6* [29]. This splicing defect leads to the omission of exon 6 from some of the transcribed RNA, and leads to a reduction in activity. *CYP2D6* 2988G > A is diagnostic of the haplotype *CYP2D6**41, which is believed to be responsible for the IM phenotype in the majority of Caucasians [30].

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