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PharmGKB summary: very important pharmacogene information for CYP3A5

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Introduction

The aim of a PharmGKB VIP summary is to provide a simple overview of a gene with respect to drug effects. In some cases, there may be extensive evidence of variants that have known pharmacogenomic relevance, whereas in other cases, the summary may serve to highlight the gaps in knowledge where further study would aid the field. This summary points to the PharmGKB website to provide an interactive version that is linked to annotated publications and to related drugs, diseases, and pathways.

The human CYP3A subfamily, CYP3A4, CYP3A5, CYP3A7, and CYP3A43, is one of the most versatile of the biotransformation systems that facilitate the elimination of drugs (37% of the 200 most frequently prescribed drugs in the US [1]). Together, CYP3A4 and CYP3A5 account for ~30% of hepatic cytochrome P450, and approximately half of the medications that are oxidatively metabolized by P450 are CYP3A substrates. Both *CYP3A4* and *CYP3A5* are expressed in the liver and intestine, with *CYP3A5* being the predominant form expressed in extrahepatic tissues. The *CYP3A5* cDNA sequence was first described independently by Aoyama *et al.* [2] and Schuetz *et al.* [3]. The *CYP3A5* gene is located on chromosome 7q22.1 along with other *CYP3A* family members. The gene is on the minus chromosomal strand, consists of nine exons, and encodes a 502-amino-acid protein.

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Additional information, including detailed mapping information for *CYP3A5* (PharmGKB PA131) variants and lists of linked drugs and diseases, is presented at <http://www.pharmgkb.org/vip/PA131>.

Conflicts of interest

There are no conflicts of interest.

Variant information

CYP3A5 expression is highly polymorphic [4], with 25 allelic variants of *CYP3A5* (alleles numbered *1–*9) reported by various investigators and listed on the *CYP* allele nomenclature web site (<http://www.cypalleles.ki.se/cyp3a5.htm>). Functional *CYP3A5* is encoded by the *CYP3A5*1* allele.

The most common nonfunctional variant of *CYP3A5* is designated as *CYP3A5*3* [4]. Genbank sequence AC005020, which has a G at position 22 893, represents the *CYP3A5*3* allele. *CYP3A5*3* is assigned dbSNP #rs776746. On the *CYP* allele nomenclature website, it is designated as 6986A > G (*CYP3A5*1* has an A at this position). A change from A to G at this position creates a cryptic splice site in intron 3, resulting in altered mRNA splicing. The alternatively spliced isoform has an insertion from intron 3, which alters the reading frame and results in a premature termination codon and hence a nonfunctional protein [4]. Individuals with the *CYP3A5*3/*3* genotype are considered to be *CYP3A5* nonexpressors.

*CYP3A5*3* is the most frequent and well-studied variant allele of *CYP3A5*. Its frequency varies widely across human populations. In White populations, the estimated allele frequency of *CYP3A5*3* is 0.82–0.95 [4–8]. The allele frequency in other ethnic groups is as follows: African American, 0.33 [4]; Japanese, 0.85; Chinese, 0.65; Mexicans, 0.75; Southeast Asians (excluding Japanese and Chinese), 0.67; Pacific Islanders, 0.65; and Southwest American Indians, 0.4. [4]. In one study that used the HGDP-CEPH panel, the frequency ranged from 0.06 in Yorubans (Nigerians) to 0.96 in Basques and was significantly correlated with population distance from the equator [6].

The other two most studied *CYP3A5* alleles are *6 and *7. *CYP3A5*6* (14690G > A; rs10264272) is a nonfunctional allele, present predominantly in the African American population and occasionally found in other populations [4]. *CYP3A5*6* causes alternative splicing of *CYP3A5* (a G-to-A transition in exon 7 results in exon 7 skipping), and protein truncation, resulting in the absence of the *CYP3A5* protein [4]. *CYP3A5*6* alleles are relatively frequent in Black individuals (7–17% [4,5,9]), but are very rare in White populations [4,5] and in Asian populations [5,10].

*CYP3A5*7* (rs76293380; 27131–27132ins T) is an insertion polymorphism that resides between codons 345 and 346 and results in a shift in reading frame [9]. This shift introduces a premature termination codon at position 348 (D348), resulting in a truncated and nonfunctional protein. *CYP3A5*7* occurs at a frequency of about 8% in the African population [5] but has not been found in White [5,9,11] or Asian populations [5,12].

*CYP3A5*2* (rs28365083; g.27289C > A; T398N), considered to be not fully functional [11], was found at a frequency of 1% in a group of 500 Dutch Whites [11], 1.3% in a population of 124 Whites [13], and 0.3% in a group of 146 Bulgarian Whites [14]. This variant has not been found when assayed for in other populations [15–18].

Variant-drug associations

Individuals with *CYP3A5* expressor genotypes (*CYP3A5*1/*1* and **1/*3*) metabolize some *CYP3A* substrates more rapidly than do *CYP3A5* nonexpressors (e.g. **3/*3*). One such substrate is tacrolimus, which is used to prevent post-transplantation organ rejection. *CYP3A5*1* carriers have a higher rate of tacrolimus clearance than those with the other genotypes, with **1/*1* individuals having a higher clearance than **1/*3* individuals, who have higher clearance than **3/*3* individuals [19]. In ideal situations, the target tacrolimus concentration must be high enough to prevent transplant rejection [20,21], but low enough to minimize toxicity [22]. Tacrolimus trough concentrations are routinely monitored after

transplantation, and the dose is appropriately adjusted. Despite the well-established association of the *CYP3A5* genotype with clearance rate and trough levels [23–31], it has not been consistently shown to be associated with the risk of acute organ rejection. It has also not yet been shown that genotype-guided dosing leads to improved clinical outcomes. A recent study comparing genotype-guided dosing with the standard regimen demonstrated more rapid attainment of the target concentration, but did not demonstrate improved clinical outcomes [32]. A tacrolimus dosing equation that includes the *CYP3A5* genotype along with days post-transplant, age, transplant at a steroid sparing center or not, and calcium channel blocker use was recently published [19] for use in adult kidney transplant recipients, and the results await validation and prospective testing. This equation for calculating tacrolimus clearance is $38.4 \times [(0.86, \text{if days } 6\text{--}10) \text{ or } (0.71, \text{if days } 11\text{--}180)] \times [(1.69, \text{if } CYP3A5^*1/*3 \text{ genotype}) \text{ or } (2.00, \text{if } CYP3A5^*1/*1 \text{ genotype})] \times (0.70, \text{if receiving a transplant at a steroid sparing center}) \times [(age \text{ in years}/50)^{-0.4}] \times (0.94, \text{if calcium channel blocker is present})$. Then this clearance rate estimate is used to determine the tacrolimus dose to achieve the desired trough.

Liver microsomes from individuals homozygous for the nonfunctional *CYP3A5**3 allele had less than half the overall CYP3A catalytic activity toward midazolam (which is a substrate for CYP3A5 and CYP3A4) compared with individuals with at least one wild-type *CYP3A5**1 allele [4,33]. In African Americans, *CYP3A5**1/*3 individuals had eight-fold and 18-fold higher mean kidney microsomal CYP3A5 content and CYP3A catalytic activity, respectively, compared with *CYP3A5**3/*3 individuals [34]. *In vivo*, in a study group of 23 Whites and 34 African Americans, oral clearance of midazolam after rifampicin induction showed a relationship with the *CYP3A5**3 genotype [the magnitude of induction by rifampicin of CYP3A activity was greater in CYP3A5 nonexpressors than that in expressors [35], but it did not attain significance (this result could be because of the linked *CYP3A4**1B)]. No association was observed with induced systemic midazolam clearance or with the magnitude of clearance in this group [35]. No significant relationship was found between the *CYP3A5* genotype and midazolam pharmacokinetics in another study group, which included 19 Whites and two Africans [36]. The *CYP3A5**3 genotype affects the extent of drug interactions, and the extent of itraconazole inhibition of CYP3A-mediated midazolam hydroxylation is greater in CYP3A5 nonexpressors than in expressors, likely because of the relatively *CYP3A4*-specific inhibition by itraconazole [37].

The *CYP3A5**1/*3 genotype has been associated with more rapid clearance of the antiretroviral drug saquinavir compared with *3/*3 [38,39]. The *CYP3A5* genotype may also have dose-dependent effects on ABT-773 plasma levels [40]. CYP3A5 expressors have a higher rate of ifosfamide *N*-demethylation in the liver and kidney [41] and of cyclosporine A metabolism in the kidney [42].

In pediatric patients with precursor B-cell acute lymphoblastic leukemia (ALL) treated with vincristine, *CYP3A5* expressors had less treatment-related neurotoxicity [43]. In a recent study of advanced renal-cell carcinoma patients treated with sunitinib, *CYP3A5**1 was associated with an increased risk of dose reductions because of toxicity [44].

CYP3A5 has been implicated as a genetic determinant of differences in lipid-lowering responses to statin drugs, but the results have been inconsistent [45]. In one study, lovastatin, simvastatin, and atorvastatin were significantly less effective in *1 individuals than in *3/*3 individuals [46]. In contrast, another study found that *3 carriers showed a reduced response to atorvastatin [47]. The *CYP3A5* genotype has also been associated with the severity of side effects because of statin treatment [48] (*3/*3 patients taking atorvastatin who developed myalgia were more likely to sustain greater muscle damage).

Variant-disease associations

There have also been inconsistent results from studies of *CYP3A5* genotype association with blood pressure/hypertension (see review [49]). Studies showing an association of the *1 allele with higher blood pressure or with hypertension have all been carried out in individuals of African descent or in older White individuals [49]. In a recent meta-analysis (for hypertension: 10 studies including more than 9500 individuals, and for blood pressure: 12 studies including more than 9000 individuals), no association was found overall with the *CYP3A5* genotype, and, in Whites, a modest association was observed between *1 and lower systolic blood pressure [50].

One study, performed in a White (Nordic) population, showed that the risk of developing childhood ALL is higher for *CYP3A5* expressors than for nonexpressors; in a study of 616 pediatric ALL patients and 203 controls, the odds ratio for individuals with at least one expressor allele was 1.64 (95% confidence interval: 1.009–2.657; $P = 0.044$) [51]. For T-ALL, event free survival (EFS) was better in expressors (EFS = 94.1%) than in non-expressor patients (EFS = 61.5%; $P = 0.015$) [51]. In Asian Indians, the *CYP3A5* *3 allele has recently been shown to be associated with a risk of developing chronic myeloid leukemia (44.2% *3/*3 in chronic myeloid leukemia patients vs. 19.1% in controls; $P < 0.0001$) [52].

Japanese women who are *CYP3A5* expressors were shown to have a higher risk for breast cancer than those who are nonexpressors (odds ratio: 1.49; 95% confidence interval: 1.10–2.04; study size: 403 case–control pairs) [53]. In one small study (48 African American and 50 White women), the association between tamoxifen level/side effects during treatment for breast cancer and *1 versus *3 versus *6 was examined, and no association was found. The authors report that the study had sufficient power. However, a significant association ($P < 0.02$) was found between larger tumor size and having at least one copy of *6 [54].

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