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PharmGKB summary: very important pharmacogene information for CYP1A2

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Background

CYP1A2 is part of the cytochrome P450 (CYP) family of drug-metabolizing enzymes. The *CYP1A2* gene is found in a cluster with *CYP1A1* and *CYP1B1* on chromosome 15 [1]. *CYP1A2* and *CYP1A1* share a 5′-flanking region of approximately 23 kb, which contains shared regulatory elements, although the genes are positioned back to back and transcription occurs in opposite directions [2]. The *CYP1A2* gene spans around 7.8 kb and features seven exons and six introns, the first being a 55-bp-long noncoding exon. CYP1A2 is a 515-residue protein with a molecular mass of 58 294 Da [1].

CYP1A2 is an important metabolizing enzyme in the liver, comprising approximately 13% of all CYP protein (compared with CYP2D6 at 2%) [3]. There are over 100 substrates reported for CYP1A2, including many clinically important drugs (e.g. clozapine, tacrine), procarcinogens (e.g. benzopyrene and aflatoxin b1), and endogenous substrates (e.g. steroids and arachidonic acid) [1]. However, compared with other CYPs, there have been relatively few reports of PGx relationships. This may be explained by the smaller number of prescription drugs for which CYP1A2 is a metabolizing enzyme (9% compared with 37% for CYP3A4/5, 17% for CYP2C9, and 15% for CYP2D6) and by the fact that for many drugs CYP1A2 is not the sole metabolizing enzyme, nor is it active at the rate-limiting step [4]. This may also be because of fewer reported variants that impact CYP1A2 activity. The genetic component of variation in CYP1A2 activity is estimated at up to 75%, with environmental factors making up the remaining difference, such as smoking (induction) and oral contraceptive use in women (inhibition) [5]. However, a recent pathway-based analysis in human liver samples estimated that the genetic variation of CYP1A2 activity may only account for 42, 38, and 33% of the catalytic activity, protein expression, and mRNA levels, respectively [6]. Given the predominant role of CYP1A2 in activation of toxic xenobiotics compared with its metabolism of prescription drugs, there are many epidemiological reports examining the role of variant *CYP1A2*, metabolism of procarcinogens, and cancer risk.

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Conflicts of interest

There are no conflicts of interest.

CYP1A2 regulation

CYP1A2 is constitutively highly expressed in liver and is inducible in the liver, lung, pancreas, gastrointestinal tract, and brain [7]. Drug–drug interactions and interactions with smoking have been reported to alter drug response [1]. Smoking, dietary cruciferous vegetables, polyamine hydrocarbons from grilled meat, and omeprazole and other proton pump inhibitors have been [3] shown to induce *CYP1A2* [8]. Oral contraceptives, fluvoxamine, and fluoroquinolone antibiotics reduce expression [8].

The shared promoter of *CYP1A2* and *CYP1A1* has at least 13 response elements for the aryl hydrocarbon receptor (AHR) [7] (see the very important pharmacogene information for AHR at http://www.pharmgkb.org/search/annotatedGene/ahr/index.jsp). The transcription factor binding sites are palindromic and may therefore influence transcription in both directions, that is, either the CYP1A2 or the CYP1A1 promoter. These elements are involved in the activation response to xenobiotics, cruciferous vegetables, and polyamine hydrocarbons. Studies examining variants in the promoter have tended to look at their effects on the gene they are closest to.

Omeprazole and primaquine activate both human *CYP1A1* and *CYP1A2* expression through the common regulatory region in a mechanism that may be independent of AHR [9]. Lansoprazole and albendazole also activate *CYP1A1* and *CYP1A2*, although they preferentially induce *CYP1A1* [9]. The nuclear receptor CAR (coded for by *NR1I3*) transactivates human *CYP1A1* and *CYP1A2* in human hepatocytes through the common *cis*-element ER8 [10].

CYP1A2 variation

Many variants have been reported for *CYP1A2*, with some having an impact on drug metabolism. For a full list of variants, see the CYP allele nomenclature. No copy number polymorphisms for *CYP1A2* have been reported to date [11]. There is approximately 40% variability in liver expression of the *CYP1A2* gene and 60% variability in caffeine metabolism, the probe drug used most often for CYP1A2 [8]. Unlike other drug-metabolizing CYPs, few variants that could clearly explain the phenotypic variability in *CYP1A2* gene expression or inducibility have been identified [12]. The coding sequence variants reported have been seen at very low frequency in White and Asian populations [12]. A recent paper examining *CYP1A2* variation in Ethiopians suggested that because of the overall greater incidence of variation, including some novel presumable deleterious variants, there could be some individuals devoid of any CYP1A2 activity in this population [11].

There is some variability of numbering of variants in the literature. PharmGKB uses the numbering from the CYP allele nomenclature. For details on selected haplotypes and variants of pharmacogenomic interest, see below.

CYP1A2 drug metabolism

Caffeine is the main probe drug used to assess CYP1A2 activity *in vivo*. Theophylline and melatonin are also sometimes used as probe drugs, whereas in-vitro studies often use phenacetin [8]. CYP1A2 is responsible for more than 95% of the primary metabolism of caffeine [13]. For details of the metabolism of caffeine and the genes involved see http://www.pharmgkb.org/do/serve?objId=PA165884757&objCls=Pathway. Some studies have also examined caffeine as a modulator of disease etiology, looking at intake of caffeine containing foods and beverages with respect to disease risk (see individual variant descriptions for more details). Two recent independent genome-wide association studies have looked at the influence of variants on caffeine intake. Interestingly, both found

associated variants in the regulatory region of *CYP1A2* (rs2472304 and rs2472297) and in its regulator AHR (rs4410790 and rs6968865) [14,15].

CYP1A2 has been shown to be important for dosing of several antipsychotics and for assessing both drug efficacy and adverse drug reactions. CYP1A2 is the main CYP isoform involved in clozapine metabolism [16]. Case studies have shown ultrarapid metabolizers of clozapine that presented as resistant to treatment. Improved patient outcomes were obtained by increased clozapine doses and coadministration with the CYP1A2 inhibitor fluvoxamine [17,18]. There have also been discussions on the interaction of smoking and drug response and the potential dangers of smoking cessation in patients with schizophrenia [19].

CYP1A2 also influences the antithrombotic drug clopidogrel. Smoking increases clopidogrel-mediated platelet inhibition [20,21]. This is likely by induction of CYP1A2, causing it to play a larger role in the generation of active drugs.

Important haplotypes

CYP1A2*1A

This is considered the reference or ‘wild-type’ allele to which all variants are compared.

CYP1A2*1F

The *CYP1A2*1F* haplotype has been associated in many studies with an altered phenotype [12]. Generally, it is considered to have increased activity (ultrarapid metabolizer) because of increased induction of expression. The phenotype effect is observed only in the presence of an inducer, such as smoking or heavy coffee consumption [22,23].

There is some confusion in the literature regarding the designation of this haplotype [24]. The variant that defines this haplotype, *CYP1A2*: −163C> A (rs762551), has different frequencies in different populations and the assignment of major and minor alleles therefore varies. Most publications have listed **1Fas* C > A [24], but others have A > C [25]. Most studies that reported results for *CYP1A2*1F* actually only measured rs762551; as rs762551:C > A is part of other haplotypes (*CYP1A2*1J*, **1K*, **17*, **21* and several other predicted haplotypes), we have included those results in the discussion of rs762551.

A study of *CYP1A2*1F* in which they excluded other haplotypes containing rs762551A showed that rs762551AA was associated with increased metabolism of caffeine in Swedish smokers [12] as well as in Swedish and Serbian heavy coffee consumers [22]. Other haplotypes that included rs762551:C > A did not have a significantly altered metabolism of caffeine [12].

A study of nonsmoking healthy individuals taking omeprazole showed increased induction of caffeine metabolism in *CYP1A2*1F/*1F* homozygotes compared with *CYP1A2*1C/*1F* heterozygotes [26].

CYP1A2*1C

The defining and only single-nucleotide polymorphism (SNP) for this haplotype is −3860G > A (rs2069514), also seen in the literature as −2964G > A [27]. This haplotype has been reported to have decreased activity. See important variant rs2069514:G > A for more details.

CYP1A2*1K

There are three variants that define this haplotype: −739T > G (rs2069526), −729C > T (rs12720461), and −163C > A (rs762551). This allele was reported originally in Ethiopians

at a frequency of 3% (n = 173), in Spaniards at a frequency of 0.5% (n = 117), and in Saudi Arabians at 3.6% (n = 136) [28]. *CYP1A2*1K* allele had significantly reduced CYP1A2 activity in nonsmokers compared with *1A or *1F, using caffeine as a probe substrate [28]. This haplotype has not been observed in Japanese (n = 350) [29] and Koreans (n = 50) and occurs at a very low frequency in Swedes (n = 193, 0.3%) [12]. Therefore, follow-up functional studies have been unable to confirm effects on drug metabolism.

Important variants

rs762551, CYP1A2: - 163C > A, NM_000761.3:c.-9-154C > A

This SNP is the most well-studied genetic variant in *CYP1A2*. It is the sole variant of the *CYP1A2*1F* haplotype and found with other variants in several haplotypes (*1J, *1K, *21, and others that have not been confirmed). It is located in the intron between the noncoding exon 1 and exon 2, where the coding sequence begins [8]. The frequency of rs762551:C > A varies widely with populations: the C allele frequencies range from 0.3 to 0.39 in Asians, from 0.4 to 0.51 in Blacks or African Americans, and from 0.29 to 0.33 in Whites [8].

This variant was reported as showing increased caffeine metabolism in Caucasian smokers with the AA genotype compared with the CA and CC genotypes, but the effect was not seen in nonsmokers [30]. This effect was also not seen in pregnant Swedish smokers [31]. In a study on Ethiopian smokers, the *CYP1A2*1F* haplotype (i.e. solely rs762551) was not associated with increased caffeine metabolism compared with *CYP1A1*1A*; however, *CYP1A2*1K*, rs762551:C > A plus rs2069526:T > G, and rs12720461:C > T showed decreased metabolism [28]. A study on Japanese patients and healthy volunteers found no association of this variant when challenged with both theophyline and caffeine [29]. In a study of *CYP1A2*1F*, in which other haplotypes containing rs762551:C > A were excluded, rs762551AA was associated with increased metabolism of caffeine in Swedish smokers [12]. This suggests that rs762551:C > A may not be the causative variant and its effects may differ in different populations because of differences in linkage, diet, drug, or environmental exposures.

A few studies have examined dietary caffeine effects on disease risk. In a study on South Americans, the authors stated that ‘slow’ caffeine metabolizers genotyped for the rs762551:C > A variant had increased risk of myocardial infarction [25]. There was some confusion because of incorrect use of nomenclature in this paper, which was later clarified in a letter stating that the AA genotype was considered ‘fast’ caffeine metabolizer and the C allele ‘slow’ [24,32]; however, this is still an oversimplification because, as mentioned above, the fast metabolizer phenotype for rs762551AA is only observed under induction by smoking or high habitual coffee intake. Some studies have examined the role of caffeinated coffee intake and protection against Parkinson’s disease in conjunction with variant *CYP1A2*. One study showed that individuals with the CC genotype had decreased risk [33], but other studies have not observed this [34,35].

Several papers have reported the influence of rs762551:C > A on response or adverse effects with antipsychotic drugs; with the A allele leading to lower serum drug concentrations and higher risk for nonresponse and the C allele leading to higher plasma drug levels and greater risk for side effects. Various case studies have shown that individuals with the AA genotype are at risk for nonresponse to clozapine (see overview section) [17,18]. Individuals with the AA genotype receiving olanzepine also have lower serum drug concentrations and decreased treatment efficacy [36]. Some studies have associated the CC genotype with increased incidence or severity of tardive dyskinesia in people with schizophrenia treated with antipsychotics. However, other studies did not see this effect and a meta-analysis also failed to see any association even when accounting for smoking behavior and ethnicity [37-42].

The C allele is associated with increased QT interval in patients with schizophrenia treated with antipsychotics, in which CYP1A2 contributes to their metabolism, namely chlorpromazine, fluphenazine, trifluoperazine, and thioridazine [43].

The A allele was associated with an increased dose of paroxetine and also with increased likelihood of experiencing drug-related fatigue in Han Chinese patients with Major Depressive Disorder [44].

rs2069514, *CYP1A2*: - 3860G > A

Originally called −2964G > A [27], the CYP nomenclature site now calls it −3860G > A; this SNP is also known as *CYP1A2*1C*. It is found at frequencies of 7% in Blacks or African Americans, at 6–25% in Asians, and at 0.4–1% in Whites [23,29,41,45–47]. This variant was associated with decreased rate of caffeine demethylation in Japanese smokers but not in nonsmokers. The variant alters a transcription factor binding site in the gene promoter, although the factor was not defined [27].

The A allele was associated with increased severity of tardive dyskinesia in Indian smokers with schizophrenia taking typical antipsychotics [41]. However, after restricting the analysis by smoking and drug type, the sample size was very small. This association was not seen in a Japanese population [48].

The A allele is associated with lower clearance of theophylline in a study on Japanese nonsmoking asthmatics [27]. However, a later study found no association of this variant when challenged with both theophyline and caffeine [29].

rs12720461, *CYP1A2*: - 729C > T

Also called *CYP1A2*: −730C > T, this variant was shown *in vitro* to affect binding of an E-twenty six transcription factor [28]. Reporter constructs with this variant had lower inducibility with 2,3,7,8-tetrachlorodibenzo-p-dioxin in human hepatoma cells and may affect bioactivation and sensitivity to carcinogens [28]. This may also explain the lower caffeine metabolism seen for the *CYP1A2*1K* haplotype, which is the only haplotype that contains this variant.

Conclusion

Understanding the pharmacogenomic effects of *CYP1A2* variation is still at an early stage compared with that of other CYP enzymes. There is a need for well-defined phenotype groups so that studies have adequate power to discern effects of genomic variants against the background of potential inducers (caffeine, smoking, diet, etc.). For example, the studies on associations of *CYP1A2* with antipsychotics have had conflicting results; however, larger studies in which the drugs are specified, or limited to those primarily metabolized by CYP1A2, and that provides details of all inducers and *CYP2D6* status may provide a clearer picture. There is also the need to fully assess all other variants before assigning a haplotype. Early studies may have mistakenly categorized individuals as *CYP1A1*1A* or **1F*. Recent studies have identified several new predicted haplotypes that include rs762551, including variants such as rs2472304 (2159G > A) and rs2470890 (5347C > T) that were found at high frequencies in an Ethiopian population (43 and 33%, respectively) and at moderate frequencies in a Japanese population (17.4 and 23%, respectively) [11,49]. There is a great need for functional studies to determine the impact of these variants and define whether measurement of rs762551 alone in PGx studies misses the full picture. Caution should be used when inferring activity with probe substrates to other drugs as there may be different autoinductions of *CYP1A2*.

The presence of allelic imbalance in CYP1A2 expression and the importance of epigenetic genetic variation in influencing CYP1A2 mRNA expression and enzyme activity *in vitro* using human liver were reported recently [50]. Apart from genetic variation, epigenetic and environmental factors play a role in determining interindividual and interethnic variability in CYP1A2 expression and enzyme activity.

This PharmGKB summary briefly discusses the very important pharmacogene *CYP1A2* and its haplotypes and variants that can influence drug responses. A fully interactive version of this short review, with links to individual paper annotations and population descriptions, can be found at http://www.pharmgkb.org/search/annotatedGene/cyp1a2/index.jsp.

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