PharmGKB summary: cytochrome P450, family 2, subfamily J, polypeptide 2: CYP2J2

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Keywords

Overview

CYP2J2 is a member of the cytochrome P450 (CYP) family of monooxygenases, and, in humans, is the sole member of the CYP2J subfamily [1]. Specifically, CYP2J2 is an epoxygenasethat catalyzes epoxideformation at thesite of a carbon–carbon double bond in the substrate, as other CYP epoxygenases do, such as CYP2C8 and CYP2C9 [2]. The therapeutic agents ebastine [3], astemizole, terfenadine, diclofenac, and bufurarol are metabolized by CYP2J2 [4]. A recent study, screening 139 marketed therapeutic agents and compounds, have identified albendazole, amiodarone, cyclosporine A, danazol, mesoridazine, nabumetone, tamoxifen, and thioridazine as CYP2J2 substrates [5]. These findings show the ability of CYP2J2 to metabolize structurally diverse compounds. The substrates identified for CYP2J2 were also metabolized by CYP3A4, but with differences in regioselectivity [5]. For large compounds, CYP2J2 metabolism was more restricted to a single site, compared with CYP3A4, which metabolized substrates at multiple sites [5]. A study of microsomes from human livers and human small intestines investigated the metabolism of astemizole by CYP2J2 [6]. This study found that the CYP2J2 substrates arachidonic acid (AA) and ebastine strongly inhibited astemizole *O*-demethylation in microsomes from human small intestines and in in-vitro experiments with recombinant CYP2J2 [6]. A follow-up study found an inhibition of α-naphthoflavone, ketoconazole, troglitazone, tranylcypromine, ebastine, and terfenadine on the rate of astemizole *O*-demethylation in human small intestinal microsomes and on the rate of astemizole *O*-demethylation in recombinant CYP2J2 microsomes [7].

AA and linoleic acid (LA) are endogenous substrates of CYP2J2 [2,8]. CYP epoxygenases catalyze the metabolism of AA to four regioisomeric epoxyeicosatrienoic acids (EETs): 14,15-EET, 11,12-EET, 5,6-EET, and 8,9-EET [9]. EETs have been shown to possess many biologically relevant properties, such as inducing membrane hyperpolarization and vasodilation, reducing inflammation by inhibition of transcription factor nuclear factor-κB, and increasing fibrinolytic activity (reviewed in [10]). CYP2J2-derived EETs have been

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shown to be cardioprotective after ischemia [11] and after doxorubicin treatment [12] in animal studies using a transgenic mouse model over-expressing the human CYP2J2 isoform. How these findings translate into humans needs to be investigated further. CYP2J2 activates the nuclear peroxisome proliferator-activated receptor α, a controller of lipid metabolism and inflammation, *in vitro* and *in vivo* [13].

A *CYP2J2* cDNA was cloned in 1996 by Wu et al. [14], and the *CYP2J2* genomic region was cloned in 2002 by King et al. [8]. *CYP2J2* was mapped to human chromosome 1 [1] and the genomic region spans approximately 40 kb [8], encoding a 1.9 kb transcript from which a 502 amino acid protein with a molecular mass of 57.7 kDa was produced [14]. The *CYP2J2* gene, like other *CYP2* family genes, is composed of nine exons and eight introns [8]. Four binding site consensus sequences for the SP1 transcription factor are found in the wild-type *CYP2J2* promoter [2]. As expected for members of the CYP family, there is a heme-binding motif in the CYP2J2 predicted protein sequence [14]. The presence of CYP2J2 protein in microsomes [14] is indicative of its subcellular localization to the endoplasmic reticulum. CYP2J2 is expressed at high levels in the heart, particularly in cardiac myocytes and endothelial cells in coronary arteries [14,15]. Other tissues, including the liver, kidney, lung, pancreas, and gastrointestinal tract, also express CYP2J2 [8]. CYP2J2 showed selective distribution in different brain regions [16,17]. All of these tissues also exhibit fetal expression of CYP2J2 [18].

Owing to its predicted role in cardiovascular health, CYP2J2 has been extensively studied. The role of CYP2J2 in cancer is also being investigated. In-vitro experiments showed a high and selective expression of CYP2J2 in different human tumor tissues and cell lines [19]. Inhibitors of CYP2J2 related to the drug terfenadine showed effectiveness as antitumor agents in in-vitro assays and in murine xenograft models [20]. Increased CYP2J2 expression has been observed in tumor samples from patients with advanced epithelial ovarian cancer [21]; and in-vitro studies showed that overexpression of CYP2J2 promoted human cancer metastasis [22].

Important variants: CYP2J2: G-50T, CYP2J2: G-76T, rs890293, defining single nucleotide polymorphism for CYP2J2*7

Several *CYP2J2* variants have been characterized [4,8,18]. The Human Cytochrome P450 Nomenclature Committee recognizes 10 *CYP2J2* alleles on its website (*http://cypalleles.ki.se*). By far, the best studied of these is *CYP2J2*7*, which was first identified by King *et al.*[8] in a sequencing project to identify *CYP2J2* variants. *CYP2J2*7* is the most commonly known functional *CYP2J2* variant, occurring at frequencies of 2.1–17% (Table 1). The defining single nucleotide polymorphism (SNP) for *CYP2J2*7*, rs890293, is located in the proximal promoter of *CYP2J2*, substituting 'T' for 'G' found in the wild-type gene [8]. This SNP, located 76 nucleotides upstream of the first nucleotide of the translation start codon and 50 nucleotides upstream of the transcription start site, disrupts a binding site for the SP1 transcription factor [2,8]. In-vitro assays showed that transcription was reduced to 50% in *CYP2J2*7* promoter-reporter gene constructs relative to that observed for the wild-type *CYP2J2* promoter [2].

As *CYP2J2*7* is the most common functional *CYP2J2* polymorphism discovered, many studies have looked for associations between *CYP2J2*7* and various diseases and phenotypes. However, because of conflicting results from different studies, there is no clear consensus on the in-vivo effects of *CYP2J2*7* yet. Several clinical studies investigated the association of *CYP2J2*7* with different cardiovascular and cerebrovascular diseases. The findings are summarized in Table 2.

In addition, a case–control study of a predominately Caucasian population found two *CYP2J2* intronic tag SNPs, rs10889160 and rs11572325, associated with increased risk of myocardial infarction [37]. Both the SNPs were in moderate linkage disequilibrium with the *CYP2J2*7* allele. Interestingly, rs4388726, the tag SNP in the strongest linkage disequilibrium with the *CYP2J2*7* polymorphism, showed no significant association with myocardial infarction [37]. This study found no association between these genetic variations in *CYP2J2* and ischemic stroke [37].

Other *CYP2J2* alleles

Recombinant CYP2J2 proteins individually engineered to contain the polymorphisms seen in *CYP2J2*2, CYP2J2*3*, and *CYP2J2*6* each exhibited reduced metabolism of AA and LA [8]. Recombinant protein carrying *CYP2J2*4* polymorphism showed reduced metabolism of AA only [8]. CYP2J2*5 recombinant protein produced wild-type levels of AA and LA metabolites [8]. Recombinant CYP2J2*8 almost showed a complete loss of enzymatic activity as determined by CYP2J2-catalyzed astemizole *O*-demethylation and ebastine hydroxylation, whereas recombinant CYP2J2*9 showed enzymatic activities comparable with wild-type CYP2J2 [4]. CYP2J2*10, documented in only one individual, is hypothesized to encode a reduced-function protein [18].

Acknowledgments

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Table 1

CYP2J2: G-50T allele frequency table

Population	G allele (%)	T allele (%)	Number of chromosomes	References
African	83.0	17.0	48	[8]
African–American	86.0	14.0	298	[23]
African–American	90.0	10.0	392	[24]
Asian	87.0	13.0	48	[8]
Han Chinese	97.4	2 6	768	[25]
Chinese	95.4	4.6	1100	[26]
Han Chinese	97.9	2.1	1678	[27]
Han Chinese	85.0	15.0	800	[28]
German	93.5	6.5	1920	[29]
German	94.5	5.5	510	[2]
Korean	95.8	4.2	542	[4]
White	92.0	8.0	48	[8]
Caucasian	92.0	8.0	478	[23]
Caucasian	93.3	6.7	178	[3]
Russian	96.8	3.2	1152	[30]
Ovambo	93.3	6.7	372	[31]
Mongolian	96.6	3.4	236	[31]
Japanese	93.8	6.2	676	[31]

Table 2

*CYP2J2*7* association with different disease risks

Disease	Population	Study size	Association	References
CAD	German	289 patients with CAD 255 controls	Yes – increased risk	[2]
CAD	German	2547 patients with CAD 696 controls	No	[29]
CHD	African–American	200 CHD cases 260 non-CHD cases	Yes – lower risk	[32]
CHD	Caucasian	692 CHD cases 493 non-CHD cases	No	[32]
MI	German	1350 CAD patients with MI 1197 CAD patients without MI 696 controls	No	[29]
MI	Han Chinese	200 patients 200 controls	Yes – increased frequency	[28]
MI	German	1000 individuals	No	[33]
Acute coronary syndromes; brain ischemia	German	289 patients with CAD 255 controls	No	[2]
Cerebrovascular accident risk	Chinese	200 patients with ischemic stroke 350 controls	No	[26]
Ischemic coronary events; cerebrovascular events	Swedish	5740 participants	No	[34]
Hypertension	African–American	108 patients with hypertension 107 normotensive controls	No	[24]
Hypertension	African–American	76 hypertensive patients 73 normotensive participants	No	[23]
Hypertension	Caucasian	123 hypertensive patients 116 normotensive participants	Yes – decreased risk in male patients	[23]
Hypertension	Russian	295 patients with hypertension 281 healthy controls	Yes – increased risk	[30]
Asthma	Russian	215 patients with asthma 214 healthy controls	Yes – increased susceptibility	[35]
Calcineurin inhibitor induced nephrotoxicity	Caucasian	163 participants	No	[36]

CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction.