CYP4B1 (cytochrome P450, family 4, subfamily B, polypeptide 1)

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Identity

Other names: CYPIVB1, P-450HP
HGNC (Hugo): CYP4B1
Location: 1p33

DNA/RNA

Description

The CYP4B1 gene has 12 exons resulting in an open reading frame of 1533 bp (isoform 1). The CYP4B1 locus is depicted in figure 1 (NCBI).

Transcription

Two major transcripts are known to derive from alternative splicing (NM_000779.3, NM_001099772.1). Isoform 1 encodes a 511 amino acid protein, while isoform 2 encodes a 512 amino acid protein with a Ser206 insertion. It should be noted that this is a complicated locus with many other possibilities for alternative splicing.

Pseudogene

No pseudogene is known for CYP4B1.

Figure 1. Localization of the CYP4B1 locus to chromosome 1p33 and sites (exons 5, 8 and 9) of polymorphic variants that describe the 7 allelic variants of CYP4B1 (see table 1 for details).
**Protein**

**Note**
CYP4B1 belongs to the mammalian CYP4 enzyme family that also includes CYP4A, 4F and the recently discovered CYP 4V, 4X and 4Z sub-families (Rettie and Kelly, 2008). P450 enzymes usually function as monooxygenases in that they incorporate one atom of molecular oxygen into their substrates and reduce the other to water.

CYP4 enzymes typically catalyze fatty acid ω-hydroxylase reactions.

**Description**
Structurally, P450 enzymes all share a similar fold featuring a β-sheet rich N-terminus and an α-helix rich C-terminus. The hydrophobic N-terminus of eukaryotic P450s functions as membrane anchor, whereas the C-terminal region houses the cysteinyl heme (iron protoporphyrin IX) cofactor that binds and activates molecular oxygen. Many CYP4 enzymes, including CYP4B1, possess a unique post-translational modification at the heme active center, wherein a conserved glutamate residue in the core I-helix forms a covalent, ester linkage at the C-5 methyl group of the heme (Henne et al., 2001). The function of the unusual modification has not been established, although it may serve to rigidify the enzyme's active site and modulate the substrate selectivity of CYP4B1.

The CYP4B1 enzyme is highly conserved across species - see figure 2 below that also highlights the position of the cysteinyl ligand and the I-helix glutamate.

**Expression**
CYP4B1 mRNA and/or protein are found typically at the highest levels in lung and airway tissue. Liver levels of the enzyme are usually much lower, but inducible by phenobarbital. Expression of the enzyme in mouse kidney is regulated by androgens. CYP4B1 is highly expressed in several cancer types, including colon, adrenal gland, lung and gastric cancers.

**Localisation**
CYP4B1 is located in the ER membrane, although one report suggests that the rat enzyme may be a secreted protein in respiratory mucosa (Genter et al., 2006).
Figure 2. Multiple sequence alignment of vertebrate CYP4B proteins. The covalently heme-linked glutamate residue is indicated in bold italics and the heme-coordinating cysteinyl ligand depicted in bold underline. The Pro>Ser substitution at position 427 in human CYP4B1 is depicted in italics. Alignments determined using the ClustalW2 multiple sequence alignment program available online at EMBL-EBI.
Mutations

Note
Seven alleles (CYP4B1*1-*7) are listed at http://www.cypalleles.ki.se/cyp4b1.htm and summarized in table 1 below. The CYP4B1*1 allele is described by a composition of the major alleles shown in table 1. CYP4B1*2 contains the haplotype of the 294 frameshift along with M331I, R340C and R375C. CYP4B1*7 is the same haplotype minus the R375C variant. CYP4B1*3/4/5 are described by the R173W, S322G and M331I polymorphisms, respectively. CYP4B1*6 is R173W in combination with V345I.

<table>
<thead>
<tr>
<th>Nucleotide Change, cDNA position</th>
<th>Protein Coding Sequence Change</th>
<th>Heterozygosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>517C&gt;T</td>
<td>R173W</td>
<td>0.28</td>
</tr>
<tr>
<td>881_882ΔAT</td>
<td>294 frameshift (STOP)</td>
<td>0.34</td>
</tr>
<tr>
<td>964A&gt;G</td>
<td>S322G</td>
<td>0.02</td>
</tr>
<tr>
<td>993G&gt;A</td>
<td>M331I</td>
<td>0.40</td>
</tr>
<tr>
<td>1018C&gt;T</td>
<td>R340C</td>
<td>0.22</td>
</tr>
<tr>
<td>1033G&gt;A</td>
<td>V345I</td>
<td>ND</td>
</tr>
<tr>
<td>1123C&gt;T</td>
<td>R375C</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Table 1. CYP4B1 polymorphic variants including nucleotide changes and effect on protein coding sequences. The values for heterozygosity of the minor alleles are taken from NCBI. ND: not determined.

Recent exome sequencing has revealed considerable additional polymorphism (>75 total SNPs) in the human CYP4B1 gene (search at Exome Variant Server).

Implicated in

Various cancers

Note
CYP4B1 mRNA and/or protein are highly expressed in some cancer types. In particular Imaoka et al. demonstrated increased CYP4B1 in bladder tumor tissue at both the mRNA and protein level (Imaoka et al., 2000). This finding is also consistent with rodent studies demonstrating localization of CYP4B1 in mouse and rat bladder tissue (Imaoka et al., 1997; Imaoka et al., 2001). However, Czerwinski et al. observed down regulation of CYP4B1 mRNA in lung tumors relative to normal lung (Czerwinski et al., 1994). With breast cancer, there does not appear to be any difference in expression of CYP4B1 when comparing tumor tissue with surrounding healthy tissue, but these studies did not use disease-free subjects as a comparator (Iscan et al., 2001). Relatively high expression of constitutive CYP4B1 mRNA has been found in human urothelial cells (Roos et al., 2006). Peripheral blood mononuclear cell CYP4B1 mRNA expression correlated with human liver expression and therefore has been suggested as a surrogate marker for hepatic bioactivation of environmental pro-toxins (Furukawa et al., 2004). An increased risk of bladder cancer (OR of 1.03-2.95) has been reported in Japanese patients carrying the CYP4B1*2 allele (Sasaki et al., 2008). One potential explanation could be that CYP4B1 is known to play a role in aromatic amine bioactivation (Windmill et al., 1997) and these compounds are known bladder carcinogens and present in cooked meats (Jägerstad and Skog, 2005) and cigarette smoke (Smith et al., 1997), among other sources. However, no association was found between lung cancer risk and CYP4B1*1-*7 polymorphisms in Japanese (Tamaki et al., 2011).

Angiogenesis

Note
Studies conducted in a rabbit model of corneal wound healing have implicated that CYP4B1 may play a role in production of inflammatory eicosanoids and corneal neovascularization (Mastyugin et al., 2001). These observations are corroborated by findings in mice, whereby heme oxygenase-I induction attenuates corneal inflammation and is associated with a lack of CYP4B1 induction (and eicosanoid production) (Patil et al., 2008).

Conversely, retinoic acid (RA) has been shown to increase CYP4B1 gene expression in ocular organ cultures, resulting in increased metabolism of arachidonic acid to 12-HETE and 12-HETrE (Ashkar et al., 2004). These effects were shown to be mediated, at least in part, by transcriptional regulation of the rabbit CYP4B1 promoter, which contains several RAR/RXR binding motifs (Ashkar et al., 2004). While RA is typically associated with corneal wound healing, the induction of CYP4B1 by RA suggests it may also have a pro-inflammatory role in wound healing. This is supported by the observation that systemic treatment with 13-cis-retinoic acid (Accutane™) for cystic acne is associated with conjunctivitis, eyelid inflammation and keratitis, along with other ocular effects (Lebowitz and Berson, 1988).

Further evidence that CYP4B1 is important in ocular inflammation, eicosanoid production and neovascularization is shown in a study by Seta et al., using in vivo siRNA targeting of CYP4B1 in a rabbit model of corneal wound healing. It was found that down-regulation of CYP4B1 inhibited production of 12-HETrE and VEGF in addition to decreasing neovascularization (Seta et al., 2007).

Colitis

Note
Several recent studies have implicated a potential role for CYP4B1 in inflammatory bowel disease (IBD). In a mouse model of dextran sodium sulfate (DSS)-induced colitis, Ye et al. found that caffeic acid treatment decreased disease severity and this was associated with increased expression of Cyp4b1 in affected tissues (Ye
et al., 2009). In a subsequent study looking at the role of caffeic acid bioavailability in this model, they found that mice treated with DSS alone had lower colonic Cyp4b1 expression when compared to DSS plus caffeic acid treated mice (Ye et al., 2011). In a different mouse model of IBD, Liu et al. also found evidence that Cyp4b1 gene expression is altered in this disease state (Liu et al., 2009). It was found that IBD induced by infection with Helicobacter bilis resulted in changes in mucosal gene expression patterns. Using microarray analysis, it was found that H. bilis infection resulted in decreased expression of Cyp4b1. These authors also examined mice with IBD induced by DSS and, akin to Liu et al., found decreased expression of Cyp4b1 in diseased tissue. These findings suggest an anti-inflammatory role for CYP4B1 in IBD, but these preclinical studies must be weighed against what is known about gastrointestinal expression of CYP4B1 and human IBD. While rodents and rabbits and other species are known to express CYP4B1 in the gut, there are species-specific differences, with humans expressing little CYP4B1 in this tissue (McKinnon et al., 1994). Whether the CYP4B1 gene plays any role in IBD is unclear, particularly in light of the functionality of the Pro427Ser human protein (Zheng et al., 1998). Finally, in considering risk of developing IBD, a genome wide association study by The Wellcome Trust Examining 2000 cases of Crohn's with 3000 controls, found no significant association between CYP4B1 genetic variants and disease incidence (Wellcome Trust Case Control Consortium, 2007).

References


. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007 Nov 2;277(3):776-80


Rettie AE, Kelly EJ.. The CYP4 Family Issues in Toxicology. Cytochrome P450: Role in the metabolism and toxicity of drugs


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