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Cytochrome P450 2C9-CYP2C9

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Overview

<http://www.pharmgkb.org/search/annotatedGene/cyp2c9/index.jsp> CYP2C9 is a phase I drug-metabolizing cytochrome P450 (CYP450) enzyme isoform that plays a major role in the oxidation of both xenobiotic and endogenous compounds. Gray et al. [1] identified *CYP2C9* as one of several *CYP2C* genes clustered in a 500 kb region on chromosome 10q24. The cluster comprises four genes arranged in the order *CYP2C8-CYP2C9-CYP2C19-CYP2C18* [1]. Several studies identified a single nucleotide polymorphism (SNP) linkage between the *CYP2C8* and *CYP2C9* genes [2-4]. *CYP2C9* is primarily expressed in the liver, and the expression level is reported to be the second highest among CYP isoforms [5]. Only the CYP enzyme CYP3A4 is quantitatively more highly expressed in the human liver [6].

Substrates

It has been estimated that CYP2C9 is responsible for the metabolic clearance of up to 15-20% of all drugs undergoing phase I metabolism [7,8]. Table 1 is a partial list showing examples of the broad substrate spectrum of drugs that are metabolized by CYP2C9, including relevant references. Further information is also available at <http://medicine.iupui.edu/clinpharm/ddis/table.asp> and in the following reviews [6,9].

Inducer and inhibitors

CYP2C9 is induced by rifampicin [38]. Treatment with rifampicin has been shown consistently to increase the clearance of drugs eliminated by CYP2C9. The clearance of losartan, phenytoin, tolbutamide, and S-warfarin is approximately doubled in healthy volunteers or patients treated with rifampicin [9,39].

CYP2C9 is inhibited by amiodarone, fluconazole, and sulphaphenazole among other drugs [9]. Dangerous drug- drug interaction can arise when an inhibitor such as one of these is added to a therapeutic regime that includes drugs with a low therapeutic index, such as S-warfarin, tolbutamine, and phenytoin [40-42]. For example, there are numerous studies documenting potentiation of the anticoagulant effect of warfarin in patients coadministered with amiodarone [43-45].

Structure

CYP2C9 is the enzyme responsible for the metabolism of the S-isomer of warfarin that is principally responsible for the anticoagulant effect of the drug. The crystal structure of human CYP2C9 was described by Williams et al. [46], for both CYP2C9 in complex with warfarin and unliganded CYP2C9 (Protein Data Bank ID: 1OG2 and 1OG5, respectively). The structure showed unanticipated interactions between CYP2C9 and warfarin, revealing a new binding pocket, suggesting that CYP2C9 may simultaneously accommodate multiple ligands during its biological function [46]. Structural analysis suggested that CYP2C9 may undergo an allosteric change when binding warfarin [46]. An X-ray crystal structure of CYP2C9, in complex with the NSAID flurbiprofen, has also been described (Protein Data Bank ID: 1R9O) [47].

Genetic phenotypes and adverse drug reactions

The gene coding for the CYP2C9 enzyme is highly polymorphic, including functional variants of major pharmacogenetic importance. Changes in metabolic activity caused by genetic variants in *CYP2C9* play a major role in pathogenesis caused by adverse drug reactions. Patients with low enzyme activity are at risk of adverse drug reaction, especially for CYP2C9 substrates with a narrow therapeutic window, such as S-warfarin, phenytoin, glipizide, and tolbutamide [48].

A large body of literature investigates two common non-synonymous variants within *CYP2C9* (R144C, rs1799853 and I359L, rs1057910), leading to poor metabolism phenotypes. Both variants have significantly lower frequencies in African and Asian populations compared with Caucasian populations [8,49], see frequency tables (Tables 2 and 3) below.

Individuals with these variants are at risk of prolonged bleeding time and increased incidence of severe bleeding in warfarin therapy [65], higher possibility of low blood sugar levels during glipizide and tolbutamide therapy [31], and more frequent symptoms of overdose in phenytoin therapy [66].

Patients with the poor metabolizer *2 (identified by R144C) and *3 (identified by I359L) haplotypes require lower doses of warfarin to achieve a similar anticoagulant as patients with at least one *1 (wild-type) haplotype [65,67]. However, it is now known that *CYP2C9* genotype accounts for only part of the variability in warfarin sensitivity [68,69], because *VKORC1* genotype, age, and weight are also key factors in predicting the therapeutic dose for warfarin [54].

CYP2C9 is responsible for about 90% of phenytoin metabolism, and the *CYP2C9**2 and *3 haplotypes decrease the metabolism of phenytoin [70-72].

Besides the two variants mentioned above, a large number of SNPs have been described in the regulatory and coding regions of the *CYP2C9* gene (<http://www.cypalleles.ki.se/cyp2c9.htm>). Some of the polymorphisms are associated with reduced enzyme activity compared with wild-type in in-vitro experiments; only a few enzyme experiments have been done *in vivo*. *CYP2C9**6 (818delA, rs9332131) is a rare (1 allele in 158 African-Americans, 0 in Caucasians) null allele with lack of activity because of a splicing mutation that causes a frameshift resulting in a truncated protein [73]. The variant I359T (*CYP2C9**4) is also a rare (0.5% in African-Americans, 6% in Caucasians) polymorphism [53,74]. Both have been detected in patients who had adverse reactions to phenytoin [73,75]. *CYP2C9**5 (D360E, rs28371686), *6, *8 (R150H, rs7900194), and *11 (R335W, rs28371685) variants were associated with decreased phenytoin metabolism in a black population [76].

The *CYP2C9* promoter contains important regulatory elements: two HNF4 α sites, a nuclear receptor pregnane X receptor binding site, a constitutive androstane receptor/PXR site, and a glucocorticoid responsive element [59,77,78]. There have been multiple polymorphisms detected in the 5' untranslated region of *CYP2C9* but these have not yet been shown to contribute to response to warfarin [79,80] or phenytoin [72] *in vivo*, beyond those which seem to be in linkage disequilibrium with known exonic variants [79,81,82]. A recent study investigating 22 known and 9 novel promoter SNPs with an in-vitro promoter activity assay suggests that genetic variation within *CYP2C9* regulatory sequences is likely to contribute to differences in *CYP2C9* phenotype, both within and among different populations, independent from known exonic variants [83].

Important variants

CYP2C9: R144C; 144Arg > Cys; 430C > T (rs1799853)

This variant in exon 3 is the defining allele for the *CYP2C9**2 haplotype. Other variant positions delineate between haplotypes in the *2 series (see <http://www.imm.ki.se/CYPalleles> for defining website), but a T allele at this position defines a *CYP2C9**2 haplotype. For further information about the *CYP2C9**2 haplotype (see <http://www.pharmgkb.org/search/annotatedGene/cyp2c9/haplotype.jsp>).

According to most in-vitro data, substrate affinity is not affected substantially by the *2 haplotype, but the maximum rate of metabolism (V_{max}) is reduced to approximately 50% of that for *CYP2C9**1 (wild-type) [8,84-86].

Individuals homozygous for this variant have been found to have much lower clearance values for S-acenocoumarol, S-warfarin, phenytoin, tolbutamide, ibuprofen, nateglinide, fluvastatin, phenprocoumon, when compared to individuals homozygous for R (Arg) [84,87]. Homozygotes for this variant also have a lower clearance as compared with individuals homozygous for R (Arg) (68-90%) for the following drugs: phenytoin, tolbutamide, ibuprofen, nateglinide, fluvastatin, phenprocoumon [84].

The R144C variant has been genotyped in various populations (Table 2). The variant exists in about 10-20% of the Caucasian population, and is rare in the tested Asian and African-American populations [49,88].

CYP2C9: I359L; 359Ile > Leu; 1075A > C (rs1057910)

The variant at this position is the defining allele for the *CYP2C9**3 haplotype. Other variant positions delineate between haplotypes in the *3 series (see <http://www.imm.ki.se/CYPalleles> for defining website), but a C allele at this position defines a *CYP2C9**3 haplotype. For further information about the *CYP2C9**3 haplotype see <http://www.pharmgkb.org/search/annotatedGene/cyp2c9/haplotype.jsp>

The catalytic activity of the *3 haplotype is significantly reduced for most CYP2C9 substrates because of both an increase in K_m and a reduction in V_{max} [8,84,85].

Leu/Leu homozygotes have lower metabolic activity for CYP2C9 substrates in general, including tolbutamide and phenytoin [89]. However, much of the supporting data are from in-vitro studies and homozygous individuals are rare [90]. In other studies, it has been found that heterozygotes have about half the clearance as wild-type, for the following drugs: S-warfarin, tolbutamide, fluvastatin, glimepiride, tenoxicam, candesartan, celecoxib, phenytoin [84].

The clearance of S-ibuprofen is reduced in *CYP2C9**3/*3 homozygotes compared with wild-type homozygotes [3]. In in-vivo studies, the *CYP2C9**3 haplotype in heterozygotes has been associated with a lower clearance and longer half-life of flurbiprofen [91]. The I359L variant has been genotyped in various populations (Table 3). Supplemental digital content for the CYP2C9 gene (PA126) and VIP is available at <http://www.pharmgkb.org/search/annotatedGene/cyp2c9/>.

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Table 1
Examples of substrates that are metabolized by CYP2C9

Drug name	Class	References
Irbesartan	Angiotensin II blocker	[10,11]
Losartan	Angiotensin II blocker	[12]
Phenytoin	Antiepileptic	[13]
Cyclophosphamide	Alkylating agent	[14,15]
Tamoxifen	Anti-estrogen	[16]
Fluvastatin	Statin	[17]
Celecoxib	NSAID	[18,19]
Diclofenac	NSAID	[20,21]
Ibuprofen	NSAID	[22]
Lornoxicam	NSAID	[23,24]
Meloxicam	NSAID	[25]
Naproxen	NSAID	[26,27]
Glibenclamide	Sulfonylurea	[28]
Glimepiride	Sulfonylurea	[29,30]
Glipizide	Sulfonylurea	[31,32]
Tolbutamide	Sulfonylurea	[33]
Warfarin	Anticoagulant	[34-37]

Table 2
Frequency of the 144C allele in different populations

Population	No. of subjects	Allele frequency of 144C	References
Chinese (Shanghai)	394	0.001	[50]
Korean	574	0.000	[51]
Japanese	147	0.000	[52]
Japanese	140	0.000	[53]
Japanese	64	0.000	[54]
Vietnamese (Kinh)	157	0.000	[55]
Iranian	200	0.128	[56]
Turkish	499	0.106	[57]
Ashekenazi Jew	100	0.085	[52]
Yemenite Jew	99	0.051	[52]
Moroccan Jew	100	0.095	[52]
Libyan Jew	89	0.152	[52]
Egyptian	247	0.120	[58]
Ethiopian	150	0.040	[59]
African-American	66	0.000	[54]
US-Caucasians	115	0.143	[54]
Russian	290	0.105	[60]
Croatian	200	0.165	[61]
French-Caucasians	151	0.150	[50]
German	118	0.140	[62]
Swedish	430	0.107	[63]
Spanish	157	0.143	[64]
Italian	157	0.110	[59]

Table 3
Frequency of the 359Leu allele in different populations

Population	No. of subjects	Allele frequency of 359Leu	References
Chinese (Shanghai)	394	0.036	[50]
Korean	574	0.011	[51]
Japanese	147	0.007	[52]
Japanese	140	0.054	[53]
Japanese	64	0.016	[54]
Vietnamese (Kinh)	157	0.022	[55]
Iranian	200	0.000	[56]
Turkish	499	0.100	[57]
Ashekenazi Jew	100	0.080	[52]
Yemenite Jew	99	0.081	[52]
Moroccan Jew	100	0.115	[52]
Libyan Jew	89	0.174	[52]
Egyptian	247	0.060	[58]
Ethiopian	150	0.020	[59]
African-American	66	0.008	[54]
US-Caucasian	115	0.109	[54]
Russian	290	0.067	[60]
Croatian	200	0.095	[61]
French-Caucasians	151	0.080	[50]
German	118	0.050	[62]
Swedish	430	0.074	[63]
Spanish	157	0.162	[64]
Italian	157	0.090	[59]