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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

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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 coadminis- tered 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 poly- morphic, including functional variants of major pharma- cogenetic 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, pheny- toin, 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].

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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 muta- tion that causes a frameshift resulting in a truncated protein [73]. The variant I359T (*CYP2C*4*) is also a rare (0.5% in African-Americans, 6% in Caucasians) polymorph- ism [53,74]. Both have been detected in patients who had adverse reactions to phenytoin [73,75]. *CYP2C9*5* (D360E, rs28371683), **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 HNF4α sites, a nuclear receptor pregnane X receptor binding site, a constitutive androstane receptor/PXR site, and a glucocorticoid responsive ele- ment [59,77,78]. There have been multiple polymorph- isms 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 likelyto 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 maxi- mum 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, nategli- nide, fluvastatin, phenprocoumon, when compared to individuals homozygous for R (Arg) [84,87]. Homozy- gotes for this variant also have a lower clearance as com- pared with individuals homozygous for R (Arg) (68-90%) for the following drugs: phenytoin, tolbutamide, ibupro- fen, nateglinide, fluvastatin, phenprocoumon [84].

The R144C variant has been genotyped in various popu- lations (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

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defines a *CYP2C9*3* haplotype. For further infor- mation 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, fluvas- tatin, glimepiride, tenoxicam, candesartan, celecoxib, phenytoin [84].

The clearance of S-ibuprofen is reduced in *CYP2C9*3/*3* homozygotes compared with wild-type homogozygotes [3]. In in-vivo studies, the *CYP2C9*3* haplotype in hetero-zygotes 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]

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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]

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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]