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PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 19

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Abstract

This PharmGKB summary briefly discusses the *CYP2C19* gene and current understanding of its function, regulation, and pharmacogenomic relevance.

Keywords

antidepressants; clopidogrel; *CYP2C19**17; *CYP2C19**2; *CYP2C19*; proton pump inhibitors; rs4244285

Introduction

The cytochrome P450, family 2, subfamily C, polypeptide 19 (*CYP2C19*) gene is located within a cluster of cytochrome P450 genes (centromere-*CYP2C18*-*CYP2C19*-*CYP2C9*-*CYP2C8*-telomere) on chromosome 10q23.33. The *CYP2C19* enzyme contributes to the metabolism of a large number of clinically relevant drugs and drug classes such as antidepressants [1], benzodiazepines [2], mephenytoin [3], proton pump inhibitors (PPIs) [4], and the antiplatelet prodrug clopidogrel [5]. Similar to other CYP450 genes, inherited genetic variation in *CYP2C19* and its variable hepatic expression contributes to the interindividual phenotypic variability in *CYP2C19* substrate metabolism. The *CYP2C19* 'poor-metabolism' phenotype was initially discovered by studies on impaired mephenytoin

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Conflicts of interest

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metabolism and the major molecular defect responsible for the trait is the *CYP2C19*2* (c. 681G > A; rs4244285) loss-of-function allele [3]. *CYP2C19* genotype has since been shown to affect the metabolism of several drugs and clinical *CYP2C19* genetic testing is currently available [6,7].

Expression

CYP2C19 is predominantly expressed in the liver and, to a lesser extent, in the small intestine [8]. Constitutive expression of *CYP2C19* is largely mediated by hepatic nuclear factors 4 α (HNF4α, *HNF4A*) and 3 γ (HNF3γ, *FOXA3*) [9-11], and transcriptional activation is mediated by the drug-responsive nuclear receptors CAR (*NR1I3*), PXR (*NR1I2*), and GRα (*NR3C1*) [12,13], suggesting regulation by endogenous hormones and by drugs such as rifampicin [14,15]. In addition to rifampicin, human *CYP2C19* can be induced by ritonavir, nelfinavir, hyperforin, St. John's Wort, dexamethasone, and artemisinin [16]. In-vitro expression studies have recently shown that the GATA-4 (*GATA4*) transcription factor also upregulates *CYP2C19* transcriptional activity by binding to two predicted GATA-specific promoter elements [17]. Additionally, reduced CYP2C19 activity among women using steroid oral contraceptives results from transcriptional downregulation of *CYP2C19* expression through binding of ligand-activated estrogen receptor α to a specific estrogen response element consensus half-site in the *CYP2C19* promoter [18].

Certain selective serotonin-reuptake inhibitors (e.g. fluoxetine, fluvoxamine) [19,20] and PPIs (e.g. omeprazole, lansoprazole) [21-23] have an inhibitory effect on CYP2C19, which may cause drug–drug interactions with co-administered CYP2C19-metabolized drugs. For example, early studies suggested that omeprazole (a common PPI) diminished the pharmacodynamic antiplatelet effects of clopidogrel and increased corresponding cardiovascular risks [24,25]. However, it is currently not clear whether identified changes in *ex vivo* platelet aggregation due to concomitant omeprazole and clopidogrel administration translates into clinically meaningful outcome differences (for review see [26]).

CYP2C19 gene and polymorphisms

The *CYP2C19* gene has nine exons and is highly polymorphic, with over 25 variant star (*) alleles currently defined by the Human Cytochrome P450 Allele Nomenclature Committee (http://www.cypalleles.ki.se/CYP2C19.htm) (Fig. 1). In addition, detailed mapping information for *CYP2C19* variants and lists of associated drugs and diseases are available at http://www.pharmgkb.org/search/annotatedGene/CYP2C19/variant.jsp.

Common variants that encode reduced or absent enzymatic activity

rs4244285 (c.681G > A; p.P227P)—rs4244285 (c.681G > A) is the defining polymorphism of the *CYP2C19*2* allele (previously referred to as *CYP2C19*m1) and is a synonymous G > A transition in exon 5 that creates an aberrant splice site (Fig. 1). This change alters the mRNA reading frame, which results in a truncated, nonfunctional protein (Table 1) [3]. *CYP2C19*2* is the most common *CYP2C19* loss-of-function allele, with allele frequencies of approximately 12% in Caucasians, 15% in African-Americans, and 29-35% in Asians [6].

rs4986893 (c.636G > A; p.W212X)—rs4986893 (c.636G > A) is the defining polymorphism of the *CYP2C19*3* allele (previously referred to as *CYP2C19*m2) and is a G > A transition in exon 4 that results in a premature termination codon at amino acid 212 (p.W212X; Table 1) [33]. The *CYP2C19*3* allele frequencies in most populations are below 1%; however, it is more prevalent among Asians (2–9%) [6].

Rare variants that encode reduced or unknown enzymatic activity

Less frequent *CYP2C19* alleles associated with absent or reduced enzyme activity are *CYP2C19*4* (rs28399504), **5* (rs56337013), **6* (rs72552267), *7 (rs72558186), and **8* (rs41291556; Table 1). These variants typically have allele frequencies less than 1% [6,47].

Additional variant *CYP2C19* alleles originally identified in different populations with little available functional data are also summarized in Table 1. Alleles that cause a missense amino acid substitution were subjected to PolyPhen-2 [48] and Sorting Tolerant From Intolerant [49] algorithm analyses to computationally predict their effect on protein function. Although not a substitute for actual in-vitro or in-vivo enzyme activity analyses, these data can provide a basis for potential consequences of these sequence alterations on CYP2C19 enzyme function.

Variants that encode increased enzymatic activity *rs12248560 (c. −806C > T)*

rs12248560 (c. −806C > T) is the defining polymorphism of the *CYP2C19*17* allele and is a C > T transition in the promoter that creates a consensus binding site for the GATA transcription factor family, resulting in increased *CYP2C19* expression and activity (Table 1) [39,40,44]. The *CYP2C19*17* allele frequencies are approximately 21% in Caucasians, 16% in African-Americans, and 3% in Asians [6].

Drug metabolizer categories

On the basis of the ability to metabolize *CYP2C19* substrates, individuals can be classified as ultrarapid metabolizers (UM), extensive metabolizers (EM), intermediate metabolizers (IM), or poor metabolizers (PM). EM individuals are homozygous for the *CYP2C19*1* allele, which is associated with functional CYP2C19-mediated metabolism. The IM genotype consists of one wild-type allele and one variant allele that encodes reduced or absent enzyme function (e.g., **1/*2*, **1/*3*), resulting in decreased CYP2C19 activity [47]. PM individuals have two loss-of-function alleles (e.g., **2/*2*, **2/*3*, **3/*3*), resulting in markedly reduced or absent CYP2C19 activity [47,50]. Of note, some *CYP2C19* literature uses a separate nomenclature system that includes ‘homozygous extensive metabolizers’ (e.g., **1/*1*), sometimes also referred to as ‘rapid metabolizers’; ‘heterozygous-extensive metabolizers’ (e.g., **1/*2*); and ‘PM’ (e.g., **2/*2*). Regardless of the nomenclature system, the frequency of *CYP2C19* PMs is approximately 2-5% in Caucasians and African-Americans, and approximately 15% in Asians [6].

Individuals who carry one or two *17 gain-of-function alleles (e.g., **1/*17*, **17/*17*) may be categorized as UMs. However, the phenotypic consequences of a loss-of-function allele and a *17 compound heterozygous genotype (e.g., **2/*17*) is currently unclear but may be in between the EM and IM phenotypes, and possibly may be dependent on the substrate [51,52]. An important caveat in translating genetic information into predicted metabolizer status category is that the *CYP2C19*1* allele is defined by the absence of other variants. Thus, genotyping assays that do not query all variation in the gene may misclassify some individuals. If all common variants (i.e., > 1% allele frequency) are genotyped, misclassification error will be small.

CYP2C19 genotype and Drug response

Platelet-aggregation inhibitors

Clopidogrel is a commonly prescribed antiplatelet pro-drug that is metabolized into an active metabolite by several hepatic CYP450 enzymes, predominantly CYP2C19 [53]. *CYP2C19* loss-of-function alleles have been associated with lower active metabolite exposure [54,55] and decreased platelet responsiveness *ex vivo* among clopidogrel-treated

patients [5,56,57], and increased cardiovascular event rates among clopidogrel-treated patients with acute coronary syndromes and/or those undergoing percutaneous coronary intervention [57-60]. In addition, a genome-wide association study found *CYP2C19*2* to be strongly associated with clopidogrel response [61] and recent large meta-analyses indicate that both heterozygous (e.g., **1/*2*) and homozygous (e.g., **2/*2*) clopidogrel-treated acute coronary syndromes/percutaneous coronary intervention patients are at an increased risk for serious adverse cardiovascular events with a gene-dose effect [62,63]. Interestingly, this *CYP2C19* gene-dose effect has largely been illustrated with clopidogrel by pharmacokinetic, *ex vivo* platelet aggregation, and clinical outcome studies. This effect is less evident for some other *CYP2C19* substrates, which are more so influenced by PM genotypes (e.g., *2/*2).

Some studies have identified enhanced platelet inhibition and clopidogrel response among UM patients [51,57,64,65] and possibly an increased risk of bleeding complications [44]; however, other studies have not identified an independent effect of *CYP2C19*17* on clopidogrel response [58,61,66]. Despite the heterogeneity in results among individual studies, a recent meta-analysis found *CYP2C19*17* to be associated with a lower risk of cardiovascular events and a higher risk of major bleeding [67]. However, as the variant that defines the activating allele of **17* and the variant that defines the absence of the **2* allele are in linkage disequilibrium (e.g., $D' = 1.0$ and $r^2 = 0.064$ in CEU HapMap sample; $D' = 1.0$ and $r^2 = 0.065$ in YRI HapMap sample; and $D' = 1.0$ and $r^2 = 0.074$ in CHB HapMap sample), it is unclear whether there is an independent effect of the **17* allele on platelet aggregation or whether this association is due to the relative absence of the **2* allele in these same patients. Moreover, there is significant linkage disequilibrium across the entire *CYP2C* locus [68] and **17* has been identified on haplotypes with both wild-type and variant *CYP2C8* alleles depending on ethnicity [69,70].

Proton pump inhibitors

PPIs are commonly prescribed for gastroesophageal reflux disease, gastric and duodenal ulcer disease, eradication of *Helicobacter pylori* (*H. pylori*) infection, prevention and treatment of nonsteroidal anti-inflammatory drug-associated damage, and for patients with nonvariceal upper gastrointestinal bleeding or nonulcer dyspepsia. Given most PPIs are predominantly metabolized by CYP2C19, both IMs and PMs can have reduced drug elimination and higher PPI plasma concentrations compared with EM individuals [71]. Consequently, eradication of *H. pylori* infection with omeprazole, lansoprazole, and pantoprazole has been reported to be greater among *CYP2C19* IMs and PMs compared with EMs [72-75]. In addition, the healing rates of peptic ulcers and gastroesophageal reflux disease during PPI treatment is influenced by *CYP2C19* genotype [76] as IMs and PMs have been found to respond better to PPI treatment than EMs [72,77,78].

The UM genotype (i.e., **17/*17*) has been reported to affect omeprazole pharmacokinetics resulting in increased rates of drug metabolism and subtherapeutic exposure [79]. However, not all studies have identified a significant effect of *CYP2C19*17* on PPI metabolism and *H. pylori* eradication [80,81].

Antidepressants

CYP2C19 is involved in the metabolism of the tertiary amine tricyclic antidepressants (TCAs) imipramine, amitriptyline, trimipramine and clomipramine, and of the secondary amine TCA nortriptyline. Although multiple CYP450 enzymes are involved in the metabolism of these antidepressants, their plasma concentrations and active metabolite levels have been reported to be greater in *CYP2C19* PMs than in EMs [82,83]. Adverse effects from TCAs may be associated with *CYP2C19* loss-of-function alleles, but are more

likely when *CYP2D6* genotype is also defective and/or *CYP2C19/CYP2D6* inhibitors are coadministered [47,83].

Some selective serotonin-reuptake inhibitors, such as citalopram, sertraline, fluoxetine and venlafaxine, and the reversible MAO inhibitor moclobemide are also CYP2C19 substrates. *CYP2C19* genotype has an effect on citalopram serum concentration but the clinical significance of CYP2C19 PMs for this agent is controversial [7,84,85]. For sertraline, patients with one or two *CYP2C19* loss-of-function alleles typically have higher dose-adjusted serum concentrations compared to EMs, which may have clinical utility for predicting outcome [7,86-88].

With regard to UMs, *CYP2C19*17* has been found to correlate with lower serum concentrations of several antidepressants compared with EM patients [40,89,90]; however, the exact clinical relevance of UM genotypes in antidepressant response warrants further investigation.

Others

Other drugs that may be influenced by *CYP2C19* genotype include anticonvulsants (e.g., diazepam, phenytoin) [91,92] and anti-infectives, notably the antimalarial agent proguanil [93] and the antifungal voriconazole [94].

Clinical *CYP2C19* pharmacogenetic testing

Although a number of genotyping technologies can be used to interrogate variant *CYP2C19* alleles in Clinical Laboratory Improvement Amendments-approved laboratories, two genotyping platforms have been approved by the US Food and Drug Administration at the time of this writing: the AmpliChip CYP450 Test (Roche Molecular Systems, Inc., Pleasanton, California, USA) that interrogates *CYP2C19*2* and **3* (plus *CYP2D6* variant alleles) and the Infiniti *CYP2C19* Assay (AutoGenomics, Inc., Vista, California, USA) that interrogates *CYP2C19*2*, **3*, and **17*. For test interpretation and clopidogrel dosing suggestions, see the Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP2C19* genotype and clopidogrel therapy [6] (www.pharmgkb.org). In addition, a recent clinical pharmacogenetics practice review provides dosing guidelines for clopidogrel and other CYP2C19-metabolized drugs [7] and *CYP2C19/ CYP2D6* genotype-based antidepressant dosing recommendations have been previously reported [95].

Conclusion

Clearly, *CYP2C19* is a very important pharmacogene. Although there are gaps in the knowledge, particularly with respect to how modifying dosing and/or drug substitution based on metabolizer status affects clinical outcomes, the infrastructure is now in place to implement personalized drug treatment for several key drugs based on *CYP2C19* genotyping results.

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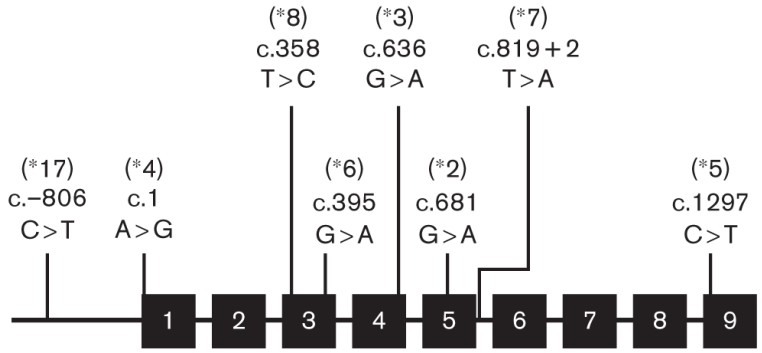

Illustration of the *CYP2C19* gene highlighting the location of selected loss-of-function (**2*–**8*) and gain-of-function (**17*) variant alleles. Exons are represented by numbered black boxes (not to scale).

Figure 1.

Illustration of the *CYP2C19* gene highlighting the location of selectedloss-of-function (**2*–**8*) and gain-of-function (**17*) variant alleles. Exons are represented by numbered black boxes (not to scale).

Table 1

Variant CYP2C19 alleles

Allele[a]	Major nucleotide variation	dbSNP number[b]	Exon	Effect on protein	PolyPhen-2 prediction	SIFT prediction	Enzyme activity	Reference
*1	-	-	-	Wild type	-	-	Normal	Richardson *et al.* [27–29]
*2[c]	c.681G>A	rs4244285	5	Splicing defect	N/A	N/A	None	de Morais *et al.* [3,30–32]
*3	c.636G>A	rs4986893	4	p.W212X	N/A	N/A	None	Fukushima-Uesaka *et al.* [31,33]
*4[d]	c.1A >G	rs28399504	1	p.M1V	Probably damaging	Affected	None	Ferguson *et al.* [34,35]
*5	c.1297C >T	rs56337013	9	p.R433W	Probably damaging	Affected	None	Ibeanu *et al.*[36]
*6	c.395G>A	rs72552267	3	p.R132Q	Possibly damaging	Affected	None	Ibeanu *et al.* [30]
*7	c.819 + 2T > A	rs72558186	Intron 5	Splicing defect	N/A	N/A	None	Ibeanu et al. [37]
*8	c.358T >C	rs41291556	3	p.W120R	Probably damaging	Affected	None	Ibeanu *et al.* [37]
*9	c.431G > A	rs17884712	3	p.R144H	Probably damaging	Tolerated	Decreased	Blaisdell *et al.* [28]
*10	c.680C > T	rs6413438	5	p.P227L	Probably damaging	Affected	Decreased	Blaisdell *et al.* [28]
*11	c.449G> A	rs58973490	3	p.R150H	Predicted benign	Tolerated	Unknown	Blaisdell *et al.* [28]
*12	c.1473A >C	rs55640102	9	p.X491CextX27	N/A	N/A	Unstable	Blaisdell *et al.* [28]
*13	c.1228C > T	rs17879685	8	p.R410C	Predicted benign	Affected	Unknown	Blaisdell *et al.* [28]
*14	c.50T>C	rs55752064	1	p.L17P	Probably damaging	Tolerated	Unknown	Blaisdell *et al.* [28]
*15	c.55A >C	rs17882687	1	p.I19L	Predicted benign	Tolerated	Unknown	Blaisdell *et al.* [28]
*16	c.1324C > T	-	9	p.R442C	Probably damaging	Affected	Unknown	Morita *et al.* [38]
*17[c,d]	c. −806C>T	rs12248560	Promoter	Increased expression	N/A	N/A	Increased	Sim *et al.* [39,40]
*18	c.986G> A	rs138142612	7	p.R329H	Predicted benign	Tolerated	Unknown	Fukushima-Uesaka *et al.* [31]
*19	c.151A >G	-	1	p.S51G	Predicted benign	Tolerated	Unknown	Fukushima-Uesaka *et al.* [31]
*22	c.557G>C	rs140278421	4	p.R186P	Probably damaging	Affected	Unknown	Matimba *et al.* [41]
*23	c.271G>C	rs118203756	2	p.G91R	Probably damaging	Affected	Unknown	Zhou *et al.* [42]
*24	c.1004G> A	rs118203757	7	p.R335Q	Probably damaging	Tolerated	Unknown	Zhou *et al.* [42]
*25	c.1344C>G	rs118203759	9	p.F448L	Predicted benign	Tolerated	Unknown	Zhou *et al.* [42]
*26	c.766G>A	-	5	p.D256N	Predicted benign	Tolerated	Unknown	Lee *et al.* [32]
*27	c. −1041G > A	rs7902257	Promoter	Decreased expression	N/A	N/A	Decreased	Drogemoller et al. [43]

dbSNP, single nucleotide polymorphism database; N/A, not applicable; PolyPhen-2: polymorphism phenotyping v2 (http://genetics.bwh.harvard.edu/pph2/); SIFT: Sorting Tolerant From Intolerant (http://sift.jcvi.org/).

[a] See Human Cytochrome P450 Allele Nomenclature Committee (http://www.cypalleles.ki.se/cyp2c19.htm) for comprehensive definitions of CYP2C19 variant alleles and updated allele information.

[b] RefSNP accession ID number (http://www.ncbi.nlm.nih.gov/snp/).

[c] There is linkage disequilibrium between c.681G and c.−806T, which means that the less common *17 variant (c. −806T) always tracks on the same allele with the more common c.681G. This complicates the interpretation of whether these two variants act independently of one another [44-46].

[d] The CYP2C19*4 loss-of-function allele has been identified in linkage disequilibrium with *17 (c. −806C >T) in certain ethnic subpopulations and this haplotype is designated CYP2C19*4B [35].