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

Stuart A. Scott, Katrin Sangkuhl, Alan R. Shuldiner, Jean-Sébastien Hulot, Caroline F. Thorn, Russ B. Altman, and Teri E. Klein

Department of Genetics and Genomic Sciences
Cardiovascular Research Center, Mount Sinai School of Medicine, New York, New York
Departments of Genetics
Bioengineering, Stanford University, Stanford, California
Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine
Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, Maryland, USA
Department of Pharmacology, Université Pierre et Marie Curie-Paris 6, INSERM UMR S 956, Pitié-Salpêtrière University Hospital, Paris, France

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 metabolism in association with a common variant of CYP2C19, *17 [1]. Since then, the CYP2C19 gene has received a lot of attention as it plays a crucial role in the metabolism of drugs such as clopidogrel, which is a prodrug used to prevent blood clots in patients after a heart attack or stroke. Mutations in the CYP2C19 gene can affect the drug’s effectiveness and the risk of adverse events.

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Correspondence to Dr Teri E. Klein, PhD, Department of Genetics, Stanford University Medical Center, 1501 California Ave, Stanford, CA 94304, USA Tel: +650 725 0659; fax: +650 725 3863; feedback@pharmgkb.org.

Conflicts of interest
S.A.S. is a consultant for USDS, Inc. A.R.S. is a consultant for Bristol-Myers Squibb and USDS, Inc. J.S.H. receives research grant support from Fondation de France, INSERM, Federation Française de Cardiologie, Biotronik, Medco Research Institute; consulting fees from Biotronik, Medco Health Solutions; and, lecture fees from Daiichi Sankyo, Eli Lilly. The other authors declare no conflict of interest.
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 4α (HNF4α, HNF4A) and 3γ (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 CYP2C19m1) 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 CYP2C19m2) 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 pharmaco-kinetic, 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 UM, $CYP2C19*17$ 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.

### Acknowledgments

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### References


69. Pedersen RS, Brasch-Andersen C, Sim SC, Bergmann TK, Halling J, Petersen MS, et al. Linkage disequilibrium between the CYP2C19*17 allele and wildtype CYP2C8 and CYP2C9 alleles:


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Figure 1.
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).
### Table 1

<table>
<thead>
<tr>
<th>Allele&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Major nucleotide variation</th>
<th>dbSNP number&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Exon</th>
<th>Effect on protein</th>
<th>PolyPhen-2 prediction</th>
<th>SIFT prediction</th>
<th>Enzyme activity</th>
<th>Reference</th>
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<tbody>
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<td>*1</td>
<td></td>
<td></td>
<td></td>
<td>Wild type</td>
<td></td>
<td></td>
<td>Normal</td>
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<td>rs4244285</td>
<td>5</td>
<td>Splicing defect</td>
<td></td>
<td></td>
<td>N/A</td>
<td>de Morais et al. [3,30–32]</td>
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<td>*3</td>
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<td>4</td>
<td>p.W212X</td>
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<td>N/A</td>
<td>None</td>
<td>Fukushima-Uesaka et al. [31,33]</td>
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<td>p.M1V</td>
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<td>Affected</td>
<td>None</td>
<td>Ferguson et al. [34,35]</td>
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<td>rs56337013</td>
<td>9</td>
<td>p.R433W</td>
<td>Probably damaging</td>
<td>Affected</td>
<td>None</td>
<td>Ibeanu et al. [36]</td>
</tr>
<tr>
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<td>rs72552267</td>
<td>3</td>
<td>p.R132Q</td>
<td></td>
<td>Affected</td>
<td>None</td>
<td>Ibeanu et al. [30]</td>
</tr>
<tr>
<td>*7</td>
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<td>rs72558186</td>
<td>Intron 5</td>
<td>Splicing defect</td>
<td></td>
<td></td>
<td>N/A</td>
<td>Ibeanu et al. [37]</td>
</tr>
<tr>
<td>*8</td>
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<td>rs41291556</td>
<td>3</td>
<td>p.W120R</td>
<td>Probably damaging</td>
<td>Affected</td>
<td>None</td>
<td>Ibeanu et al. [37]</td>
</tr>
<tr>
<td>*9</td>
<td>c.431G&gt;A</td>
<td>rs17884712</td>
<td>3</td>
<td>p.R144H</td>
<td></td>
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<td>Decreased</td>
<td>Blaisdell et al. [28]</td>
</tr>
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<td>3</td>
<td>p.R150H</td>
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<td>Tolerated</td>
<td>Unknown</td>
<td>Blaisdell et al. [28]</td>
</tr>
<tr>
<td>*11</td>
<td>c.1473A&gt;C</td>
<td>rs55640102</td>
<td>9</td>
<td>p.X491CextX27</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
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</tr>
<tr>
<td>*12</td>
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<td>8</td>
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<td>1</td>
<td>p.L17P</td>
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<td>Affected</td>
<td>Unknown</td>
<td>Blaisdell et al. [28]</td>
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<tr>
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<td>p.I19L</td>
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<td>Unknown</td>
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<td>Promoter</td>
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<td>N/A</td>
<td>Increased</td>
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<td>rs13814261</td>
<td>7</td>
<td>p.R329H</td>
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<td>Tolerated</td>
<td>Unknown</td>
<td>Fukushima-Uesaka et al. [31]</td>
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<td>rs140278421</td>
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<td>p.R186P</td>
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<td>Unknown</td>
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<tr>
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<td>2</td>
<td>p.G91R</td>
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<td>N/A</td>
<td>Decreased</td>
<td>Drogemoller et al. [43]</td>
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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].