Published in final edited form as:
Pharmacogenet Genomics. 2013 December ; 23(12): 721–728. doi:10.1097/FPC.0b013e3283653b27.

PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 8

Christina L. Aquilante[a], **Mikko Niemi**[d], **Li Gong**[b], **Russ B. Altman**[b,c], and **Teri E. Klein**[b]

[a]Department of Pharmaceutical Sciences, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, Colorado [b]Department of Genetics Stanford University, Palo Alto, California, USA [c]Department of Bioengineering, Stanford University, Palo Alto, California, USA [d]Department of Clinical Pharmacology, University of Helsinki, HUSLAB, Helsinki University Central Hospital, Helsinki, Finland

Keywords

CYP2C8; CYP2C8*3; metabolism; pharmacogenetics; pharmacogenomics; pharmGKB

Introduction

Cytochrome P450, family 2, subfamily C, polypeptide 8 (CYP2C8) is a phase I metabolizing enzyme that plays an integral role in the biotransformation of structurally diverse xenobiotics and endogenous compounds [1]. CYP2C8 accounts for 7% of the CYP content in the liver and is expressed to a lesser extent in the kidney, adrenal gland, mammary gland, brain, ovary, uterus, and duodenum [2–5]. Over the last decade, CYP2C8 has garnered increased attention following the elucidation of its crystal structure, identification of clinically relevant substrates and inhibitors, and characterization of functional *CYP2C8* single nucleotide polymorphisms (SNPs). This PharmGKB summary discusses *CYP2C8* and its pharmacogenomic importance. A fully interactive version of this short review, with links to individual paper annotations can be found at http://www.pharmgkb.org/gene/PA125#tabview=tab3&subtab=33.

Substrates, inhibitors, and inducers

CYP2C8 is responsible for the biotransformation of 5% of currently used drugs that undergo phase I hepatic metabolism [4]. The enzyme's substrate-binding cavity can accommodate large and structurally unrelated compounds (e.g. paclitaxel and amiodarone) [6,7]. In addition, the CYP2C8 active site is similar in size, but different in shape, from that of

Correspondence to Teri E. Klein, PhD, Department of Genetics, Stanford University, 1501 California Avenue, Palo Alto, CA 94304, USA Tel: + 1 650 736 0156; fax: + 1 650 725 3863; feedback@pharmgkb.org.

Conflicts of interest
There are no conflicts of interest.

CYP3A4 [6,8]. This likely explains why CYP2C8 and CYP3A4 often have overlapping substrates, but yield different metabolite profiles [4,9].

Table 1 provides a list of drugs for which CYP2C8 is a major contributor to metabolism. CYP2C8 also plays an intermediate or minor role in the oxidation of myriad other xenobiotics and endogenous compounds such as NSAIDs (e.g. ibuprofen and diclofenac) [24,25], statins (e.g. fluvastatin and simvastatin acid) [26,27], calcium channel blockers (e.g. verapamil) [28,29], opioids (e.g. morphine and methadone) [30,31], tyrosine kinase inhibitors (e.g. imatinib) [32,33], arachidonic acid [34,35], retinoids [36–39], and others. Further information on CYP2C8 substrates is provided at http://medicine.iupui.edu/clinpharm/ ddis/table.aspx and in comprehensive reviews [4,23,40].

In vitro, many compounds have been shown to inhibit CYP2C8 including gemfibrozil, trimethoprim, ketoconazole, montelukast, quercetin, and others [14,16,41–46]. *In vivo*, gemfibrozil is the most potent CYP2C8 inhibitor, primarily because of rapid, mechanism-based inactivation of CYP2C8 by its 1-*O*-β glucuronide metabolite [47–51]. In clinical studies, gemfibrozil has been shown to increase the plasma exposure of CYP2C8 substrates such as rosiglitazone [52], pioglitazone [53,54], repaglinide [55–57], cerivastatin [58], loperamide [59], R-ibuprofen [60], and montelukast [61]. In addition, gemfibrozil reduced imatinib metabolite formation in healthy volunteers [62].

CYP2C8 has been described as the most inducible member of the *CYP2C* subfamily [4,40]. Transcriptional activation of CYP2C8 is mediated by the pregnane X receptor (*NR1I2*), the constitutive androstane receptor (*NR1I3*), and the glucocorticoid receptor (*NR3C1*) [63,64]. Along these lines, a constitutive androstane receptor/pregnane X receptor-binding sequence in the distal promoter (– 8806 bp) is thought to play a key role in *CYP2C8* induction [63]. *In vitro*, CYP2C8 is upregulated by the inducers rifampin (rifampicin), dexamethasone, and phenobarbital [65–68]. In clinical drug–drug interaction studies, rifampin has been shown to decrease the plasma exposure of major CYP2C8 substrates such as rosiglitazone [69,70], pioglitazone [71], and repaglinide [72,73].

CYP2C8 gene and common variants

CYP2C8 is located on chromosome 10q24 in a *CYP2C* gene cluster (centromere–*CYP2C18*–*CYP2C19*–*CYP2C9*– *CYP2C8*–telomere), of which *CYP2C8* is the smallest gene (31 kb, nine exons) [5,74,75]. Given the close proximity of *CYP2C8* and *CYP2C9*, some linkage disequilibrium exists between these genes [76]. Substantial interindividual variability exists in CYP2C8 protein expression and catalytic activity [18,77,78]. This variability is due, in part, to genetic polymorphisms. Over 450 *CYP2C8* SNPs have been identified to date [40]. Some of these SNPs, particularly those in the coding region, are associated with variability in CYP2C8-mediated metabolism and altered drug disposition and response. In general, polymorphic *CYP2C8* alleles have not been assigned an activity level or phenotype classification (e.g. poor metabolizer). This is primarily because of the relatively limited *in vitro* data at present, with conflicting results; substrate-dependent functional consequences; and discrepancies between *in vitro* and *in vivo* findings. *CYP2C8*1* (or **1A*) refers to the wild-type or reference allele [5]. In general, most *CYP2C8* studies have only evaluated

individual SNPs, usually referred to by '*' alleles. Important variant alleles are summarized in Table 2, and relevant *in vitro* findings are described below.

*CYP2C8*1B and *1C*, rs7909236 (g. – 271C > A; *CYP2C8* 1B)* and rs17110453 (g. – 370G > T; *CYP2C8*1C*)

The – 271C > A SNP is designated as *CYP2C8*1B* and is present in about 23% of Whites and 10% of Asians; it is absent in Africans [79] (*http://www.ncbi.nlm.nih.gov/projects/SNP/*). The variant allele results in the creation of a C/EBPα transcription factor consensus sequence and has been associated with increased transcription factor binding and promoter activities, but not differences in protein expression, as compared with the wild-type allele [79,80]. The – 370G > T SNP is designated as *CYP2C8*1C* and is present in about 12% of Whites, 28–34% of Asians, and is rare in Africans [79] (*http://www.ncbi.nlm.nih.gov/projects/SNP/*). The functional consequences of the *CYP2C8*1C* allele have not been fully elucidated.

*CYP2C8*2*, rs11572103 (c.805A > T; p.I269F)

The c.805A > T variant is designated as *CYP2C8*2* and is located in exon 5. *CYP2C8*2* is common in Africans (19%) but is rare in Whites and Asians [81] (http://www.ncbi.nlm.nih.gov/projects/SNP/). In vitro, CYP2C8*2 has been associated with decreased enzyme activity and lower intrinsic clearance of paclitaxel, amodiaquine, and repaglinide compared with the wild-type gene [81–84].

*CYP2C8*3*, rs11572080 (c.416G > A; p.R139K) and rs10509681 (c.1196A > G; p.K399R)

*CYP2C8*3* denotes two highly linked variants, rs11572080 and rs10509681, in exons 3 and 8, respectively [81]. The *CYP2C8*3* allele is common in Whites (11–14%) but is rare in Africans and Asians [4,79,81,95,104] (http://www.ncbi.nlm.nih.gov/projects/SNP/). CYP2C8*3 is in strong partial linkage disequilibrium with *CYP2C9*2* [76,105,106]. *In vitro*, conflicting data exist with regard to the effect of *CYP2C8*3* on substrate metabolism. Compared with the wild-type enzyme, *CYP2C8*3* has been associated with decreased enzyme activity and metabolism of paclitaxel, arachidonic acid, and amodiaquine [79,81–86,103]. Other studies have found no influence of *CYP2C8*3* on paclitaxel metabolism [80,87,88]. For some substrates, such as pioglitazone, repaglinide, and cerivastatin, *CYP2C8*3* has been associated with increased metabolism [84,89,90]. It has also been shown that *CYP2C8*3* exhibits higher overall activity than *CYP2C8*1* in the presence of the redox partners, cytochrome b5 and cytochrome P450 reductase [91]. The reasons for differential effects of *CYP2C8*3* on substrate metabolism are not entirely clear. One plausible explanation is that the large binding site and multiple substrate recognition sites of CYP2C8 may allow for substrate-dependent interactions with *CYP2C8*3* [84]. In addition, the effects of cytochrome b5 and cytochrome P450 reductase may mediate substrate-dependent interactions, as described above [84,91]. Another possible explanation is linkage disequilibrium with *CYP2C9*2* [76,105,106].

*CYP2C8*4*, rs1058930 (c.792C > G; p.I264M)

The c.792C > G variant is designated as *CYP2C8*4* and is located in exon 5. *CYP2C8*4* is present in about 7% of Whites, but is rare or absent in Africans and Asians (http://www.ncbi.nlm.nih.gov/projects/SNP/). In vitro, CYP2C8*4 has been associated with reduced enzyme activity in some, but not all, studies and lower paclitaxel, repaglinide, ibuprofen, and arachidonic acid metabolism compared with the wild-type gene [79,80,83,84,86,93,94].

Rare variants

*CYP2C8*5* through *CYP2C8*14* are rare variants that are typically found in less than 1% of the population, mainly Asians (*http://www.cypalleles.ki.se/cyp2c8.htm*) [98]. Some of these variants have demonstrated functional consequences *in vitro*. *CYP2C8*5* (rs72558196, c.475delA, exon 3) causes a frame shift, which results in a premature stop codon at position 177 [92]. rs72558195 is a triallelic SNP in exon 4, which results in a premature stop codon (*CYP2C8*7*, c.556C > T, p.R186X) or an Arg to Gly change at codon 186 (*CYP2C8*8*, c.556C > G) [98]. Decreased rosiglitazone hydroxylation has been reported for the *CYP2C8*11* loss-of-function variant (c.820G > T, p.E274X, exon 6) [99]. *CYP2C8*14* (c.712G > C, p.A238P, exon 5) results in decreased paclitaxel binding affinity and decreased intrinsic clearance of amiodarone [96,100,101]. The unassigned p.P404A SNP (c.1210C > G, exon 8) has been associated with reduced protein expression and less efficient metabolism of paclitaxel and amiodarone [85,94,103]. The contribution of *CYP2C8*5* through *CYP2C8*14*, as well as other rare *CYP2C8* variants, to variability in clinical drug response or rare adverse drug reactions is not known.

CYP2C8 haplotype blocks

Although most *CYP2C8* studies have focused on individual SNPs, some work has been done to characterize *CYP2C8* haplotypes and their impact on substrate disposition. One study used HapMap data to identify *CYP2C8* tag SNPs in Whites. The authors found that *CYP2C8* was contained in one haplotype block (40 kb), and six tag SNPs revealed seven common haplotypes (i.e. A, B, C1, C2, C3, D, and E) with a frequency greater than 2% [80]. Haplotype B (which contains g. – 271C > A) was associated with increased paclitaxel metabolism, whereas haplotype C (which combines C1, C2, and C3) was associated with decreased paclitaxel metabolism *in vitro* [80]. Carriers of haplotype B or haplotype D (which contains *CYP2C8*3*) had lower repaglinide plasma exposure, whereas carriers of haplotype C had higher repaglinide plasma exposure, as compared with non-carriers [80]. The *CYP2C8* haplotype structure has also been characterized in other populations (e.g. Japanese) [96,107]. Given the close proximity of *CYP2C8* to other *CYP2C* genes, some groups have characterized haplotypes containing variants across several genes in the *CYP2C* cluster [105,106,108–111].

Clinical associations between *CYP2C8* variant alleles and drug disposition, response, and toxicity

Antidiabetic agents

Thiazolidinediones, rosiglitazone, and pioglitazone are peroxisome proliferator-activated receptor-γ agonists that are used in the treatment of type 2 diabetes. Most healthy volunteer studies have found *CYP2C8*3* to be associated with higher oral clearance and lower plasma exposure of rosiglitazone and pioglitazone than in wild-type homozygotes [112–116]. Little is known about the impact of *CYP2C8*2* on thiazolidinedione disposition, although a recent study has suggested that *CYP2C8*2* influences the ratio of metabolite to pioglitazone plasma exposure in healthy volunteers [117]. In terms of clinical outcomes, a recent study has shown that *CYP2C8*3* carriers have lower rosiglitazone trough concentrations, reduced therapeutic response, and lower risk of developing edema as compared with carriers of the *CYP2C8*1/*1* genotype [118].

Repaglinide, a nonsulfonylurea insulin secretagogue, is used to lower postprandial glucose levels in patients with type 2 diabetes. Some clinical studies have reported higher oral clearance and lower plasma exposure of subclinical doses of repaglinide in *CYP2C8*3* carriers versus wild-type homozygotes [56,119,120]. However, others have shown no association between repaglinide pharmacokinetics or pharmacokinetics and *CYP2C8*3* at clinically relevant doses [121,122].

Paclitaxel

Paclitaxel is a chemotherapeutic agent that is used to treat breast, lung, and ovarian malignancies. Most, but not all, clinical reports suggest that *CYP2C8*3* is not a major determinant of paclitaxel pharmacokinetics [123–127]. The discrepancy between *in vitro* and *in vivo* findings is likely a result of the contribution of drug transporters to paclitaxel disposition in humans [128]. Peripheral neuropathy is a troubling toxicity associated with paclitaxel therapy and is correlated with drug exposure [126,129]. Some studies have reported an association between *CYP2C8*3* and an increased risk for paclitaxel neurotoxicity [126,130–132]. Additional work is needed to elucidate the clinical utility of *CYP2C8* variants as predictors of neurotoxicity, as well as other toxicities (e.g. myelosuppression), in paclitaxel-treated patients.

Statins

Cerivastatin, an HMG-CoA reductase inhibitor and CYP2C8 substrate, was withdrawn from the market in 2001 because of a high incidence of rhabdomyolysis [133]. It is possible that rare, loss-of-function *CYP2C8* variants (e.g. *5, *7, *11) may have predisposed some individuals to this adverse effect [90,97]. For example, *CYP2C8*5* was identified in a Japanese individual who had rhabdomyolysis following cerivastatin therapy [97]. For other statins, no relationship has been observed between *CYP2C8* polymorphisms and fluvastatin pharmacokinetics [134] or simvastatin-induced myotoxicity [135].

Antimalarial agents

Amodiaquine and chloroquine are used in the treatment of malaria, particularly in Africa. Although *CYP2C8*2* has been associated with decreased amodiaquine metabolism *in vitro*, it was not a predictor of the efficacy of amodiaquine or major toxicities in African patients [82]. More recently, other data have suggested that host *CYP2C8* variants (e.g. *2 or *3) may influence the risk of amodiaquine-resistant or chloroquine-resistant malaria parasites [136,137]. The potential role of *CYP2C8* genetics in host–pathogen interactions and resistance merits further investigation.

Nonsteroidal anti-inflammatory drugs

Conflicting data exist with regards to the relationship between *CYP2C8*3* and interindividual variability in *R*-ibuprofen and *S*-ibuprofen pharmacokinetics [138–141]. This is likely due to ibuprofen being a CYP2C8/2C9 substrate and the linkage disequilibrium that exists between these genes. In terms of adverse effects, some data suggest that the combined presence of *CYP2C8*3* and *CYP2C9*2* is a determinant of NSAID-induced gastrointestinal bleeding [142]. Additional studies are needed to delineate the relative contributions of CYP2C8 and CYP2C9 to the metabolism of various NSAIDS and the ability of common *CYP2C8/2C9* haplotypes to predict NSAID efficacy and/or toxicity [143].

Other clinical associations

Bisphosphonates (e.g. zoledronic acid) are commonly used in the treatment of benign and malignant bone diseases. However, these agents are associated with the rare, but serious, adverse effect of jawbone necrosis. A genome-wide association study found an intronic *CYP2C8* SNP (rs1934951) to be significantly associated with osteonecrosis of the jaw in multiple myeloma patients treated with bisphosphonate therapy [144]. Bisphosphonates are not metabolized by cytochrome P450 enzymes; therefore, the mechanism underlying this association is unclear, but it may be due to the influence of *CYP2C8* on vascular tone, angiogenesis, and/or inflammation. However, other studies in different patient populations have not been able to replicate the findings of the genome-wide association study [145–147]. As such, additional clinical and mechanistic work is needed to determine whether *CYP2C8* SNPs are predictors of bisphosphonate-related osteonecrosis of the jaw.

Calcineurin inhibitors (i.e. cyclosporine and tacrolimus) are key agents used to prevent allograft rejection in solid organ transplantation; however, they are associated with a high incidence of renal dysfunction. Data suggest that *CYP2C8* polymorphisms may influence the risk for renal dysfunction in liver and kidney transplant patients treated with these agents. One study has reported that *CYP2C8*3* is a predictor of renal toxicity in liver transplant patients treated with calcineurin inhibitors, particularly tacrolimus [86]. CYP2C8 is responsible for the metabolism of endogenous arachidonic acid to vasodilatory epoxyeicosatrienoic acid (EET) metabolites, which are thought to have protective functions in the kidney. It is hypothesized that diminished 14,15-EETand 11,12-EET production, as a result of *CYP2C8*3*, may predispose individuals to calcineurin inhibitor nephrotoxicity [86]. Similar findings have recently been observed in renal transplant recipients [148]. In terms of other immunosuppressant agents, studies have reported that the *CYP2C8* SNPs, rs11572103

(*2) and rs11572076, are significantly associated with mycopheno-late-related anemia following kidney transplantation [149,150].

Conclusion

CYP2C8 plays a major role in the metabolism of many commonly used drugs, and several *CYP2C8* SNPs have functional consequence *in vivo*. As a result, *CYP2C8* has emerged as a significant pharmacogene. The *CYP2C8* genotype may be important in determining the dosage of drugs and/or in selecting drugs to optimize efficacy and reduce adverse drug reactions. Additional clinical studies are needed to further elucidate the impact and clinical significance of key *CYP2C8* variants and haplotypes on heterogeneity in drug disposition and response pheno-types in humans.

Acknowledgments

This work is supported by the NIH/NIGMS (R24 GM61374).

References

1. Goldstein JA, de Morais SM. Biochemistry and molecular biology of the human CYP2C subfamily. Pharmacogenetics. 1994; 4:285–299. [PubMed: 7704034]
2. Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther. 1994; 270:414–423. [PubMed: 8035341]
3. Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. Drug Metab Rev. 1997; 29:413–580. [PubMed: 9187528]
4. Totah RA, Rettie AE. Cytochrome P450 2C8: substrates, inhibitors, pharmacogenetics, and clinical relevance. Clin Pharmacol Ther. 2005; 77:341–352. [PubMed: 15900280]
5. Klose TS, Blaisdell JA, Goldstein JA. Gene structure of CYP2C8 and extrahepatic distribution of the human CYP2Cs. J Biochem Mol Toxicol. 1999; 13:289–295. [PubMed: 10487415]
6. Schoch GA, Yano JK, Wester MR, Griffin KJ, Stout CD, Johnson EF. Structure of human microsomal cytochrome P450 2C8. Evidence for a peripheral fatty acid binding site. J Biol Chem. 2004; 279:9497–9503. [PubMed: 14676196]
7. Schoch GA, Yano JK, Sansen S, Dansette PM, Stout CD, Johnson EF. Determinants of cytochrome P450 2C8 substrate binding: structures of complexes with montelukast, troglitazone, felodipine, and 9-cisretinoic acid. J Biol Chem. 2008; 283:17227–17237. [PubMed: 18413310]
8. Yano JK, Wester MR, Schoch GA, Griffin KJ, Stout CD, Johnson EF. The structure of human microsomal cytochrome P450 3A4 determined by X-ray crystallography to 2.05-A resolution. J Biol Chem. 2004; 279:38091–38094. [PubMed: 15258162]
9. Johnson EF, Stout CD. Structural diversity of human xenobioticmetabolizing cytochrome P450 monooxygenases. Biochem Biophys Res Commun. 2005; 338:331–336. [PubMed: 16157296]
10. Ohyama K, Nakajima M, Nakamura S, Shimada N, Yamazaki H, Yokoi T. A significant role of human cytochrome P450 2C8 in amiodarone *N*-deethylation: an approach to predict the contribution with relative activity factor. Drug Metab Dispos. 2000; 28:1303–1310. [PubMed: 11038157]
11. Li XQ, Bjorkman A, Andersson TB, Ridderstrom M, Masimirembwa CM. Amodiaquine clearance and its metabolism to *N*-desethylamodiaquine is mediated by CYP2C8: a new high affinity and turnover enzyme-specific probe substrate. J Pharmacol Exp Ther. 2002; 300:399–407. [PubMed: 11805197]

12. Projean D, Baune B, Farinotti R, Flinois JP, Beaune P, Taburet AM, et al. In vitro metabolism of chloroquine: identification of CYP2C8, CYP3A4, and CYP2D6 as the main isoforms catalyzing *N*-desethylchloroquine formation. Drug Metab Dispos. 2003; 31:748–754. [PubMed: 12756207]
13. Kim KA, Park JY, Lee JS, Lim S. Cytochrome P450 2C8 and CYP3A4/5 are involved in chloroquine metabolism in human liver microsomes. Arch Pharm Res. 2003; 26:631–637. [PubMed: 12967198]
14. Wang JS, Neuvonen M, Wen X, Backman JT, Neuvonen PJ. Gemfibrozil inhibits CYP2C8-mediated cerivastatin metabolism in human liver microsomes. Drug Metab Dispos. 2002; 30:1352–1356. [PubMed: 12433802]
15. Filppula AM, Laitila J, Neuvonen PJ, Backman JT. Reevaluation of the microsomal metabolism of montelukast: major contribution by CYP2C8 at clinically relevant concentrations. Drug Metab Dispos. 2011; 39:904–911. [PubMed: 21289076]
16. Rahman A, Korzekwa KR, Grogan J, Gonzalez FJ, Harris JW. Selective biotransformation of taxol to 6 alpha-hydroxytaxol by human cytochrome P450 2C8. Cancer Res. 1994; 54:5543–5546. [PubMed: 7923194]
17. Cresteil T, Monsarrat B, Dubois J, Sonnier M, Alvinerie P, Gueritte F. Regioselective metabolism of taxoids by human CYP3A4 and 2C8: structure–activity relationship. Drug Metab Dispos. 2002; 30:438–445. [PubMed: 11901098]
18. Baldwin SJ, Clarke SE, Chenery RJ. Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. Br J Clin Pharmacol. 1999; 48:424–432. [PubMed: 10510156]
19. Jaakkola T, Laitila J, Neuvonen PJ, Backman JT. Pioglitazone is metabolised by CYP2C8 and CYP3A4 in vitro: potential for interactions with CYP2C8 inhibitors. Basic Clin Pharmacol Toxicol. 2006; 99:44–51. [PubMed: 16867170]
20. Yamazaki H, Shibata A, Suzuki M, Nakajima M, Shimada N, Guengerich FP, et al. Oxidation of troglitazone to a quinone-type metabolite catalyzed by cytochrome P-450 2C8 and P-450 3A4 in human liver microsomes. Drug Metab Dispos. 1999; 27:1260–1266. [PubMed: 10534310]
21. Bidstrup TB, Bjornsdottir I, Sidelmann UG, Thomsen MS, Hansen KT. CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide. Br J Clin Pharmacol. 2003; 56:305–314. [PubMed: 12919179]
22. Attar M, Dong D, Ling KH, Tang-Liu DD. Cytochrome P450 2C8 and flavin-containing monooxygenases are involved in the metabolism of tazarotenic acid in humans. Drug Metab Dispos. 2003; 31:476–481. [PubMed: 12642475]
23. Daily EB, Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. Pharmacogenomics. 2009; 10:1489–1510. [PubMed: 19761371]
24. Hamman MA, Thompson GA, Hall SD. Regioselective and stereoselective metabolism of ibuprofen by human cytochrome P450 2C. Biochem Pharmacol. 1997; 54:33–41. [PubMed: 9296349]
25. Bort R, Mace K, Boobis A, Gomez-Lechon MJ, Pfeifer A, Castell J. Hepatic metabolism of diclofenac: role of human CYP in the minor oxidative pathways. Biochem Pharmacol. 1999; 58:787–796. [PubMed: 10449188]
26. Fischer V, Johanson L, Heitz F, Tullman R, Graham E, Baldeck JP, et al. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor fluvastatin: effect on human cytochrome P-450 and implications for metabolic drug interactions. Drug Metab Dispos. 1999; 27:410–416. [PubMed: 10064574]
27. Prueksaritanont T, Ma B, Yu N. The human hepatic metabolism of simvastatin hydroxy acid is mediated primarily by CYP3A, and not CYP2D6. Br J Clin Pharmacol. 2003; 56:120–124. [PubMed: 12848784]
28. Busse D, Cosme J, Beaune P, Kroemer HK, Eichelbaum M. Cytochromes of the P450 2C subfamily are the major enzymes involved in the O-demethylation of verapamil in humans. Naunyn Schmiedebergs Arch Pharmacol. 1995; 353:116–121. [PubMed: 8750925]
29. Tracy TS, Korzekwa KR, Gonzalez FJ, Wainer IW. Cytochrome P450 isoforms involved in metabolism of the enantiomers of verapamil and norverapamil. Br J Clin Pharmacol. 1999; 47:545–552. [PubMed: 10336579]

30. Projean D, Morin PE, Tu TM, Ducharme J. Identification of CYP3A4 and CYP2C8 as the major cytochrome P450 s responsible for morphine *N*-demethylation in human liver microsomes. Xenobiotica. 2003; 33:841–854. [PubMed: 12936704]
31. Wang JS, DeVane CL. Involvement of CYP3A4, CYP2C8, and CYP2D6 in the metabolism of (*R*)- and (*S*)-methadone in vitro. Drug Metab Dispos. 2003; 31:742–747. [PubMed: 12756206]
32. Nebot N, Crettol S, d'Esposito F, Tattam B, Hibbs DE, Murray M. Participation of CYP2C8 and CYP3A4 in the *N*-demethylation of imatinib in human hepatic microsomes. Br J Pharmacol. 2010; 161:1059–1069. [PubMed: 20977456]
33. Filppula AM, Neuvonen M, Laitila J, Neuvonen PJ, Backman JT. Autoinhibition of CYP3A4 leads to important role of CYP2C8 in imatinib metabolism: variability in CYP2C8 activity may alter plasma concentrations and response. Drug Metab Dispos. 2013; 41:50–59. [PubMed: 23028140]
34. Rifkind AB, Lee C, Chang TK, Waxman DJ. Arachidonic acid metabolism by human cytochrome P450s 2C8, 2C9, 2E1, and 1A2: regioselective oxygenation and evidence for a role for CYP2C enzymes in arachidonic acid epoxygenation in human liver microsomes. Arch Biochem Biophys. 1995; 320:380–389. [PubMed: 7625847]
35. Zeldin DC, DuBois RN, Falck JR, Capdevila JH. Molecular cloning, expression and characterization of an endogenous human cytochrome P450 arachidonic acid epoxygenase isoform. Arch Biochem Biophys. 1995; 322:76–86. [PubMed: 7574697]
36. Leo MA, Lasker JM, Raucy JL, Kim CI, Black M, Lieber CS. Metabolism of retinol and retinoic acid by human liver cytochrome P450IIC8. Arch Biochem Biophys. 1989; 269:305–312. [PubMed: 2916844]
37. Nadin L, Murray M. Participation of CYP2C8 in retinoic acid 4-hydroxylation in human hepatic microsomes. Biochem Pharmacol. 1999; 58:1201–1208. [PubMed: 10484078]
38. McSorley LC, Daly AK. Identification of human cytochrome P450 isoforms that contribute to all-trans-retinoic acid 4-hydroxylation. Biochem Pharmacol. 2000; 60:517–526. [PubMed: 10874126]
39. Marill J, Cresteil T, Lanotte M, Chabot GG. Identification of human cytochrome P450s involved in the formation of all-trans-retinoic acid principal metabolites. Mol Pharmacol. 2000; 58:1341–1348. [PubMed: 11093772]
40. Lai XS, Yang LP, Li XT, Liu JP, Zhou ZW, Zhou SF. Human CYP2C8: structure, substrate specificity, inhibitor selectivity, inducers and polymorphisms. Curr Drug Metab. 2009; 10:1009–1047. [PubMed: 20214592]
41. Ong CE, Coulter S, Birkett DJ, Bhasker CR, Miners JO. The xenobiotic inhibitor profile of cytochrome P4502C8. Br J Clin Pharmacol. 2000; 50:573–580. [PubMed: 11136296]
42. Wen X, Wang JS, Backman JT, Laitila J, Neuvonen PJ. Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively. Drug Metab Dispos. 2002; 30:631–635. [PubMed: 12019187]
43. Bun SS, Ciccolini J, Bun H, Aubert C, Catalin J. Drug interactions of paclitaxel metabolism in human liver microsomes. J Chemother. 2003; 15:266–274. [PubMed: 12868554]
44. Walsky RL, Gaman EA, Obach RS. Examination of 209 drugs for inhibition of cytochrome P450 2C8. J Clin Pharmacol. 2005; 45:68–78. [PubMed: 15601807]
45. Pedersen RS, Damkier P, Brosen K. The effects of human CYP2C8 genotype and fluvoxamine on the pharmacokinetics of rosiglitazone in healthy subjects. Br J Clin Pharmacol. 2006; 62:682–689. [PubMed: 16856883]
46. Kim MJ, Lee JW, Oh KS, Choi CS, Kim KH, Han WS, et al. The tyrosine kinase inhibitor nilotinib selectively inhibits CYP2C8 activities in human liver microsomes. Drug Metab Pharmacokinet. 2013 [Epub ahead of print].
47. Shitara Y, Hirano M, Sato H, Sugiyama Y. Gemfibrozil and its glucuronide inhibit the organic anion transporting polypeptide 2 (OATP2/ OATP1B1:SLC21A6)-mediated hepatic uptake and CYP2C8-mediated metabolism of cerivastatin: analysis of the mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil. J Pharmacol Exp Ther. 2004; 311:228–236. [PubMed: 15194707]
48. Ogilvie BW, Zhang D, Li W, Rodrigues AD, Gipson AE, Holsapple J, et al. Glucuronidation converts gemfibrozil to a potent, metabolism-dependent inhibitor of CYP2C8: implications for drug-drug interactions. Drug Metab Dispos. 2006; 34:191–197. [PubMed: 16299161]

49. Baer BR, DeLisle RK, Allen A. Benzylic oxidation of gemfibrozil-1-O-beta-glucuronide by P450 2C8 leads to heme alkylation and irreversible inhibition. Chem Res Toxicol. 2009; 22:1298–1309. [PubMed: 19445523]
50. Honkalammi J, Niemi M, Neuvonen PJ, Backman JT. Gemfibrozil is a strong inactivator of CYP2C8 in very small multiple doses. Clin Pharmacol Ther. 2012; 91:846–855. [PubMed: 22472994]
51. Honkalammi J, Niemi M, Neuvonen PJ, Backman JT. Mechanism-based inactivation of CYP2C8 by gemfibrozil occurs rapidly in humans. Clin Pharmacol Ther. 2011; 89:579–586. [PubMed: 21368757]
52. Niemi M, Backman JT, Granfors M, Laitila J, Neuvonen M, Neuvonen PJ. Gemfibrozil considerably increases the plasma concentrations of rosiglitazone. Diabetologia. 2003; 46:1319–1323. [PubMed: 12898007]
53. Jaakkola T, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics of pioglitazone. Clin Pharmacol Ther. 2005; 77:404–414. [PubMed: 15900286]
54. Deng LJ, Wang F, Li HD. Effect of gemfibrozil on the pharmacokinetics of pioglitazone. Eur J Clin Pharmacol. 2005; 61:831–836. [PubMed: 16283275]
55. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia. 2003; 46:347–351. [PubMed: 12687332]
56. Tornio A, Niemi M, Neuvonen M, Laitila J, Kalliokoski A, Neuvonen PJ, et al. The effect of gemfibrozil on repaglinide pharmacokinetics persists for at least 12 h after the dose: evidence for mechanism-based inhibition of CYP2C8 in vivo. Clin Pharmacol Ther. 2008; 84:403–411. [PubMed: 18388877]
57. Honkalammi J, Niemi M, Neuvonen PJ, Backman JT. Dose-dependent interaction between gemfibrozil and repaglinide in humans: strong inhibition of CYP2C8 with subtherapeutic gemfibrozil doses. Drug Metab Dispos. 2011; 39:1977–1986. [PubMed: 21778352]
58. Backman JT, Kyrklund C, Neuvonen M, Neuvonen PJ. Gemfibrozil greatly increases plasma concentrations of cerivastatin. Clin Pharmacol Ther. 2002; 72:685–691. [PubMed: 12496749]
59. Niemi M, Tornio A, Pasanen MK, Fredrikson H, Neuvonen PJ, Backman JT. Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. Eur J Clin Pharmacol. 2006; 62:463–472. [PubMed: 16758263]
60. Tornio A, Niemi M, Neuvonen PJ, Backman JT. Stereoselective interaction between the CYP2C8 inhibitor gemfibrozil and racemic ibuprofen. Eur J Clin Pharmacol. 2007; 63:463–469. [PubMed: 17333159]
61. Karonen T, Filppula A, Laitila J, Niemi M, Neuvonen PJ, Backman JT. Gemfibrozil markedly increases the plasma concentrations of montelukast: a previously unrecognized role for CYP2C8 in the metabolism of montelukast. Clin Pharmacol Ther. 2010; 88:223–230. [PubMed: 20592724]
62. Filppula AM, Tornio A, Niemi M, Neuvonen PJ, Backman JT. Gemfibrozil impairs imatinib absorption and inhibits the CYP2C8-mediated formation of its main metabolite. Clin Pharmacol Ther. 2013 doi: 10.1038/clpt.2013.92. [Epub ahead of print].
63. Ferguson SS, Chen Y, LeCluyse EL, Negishi M, Goldstein JA. Human CYP2C8 is transcriptionally regulated by the nuclear receptors constitutive androstane receptor, pregnane X receptor, glucocorticoid receptor, and hepatic nuclear factor 4alpha. Mol Pharmacol. 2005; 68:747–757. [PubMed: 15933212]
64. Chen Y, Goldstein JA. The transcriptional regulation of the human CYP2C genes. Curr Drug Metab. 2009; 10:567–578. [PubMed: 19702536]
65. Gerbal-Chaloin S, Pascussi JM, Pichard-Garcia L, Daujat M, Waechter F, Fabre JM, et al. Induction of CYP2C genes in human hepatocytes in primary culture. Drug Metab Dispos. 2001; 29:242–251. [PubMed: 11181490]
66. Rae JM, Johnson MD, Lippman ME, Flockhart DA. Rifampin is a selective, pleiotropic inducer of drug metabolism genes in human hepatocytes: studies with cDNA and oligonucleotide expression arrays. J Pharmacol Exp Ther. 2001; 299:849–857. [PubMed: 11714868]

67. Raucy JL, Mueller L, Duan K, Allen SW, Strom S, Lasker JM. Expression and induction of CYP2C P450 enzymes in primary cultures of human hepatocytes. J Pharmacol Exp Ther. 2002; 302:475–482. [PubMed: 12130704]
68. Madan A, Graham RA, Carroll KM, Mudra DR, Burton LA, Krueger LA, et al. Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. Drug Metab Dispos. 2003; 31:421–431. [PubMed: 12642468]
69. Niemi M, Backman JT, Neuvonen PJ. Effects of trimethoprim and rifampin on the pharmacokinetics of the cytochrome P450 2C8 substrate rosiglitazone. Clin Pharmacol Ther. 2004; 76:239–249. [PubMed: 15371985]
70. Park JY, Kim KA, Kang MH, Kim SL, Shin JG. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. Clin Pharmacol Ther. 2004; 75:157–162. [PubMed: 15001966]
71. Jaakkola T, Backman JT, Neuvonen M, Laitila J, Neuvonen PJ. Effect of rifampicin on the pharmacokinetics of pioglitazone. Br J Clin Pharmacol. 2006; 61:70–78. [PubMed: 16390353]
72. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ, Kivisto KT. Rifampin decreases the plasma concentrations and effects of repaglinide. Clin Pharmacol Ther. 2000; 68:495–500. [PubMed: 11103752]
73. Bidstrup TB, Stilling N, Damkier P, Scharling B, Thomsen MS, Brosen K. Rifampicin seems to act as both an inducer and an inhibitor of the metabolism of repaglinide. Eur J Clin Pharmacol. 2004; 60:109–114. [PubMed: 15034704]
74. Inoue K, Inazawa J, Suzuki Y, Shimada T, Yamazaki H, Guengerich FP, et al. Fluorescence in situ hybridization analysis of chromosomal localization of three human cytochrome P450 2C genes (CYP2C8, 2C9, and 2C10) at 10q24.1. Jpn J Hum Genet. 1994; 39:337–343. [PubMed: 7841444]
75. Gray IC, Nobile C, Muresu R, Ford S, Spurr NK. A 2.4-megabase physical map spanning the CYP2C gene cluster on chromosome 10q24. Genomics. 1995; 28:328–332. [PubMed: 8530044]
76. Yasar U, Lundgren S, Eliasson E, Bennet A, Wiman B, de Faire U, et al. Linkage between the CYP2C8 and CYP2C9 genetic polymorphisms. Biochem Biophys Res Commun. 2002; 299:25–28. [PubMed: 12435384]
77. Naraharisetti SB, Lin YS, Rieder MJ, Marciante KD, Psaty BM, Thummel KE, et al. Human liver expression of CYP2C8: gender, age, and genotype effects. Drug Metab Dispos. 2010; 38:889–893. [PubMed: 20190184]
78. Sonnichsen DS, Liu Q, Schuetz EG, Schuetz JD, Pappo A, Relling MV. Variability in human cytochrome P450 paclitaxel metabolism. J Pharmacol Exp Ther. 1995; 275:566–575. [PubMed: 7473140]
79. Bahadur N, Leathart JB, Mutch E, Steimel-Crespi D, Dunn SA, Gilissen R, et al. CYP2C8 polymorphisms in Caucasians and their relationship with paclitaxel 6alpha-hydroxylase activity in human liver microsomes. Biochem Pharmacol. 2002; 64:1579–1589. [PubMed: 12429347]
80. Rodriguez-Antona C, Niemi M, Backman JT, Kajosaari LI, Neuvonen PJ, Robledo M, et al. Characterization of novel CYP2C8 haplotypes and their contribution to paclitaxel and repaglinide metabolism. Pharmacogenomics J. 2008; 8:268–277. [PubMed: 17923851]
81. Dai D, Zeldin DC, Blaisdell JA, Chanas B, Coulter SJ, Ghanayem BI, et al. Polymorphisms in human CYP2C8 decrease metabolism of the anticancer drug paclitaxel and arachidonic acid. Pharmacogenetics. 2001; 11:597–607. [PubMed: 11668219]
82. Parikh S, Ouedraogo JB, Goldstein JA, Rosenthal PJ, Kroetz DL. Amodiaquine metabolism is impaired by common polymorphisms in CYP2C8: implications for malaria treatment in Africa. Clin Pharmacol Ther. 2007; 82:197–203. [PubMed: 17361129]
83. Gao Y, Liu D, Wang H, Zhu J, Chen C. Functional characterization of five CYP2C8 variants and prediction of CYP2C8 genotype-dependent effects on in vitro and in vivo drug-drug interactions. Xenobiotica. 2010; 40:467–475. [PubMed: 20459297]
84. Yu L, Shi D, Ma L, Zhou Q, Zeng S. Influence of CYP2C8 polymorphisms on the hydroxylation metabolism of paclitaxel, repaglinide, and ibuprofen enantiomers in vitro. Biopharm Drug Dispos. 2013; 34:278–287. [PubMed: 23536207]
85. Soyama A, Saito Y, Hanioka N, Murayama N, Nakajima O, Katori N, et al. Non-synonymous single nucleotide alterations found in the CYP2C8 gene result in reduced in vitro paclitaxel metabolism. Biol Pharm Bull. 2001; 24:1427–1430. [PubMed: 11767116]

86. Smith HE, Jones JP 3rd, Kalhorn TF, Farin FM, Stapleton PL, Davis CL, et al. Role of cytochrome P450 2C8 and 2J2 genotypes in calcineurin inhibitor-induced chronic kidney disease. Pharmacogenet Genomics. 2008; 18:943–953. [PubMed: 18769365]

87. Taniguchi R, Kumai T, Matsumoto N, Watanabe M, Kamio K, Suzuki S, et al. Utilization of human liver microsomes to explain individual differences in paclitaxel metabolism by CYP2C8 and CYP3A4. J Pharmacol Sci. 2005; 97:83–90. [PubMed: 15655291]

88. Rowbotham SE, Boddy AV, Redfern CP, Veal GJ, Daly AK. Relevance of nonsynonymous CYP2C8 polymorphisms to 13-cis retinoic acid and paclitaxel hydroxylation. Drug Metab Dispos. 2010; 38:1261–1266. [PubMed: 20421446]

89. Muschler E, Lal J, Jetter A, Rattay A, Zanger U, Zadoyan G, et al. The role of human CYP2C8 and CYP2C9 variants in pioglitazone metabolism in vitro. Basic Clin Pharmacol Toxicol. 2009; 105:374–379. [PubMed: 19614891]

90. Kaspera R, Naraharisetti SB, Tamraz B, Sahele T, Cheesman MJ, Kwok PY, et al. Cerivastatin in vitro metabolism by CYP2C8 variants found in patients experiencing rhabdomyolysis. Pharmacogenet Genomics. 2010; 20:619–629. [PubMed: 20739906]

91. Kaspera R, Naraharisetti SB, Evangelista EA, Marciante KD, Psaty BM, Totah RA. Drug metabolism by CYP2C8.3 is determined by substrate dependent interactions with cytochrome P450 reductase and cytochrome b5. Biochem Pharmacol. 2011; 82:681–691. [PubMed: 21726541]

92. Soyama A, Saito Y, Komamura K, Ueno K, Kamakura S, Ozawa S, et al. Five novel single nucleotide polymorphisms in the CYP2C8 gene, one of which induces a frame-shift. Drug Metab Pharmacokinet. 2002; 17:374–377. [PubMed: 15618689]

93. Singh R, Ting JG, Pan Y, Teh LK, Ismail R, Ong CE. Functional role of Ile264 in CYP2C8: mutations affect haem incorporation and catalytic activity. Drug Metab Pharmacokinet. 2008; 23:165–174. [PubMed: 18574320]

94. Jiang H, Zhong F, Sun L, Feng W, Huang ZX, Tan X. Structural and functional insights into polymorphic enzymes of cytochrome P450 2C8. Amino Acids. 2011; 40:1195–1204. [PubMed: 20848147]

95. Nakajima M, Fujiki Y, Noda K, Ohtsuka H, Ohkuni H, Kyo S, et al. Genetic polymorphisms of CYP2C8 in Japanese population. Drug Metab Dispos. 2003; 31:687–690. [PubMed: 12756196]

96. Saito Y, Katori N, Soyama A, Nakajima Y, Yoshitani T, Kim SR, et al. CYP2C8 haplotype structures and their influence on pharmacokinetics of paclitaxel in a Japanese population. Pharmacogenet Genomics. 2007; 17:461–471. [PubMed: 17558302]

97. Ishikawa C, Ozaki H, Nakajima T, Ishii T, Kanai S, Anjo S, et al. A frameshift variant of CYP2C8 was identified in a patient who suffered from rhabdomyolysis after administration of cerivastatin. J Hum Genet. 2004; 49:582–585. [PubMed: 15365880]

98. Hichiya H, Tanaka-Kagawa T, Soyama A, Jinno H, Koyano S, Katori N, et al. Functional characterization of five novel CYP2C8 variants, G171S, R186X, R186G, K247R, and K383N, found in a Japanese population. Drug Metab Dispos. 2005; 33:630–636. [PubMed: 15716363]

99. Yeo CW, Lee SJ, Lee SS, Bae SK, Kim EY, Shon JH, et al. Discovery of a novel allelic variant of CYP2C8, CYP2C8*11, in Asian populations and its clinical effect on the rosiglitazone disposition in vivo. Drug Metab Dispos. 2011; 39:711–716. [PubMed: 21245287]

100. Hanioka N, Matsumoto K, Saito Y, Narimatsu S. Functional characterization of CYP2C8.13 and CYP2C8.14: catalytic activities toward paclitaxel. Basic Clin Pharmacol Toxicol. 2010; 107:565–569. [PubMed: 20148860]

101. Hanioka N, Matsumoto K, Saito Y, Narimatsu S. Influence of CYP2C8*13 and CYP2C8*14 alleles on amiodarone *N*-deethylation. Basic Clin Pharmacol Toxicol. 2011; 108:359–362. [PubMed: 21214863]

102. Nakajima Y, Yoshitani T, Fukushima-Uesaka H, Saito Y, Kaniwa N, Kurose K, et al. Impact of the haplotype CYP3A4*16B harboring the Thr185Ser substitution on paclitaxel metabolism in Japanese patients with cancer. Clin Pharmacol Ther. 2006; 80:179–191. [PubMed: 16890579]

103. Soyama A, Hanioka N, Saito Y, Murayama N, Ando M, Ozawa S, et al. Amiodarone *N*-deethylation by CYP2C8 and its variants, CYP2C8*3 and CYP2C8 P404A. Pharmacol Toxicol. 2002; 91:174–178. [PubMed: 12530467]

104. Muthiah YD, Lee WL, Teh LK, Ong CE, Ismail R. Genetic polymorphism of CYP2C8 in three Malaysian ethnics: CYP2C8*2 and CYP2C8*3 are found in Malaysian Indians. J Clin Pharm Ther. 2005; 30:487–490. [PubMed: 16164496]
105. Speed WC, Kang SP, Tuck DP, Harris LN, Kidd KK. Global variation in CYP2C8-CYP2C9 functional haplotypes. Pharmacogenomics J. 2009; 9:283–290. [PubMed: 19381162]
106. 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: identification of CYP2C haplotypes in healthy Nordic populations. Eur J Clin Pharmacol. 2010; 66:1199–1205. [PubMed: 20665013]
107. Arun Kumar AS, Chakradhara Rao US, Umamaheswaran G, Ramu P, Kesavan R, Shewade DG, et al. Haplotype structures of common variants of CYP2C8, CYP2C9, and ADRB1 genes in a South Indian population. Genet Test Mol Biomarkers. 2011; 15:407–413. [PubMed: 21375401]
108. Ahmadi KR, Weale ME, Xue ZY, Soranzo N, Yarnall DP, Briley JD, et al. A single-nucleotide polymorphism tagging set for human drug metabolism and transport. Nat Genet. 2005; 37:84–89. [PubMed: 15608640]
109. Suarez-Kurtz G, Genro JP, de Moraes MO, Ojopi EB, Pena SD, Perini JA, et al. Global pharmacogenomics: impact of population diversity on the distribution of polymorphisms in the CYP2C cluster among Brazilians. Pharmacogenomics J. 2012; 12:267–276. [PubMed: 21173785]
110. Pedersen RS, Christensen MM, Brosen K. Linkage disequilibrium between the CYP2C19*17 allele and other clinically important CYP2C allelic variants in a healthy Scandinavian population. Eur J Clin Pharmacol. 2012; 68:1463–1464. [PubMed: 22476388]
111. Martis S, Peter I, Hulot JS, Kornreich R, Desnick RJ, Scott SA. Multi-ethnic distribution of clinically relevant CYP2C genotypes and haplotypes. Pharmacogenomics J. 2012; 13:369–377. [PubMed: 22491019]
112. Tornio A, Niemi M, Neuvonen PJ, Backman JT. Trimethoprim and the CYP2C8*3 allele have opposite effects on the pharmacokinetics of pioglitazone. Drug Metab Dispos. 2008; 36:73–80. [PubMed: 17913794]
113. Kirchheiner J, Thomas S, Bauer S, Tomalik-Scharte D, Hering U, Doroshyenko O, et al. Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype. Clin Pharmacol Ther. 2006; 80:657–667. [PubMed: 17178266]
114. Aquilante CL, Bushman LR, Knutsen SD, Burt LE, Rome LC, Kosmiski LA. Influence of SLCO1B1 and CYP2C8 gene polymorphisms on rosiglitazone pharmacokinetics in healthy volunteers. Hum Genomics. 2008; 3:7–16. [PubMed: 19129086]
115. Aquilante CL, Kosmiski LA, Bourne DW, Bushman LR, Daily EB, Hammond KP, et al. Impact of the CYP2C8 *3 polymorphism on the drug-drug interaction between gemfibrozil and pioglitazone. Br J Clin Pharmacol. 2013; 75:217–226. [PubMed: 22625877]
116. Kadam R, Bourne D, Kompella U, Aquilante C. Effect of cytochrome P450 2 C8*3 on the population pharmacokinetics of pioglitazone in healthy Caucasian volunteers. Biol Pharm Bull. 2013; 36:245–251. [PubMed: 23370354]
117. Aquilante CL, Wempe MF, Spencer SH, Kosmiski LA, Predhomme JA, Sidhom MS. Influence of CYP2C8*2 on the pharmacokinetics of pioglitazone in healthy African-American volunteers. Pharmacotherapy. 2013 doi: 10.1002/phar.1292. [Epub ahead of print].
118. Stage TB, Christensen MM, Feddersen S, Beck-Nielsen H, Brosen K. The role of genetic variants in CYP2C8, LPIN1, PPARGC1A and PPARgamma on the trough steady-state plasma concentrations of rosiglitazone and on glycosylated haemoglobin A1c in type 2 diabetes. Pharmacogenet Genomics. 2013; 23:219–227. [PubMed: 23426382]
119. Niemi M, Backman JT, Kajosaari LI, Leathart JB, Neuvonen M, Daly AK, et al. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. Clin Pharmacol Ther. 2005; 77:468–478. [PubMed: 15961978]
120. Niemi M, Leathart JB, Neuvonen M, Backman JT, Daly AK, Neuvonen PJ. Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. Clin Pharmacol Ther. 2003; 74:380–387. [PubMed: 14534525]

121. Bidstrup TB, Damkier P, Olsen AK, Ekblom M, Karlsson A, Brosen K. The impact of CYP2C8 polymorphism and grapefruit juice on the pharmacokinetics of repaglinide. Br J Clin Pharmacol. 2006; 61:49–57. [PubMed: 16390351]
122. Tomalik-Scharte D, Fuhr U, Hellmich M, Frank D, Doroshyenko O, Jetter A, et al. Effect of the CYP2C8 genotype on the pharmacokinetics and pharmacodynamics of repaglinide. Drug Metab Dispos. 2011; 39:927–932. [PubMed: 21270106]
123. Henningsson A, Marsh S, Loos WJ, Karlsson MO, Garsa A, Mross K, et al. Association of CYP2C8, CYP3A4, CYP3A5, and ABCB1 polymorphisms with the pharmacokinetics of paclitaxel. Clin Cancer Res. 2005; 11:8097–8104. [PubMed: 16299241]
124. Marsh S, Somlo G, Li X, Frankel P, King CR, Shannon WD, et al. Pharmacogenetic analysis of paclitaxel transport and metabolism genes in breast cancer. Pharmacogenomics J. 2007; 7:362–365. [PubMed: 17224914]
125. Marsh S, Paul J, King CR, Gifford G, McLeod HL, Brown R. Pharmacogenetic assessment of toxicity and outcome after platinum plus taxane chemotherapy in ovarian cancer: the Scottish Randomised Trial in Ovarian Cancer. J Clin Oncol. 2007; 25:4528–4535. [PubMed: 17925548]
126. Green H, Soderkvist P, Rosenberg P, Mirghani RA, Rymark P, Lundqvist EA, et al. Pharmacogenetic studies of paclitaxel in the treatment of ovarian cancer. Basic Clin Pharmacol Toxicol. 2009; 104:130–137. [PubMed: 19143748]
127. Bergmann TK, Brasch-Andersen C, Green H, Mirza M, Pedersen RS, Nielsen F, et al. Impact of CYP2C8*3 on paclitaxel clearance: a population pharmacokinetic and pharmacogenomic study in 93 patients with ovarian cancer. Pharmacogenomics J. 2011; 11:113–120. [PubMed: 20368717]
128. Jabir RS, Naidu R, Annuar MA, Ho GF, Munisamy M, Stanslas J. Pharmacogenetics of taxanes: impact of gene polymorphisms of drug transporters on pharmacokinetics and toxicity. Pharmacogenomics. 2012; 13:1979–1988. [PubMed: 23215890]
129. Mielke S, Sparreboom A, Steinberg SM, Gelderblom H, Unger C, Behringer D, et al. Association of paclitaxel pharmacokinetics with the development of peripheral neuropathy in patients with advanced cancer. Clin Cancer Res. 2005; 11:4843–4850. [PubMed: 16000582]
130. Leskela S, Jara C, Leandro-Garcia LJ, Martinez A, Garcia-Donas J, Hernando S, et al. Polymorphisms in cytochromes P450 2C8 and 3A5 are associated with paclitaxel neurotoxicity. Pharmacogenomics J. 2011; 11:121–129. [PubMed: 20212519]
131. Hertz DL, Motsinger-Reif AA, Drobish A, Winham SJ, McLeod HL, Carey LA, et al. CYP2C8*3 predicts benefit/risk profile in breast cancer patients receiving neoadjuvant paclitaxel. Breast Cancer Res Treat. 2012; 134:401–410. [PubMed: 22527101]
132. Hertz DL, Roy S, Motsinger-Reif AA, Drobish A, Clark LS, McLeod HL, et al. CYP2C8*3 increases risk of neuropathy in breast cancer patients treated with paclitaxel. Ann Oncol. 2013; 24:1472–1478. [PubMed: 23413280]
133. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. N Engl J Med. 2002; 346:539–540. [PubMed: 11844864]
134. Kirchheiner J, Kudlicz D, Meisel C, Bauer S, Meineke I, Roots I, et al. Influence of CYP2C9 polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (−)-3S,5R-fluvastatin and (+)-3R,5S-fluvastatin in healthy volunteers. Clin Pharmacol Ther. 2003; 74:186–194. [PubMed: 12891229]
135. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, et al. SLCO1B1 variants and statin-induced myopathy – a genomewide study. N Engl J Med. 2008; 359:789–799. [PubMed: 18650507]
136. Paganotti GM, Gallo BC, Verra F, Sirima BS, Nebie I, Diarra A, et al. Human genetic variation is associated with *Plasmodium falciparum* drug resistance. J Infect Dis. 2011; 204:1772–1778. [PubMed: 21998472]
137. Cavaco I, Martensson A, Froberg G, Msellem M, Bjorkman A, Gil JP. CYP2C8 status of patients with malaria influences selection of *Plasmodium falciparum* pfmdr1 alleles after amodiaquine-artesunate treatment. J Infect Dis. 2013; 207:687–688. [PubMed: 23204183]

138. Garcia-Martin E, Martinez C, Tabares B, Frias J, Agundez JA. Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. Clin Pharmacol Ther. 2004; 76:119–127. [PubMed: 15289789]

139. Martinez C, Garcia-Martin E, Blanco G, Gamito FJ, Ladero JM, Agundez JA. The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (*R*)-ibuprofen enantiomer in healthy subjects. Br J Clin Pharmacol. 2005; 59:62–69. [PubMed: 15606441]

140. Lopez-Rodriguez R, Novalbos J, Gallego-Sandin S, Roman-Martinez M, Torrado J, Gisbert JP, et al. Influence of CYP2C8 and CYP2C9 polymorphisms on pharmacokinetic and pharmacodynamic parameters of racemic and enantiomeric forms of ibuprofen in healthy volunteers. Pharmacol Res. 2008; 58:77–84. [PubMed: 18694831]

141. Karazniewicz-Lada M, Luczak M, Glowka F. Pharmacokinetic studies of enantiomers of ibuprofen and its chiral metabolites in humans with different variants of genes coding CYP2C8 and CYP2C9 isoenzymes. Xenobiotica. 2009; 39:476–485. [PubMed: 19480553]

142. Blanco G, Martinez C, Ladero JM, Garcia-Martin E, Taxonera C, Gamito FG, et al. Interaction of CYP2C8 and CYP2C9 genotypes modifies the risk for nonsteroidal anti-inflammatory drugs-related acute gastrointestinal bleeding. Pharmacogenet Genomics. 2008; 18:37–43. [PubMed: 18216720]

143. Agundez JA, Garcia-Martin E, Martinez C. Genetically based impairment in CYP2C8- and CYP2C9-dependent NSAID metabolism as a risk factor for gastrointestinal bleeding: is a combination of pharmacogenomics and metabolomics required to improve personalized medicine? Expert Opin Drug Metab Toxicol. 2009; 5:607–620. [PubMed: 19422321]

144. Sarasquete ME, Garcia-Sanz R, Marin L, Alcoceba M, Chillon MC, Balanzategui A, et al. Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 CYP2C8 in multiple myeloma: a genome-wide single nucleotide polymorphism analysis. Blood. 2008; 112:2709–2712. [PubMed: 18594024]

145. English BC, Baum CE, Adelberg DE, Sissung TM, Kluetz PG, Dahut WL, et al. A SNP in CYP2C8 is not associated with the development of bisphosphonate-related osteonecrosis of the jaw in men with castrate-resistant prostate cancer. Ther Clin Risk Manag. 2010; 6:579–583. [PubMed: 21151627]

146. Such E, Cervera J, Terpos E, Bagan JV, Avaria A, Gomez I, et al. CYP2C8 gene polymorphism and bisphosphonate-related osteonecrosis of the jaw in patients with multiple myeloma. Haematologica. 2011; 96:1557–1559. [PubMed: 21685474]

147. Katz J, Gong Y, Salmasinia D, Hou W, Burkley B, Ferreira P, et al. Genetic polymorphisms and other risk factors associated with bisphosphonate induced osteonecrosis of the jaw. Int J Oral Maxillofac Surg. 2011; 40:605–611. [PubMed: 21396799]

148. Gervasini G, Garcia M, Macias RM, Benitez J, Caravaca F, Cubero JJ. CYP2C8*3 polymorphism and donor age are associated with allograft dysfunction in kidney transplant recipients treated with calcineurin inhibitors. J Clin Pharmacol. 2013; 53:427–434. [PubMed: 23426640]

149. Jacobson PA, Schladt D, Oetting WS, Leduc R, Guan W, Matas AJ, et al. Genetic determinants of mycophenolate-related anemia and leukopenia after transplantation. Transplantation. 2011; 91:309–316. [PubMed: 21107304]

150. Bouamar R, Elens L, Shuker N, van Schaik RH, Weimar W, Hesselink DA, et al. Mycophenolic acid-related anemia and leucopenia in renal transplant recipients are related to genetic polymorphisms in CYP2C8. Transplantation. 2012; 93:e39–e40. author reply e41–e32. [PubMed: 22572835]

Table 1

Examples of substrates metabolized to a major extent by CYP2C8[a]

Drug name	Drug class	Indication	References
Amiodarone	Class III antiarrhythmic	Supraventricular and ventricular arrhythmias	Ohyama *et al.* [10]
Amodiaquine, Chloroquine	4-aminoquinolines	Malaria	Li and colleagues [11–13]
Cerivastatin[b]	Statin	Hyperlipidemia	Wang *et al.* [14]
Montelukast	Leukotriene receptor antagonist	Asthma	Filppula *et al.* [15]
Paclitaxel	Taxane	Solid tumors	Rahman and colleagues [16, 17]
Pioglitazone, Rosiglitazone, Troglitazone[b]	Thiazolidinedione	Type 2 diabetes	Baldwin and colleagues [18–20]
Repaglinide	Meglitinide	Type 2 diabetes	Bidstrup *et al.* [21]
Tazarotenic acid	Retinoid derivative	Acne, psoriasis	Attar *et al.* [22]

[a] Table adapted from Totah and colleagues [4,23].

[b] Withdrawn from the market.

Table 2

Variant *CYP2C8* alleles

***CYP2C8* allele**	**dbSNP number**[a]	**Nucleotide change**	**Location**	**Effect on protein**	**Enzyme activity (*in vitro*)**	**Approximate allele frequencies in major race groups**	**References**
*1 (also known as *1A)	–	–	–	Wild type	Normal	–	Klose *et al.* [5]
*1B	rs7909236	–271C>A	Promoter	Increased promoter activity		CEU, 23%; HCB, 10%; JPT, 9%; YRI, 0%[b]	Bahadur and colleagues [79,80]
*1C	rs17110453	–370T>G	Promoter	Unknown	-	CEU, 12%; HCB, 28%; JPT, 34%; YRI, <1%[b]	Bahadur *et al.* [79]
*2	rs11572103	c.805A>T	Exon 5	p.I269F	Decreased	CEU, 0%; HCB, 0%; JPT, 0%; YRI, 19%[b]	Dai and colleagues [81–84]
*3	rs11572080	c.416G>A	Exon 3	p.R139K	Increased, decreased, or unchanged	CEU, 11–14%; HCB, 0%; JPT, 0%; YRI, 0%[b]	Bahadur and colleagues [79–92]
	rs10509681	c.1196A>G	Exon 8	p.K399R			
*4	rs1058930	c.792C>G	Exon 5	p.I264M	Decreased or unchanged	CEU, 7%; HCB, 0%; JPT, 0%; YRI, <1%[b]	Bahadur and colleagues [79,80,83,84,86,88,93,94]
*5	rs72558196	c.475delA	Exon 3	p.T159 frameshift	None	Japanese, <1%	Soyama and colleagues [92,95–97]
*6	rs142886225	c.511G>A	Exon 4	p.G171S	Unchanged	Japanese, <1%	Saito and colleagues [96,98]
*7	rs72558195	c.556C>T	Exon 4	p.R186X	None	Japanese, <1%	Saito and colleagues [96,98]
*8	rs72558195	c.556C>G	Exon 4	p.R186G	Decreased	Japanese, <1%	Saito and colleagues [96,98]
*9	–	c.740A>G	Exon 5	p.K247R	Unchanged	Japanese, <1%	Saito and colleagues [96,98]
*10	–	c.1149G >T	Exon 7	p.K383N	Unchanged	Japanese, <1%	Saito and colleagues [96,98]
*11	rs78637576	c.820G>T	Exon 6	p.E274X	None	White, 0%; Asian, ≤ 1%; African-American, 0%	Yeo *et al.* [99]
*12	rs3832694	c.1382_1384delTTG	Exon 9	p.461delV	Unknown	Japanese, <1%	Saito *et al.* [96]

CYP2C8 allele	dbSNP number[a]	Nucleotide change	Location	Effect on protein	Enzyme activity (*in vitro*)	Approximate allele frequencies in major race groups	References
*13	–	c.669T>G	Exon 5	p.I223M	Unchanged	Japanese, <1%	Saito and colleagues [96,100–102]
*14	rs188934928	c.712G >C	Exon 5	p.A238P	Decreased	Japanese, <1%	Saito and colleagues [96,100–102]
Not assigned	rs66501115	c.1210C>G	Exon 8	p.P404A	Decreased	Japanese, <1%; African, 2%	Soyama and colleagues [85,94,103]

CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; dbSNP, single nucleotide polymorphism database; HCB, Han Chinese in Beijing, China; JPT, Japanese in Tokyo, Japan; YRI, Yoruba in Ibadan, Nigeria.

[a] RefSNP accession number in dbSNP (*http://www.ncbi.nlm.nih.gov/snp/*).

[b] Frequencies based on HapMap data available in dbSNP.