

Pharmacogenetics of Drug Transporters

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Abstract: During the last decade, a greater focus has been given to impact of genetic variation in membrane transporters on the pharmacokinetics and toxicity of numerous therapeutic drugs. While the majority of transporter-related pharmacogenetic research has been in regards to classic genes encoding the outward-directed ATP-binding cassette (ABC) transporters, such as *ABCB1* (P-glycoprotein), *ABCC2* (MRP2), and *ABCG2* (BCRP), more studies have been conducted in recent years evaluating genes encoding solute carriers (SLC) that mediate the cellular uptake of drugs, such as *SLCO1B1* (OATP1B1) and *SLC22A1* (OCT1). The distribution of ABC and SLC transporters in tissues key to pharmacokinetics, such as intestine (absorption), blood-brain-barrier (distribution), liver (metabolism), and kidneys (excretion), strongly suggests that genetic variation associated with changes in protein expression or function of these transporters may have a substantial impact on systemic drug exposure and toxicity. In this current article, we will review recent advances in understanding the contribution of critical ABC and SLC transporters to interindividual pharmacokinetic and dynamic variability of substrate drugs.

INTRODUCTION

Drug transporter proteins are of increasing interest across numerous therapeutics areas, including oncology, due to their role both in processes regulating pharmacokinetic properties of drugs (absorption, distribution and elimination) and the development of cellular drug resistance through decreased uptake or increased efflux. The two most commonly studied membrane transporters include members of the ATP-binding cassette transporters and solute carriers. Between these two classes of transporter proteins there are almost 400 individual proteins that have been identified to date. Their ubiquitous distribution throughout the body, depending on individual transporter, and their role in the cellular uptake and efflux of both endogenous compounds and xenobiotics gives strength to the hypothesis that they may play a crucial role in the pharmacokinetics of therapeutic drugs used clinically (Fig. 1). Only recently has the functional impact of genetic variation in these transporters been studied *in vivo*, and unfortunately the pharmacogenetics of transporters is still not sufficiently studied. This review article will focus on known variants in select genes encoding ATP-binding cassette transporters and solute carriers that have been identified as impacting drug pharmacokinetics and/or toxicity.

ATP-BINDING CASSETTE TRANSPORTERS

Among the 48 genes in the ATP-binding cassette (ABC) family, most research has focused on *ABCB1* (P-glycoprotein) and *ABCG2* (BCRP, MXR, ABCP). The genes in this family, including *ABCB1* and *ABCG2*, encode transmembrane proteins that bind and subsequently hydrolyze ATP, using the energy to drive the transport of various molecules across cell membranes [1-3]. ABC transporter proteins are believed to play a major role in host detoxification and protection against xenobiotic substances, though their importance appears to be highly substrate-dependent [4]. Mouse knock-out models of ABC transporter genes have shown alterations in blood-brain barrier function [5, 6], intestinal drug absorption [7, 8], fetal drug exposure [9], and drug-induced damage to testicular tubules [10]. Furthermore, re-sequencing of various human ABC transporter genes has revealed a number of naturally-occurring allelic variants, many of which appear to affect the functional activity of the encoded protein *in vivo* [11-13]. This genetic variation may potentially modulate transporter phenotypes in humans and thereby

affect toxicity and response to drug treatment or predisposition to disease.

ABCB1 (*ABCB1*)

The *ABCB1* gene, the first ABC transporter identified and the best characterized, maps to chromosome 7q21.1 and consists of 28 translated exons and 27 introns. Formerly known as *MDR1* or *PGY1*, *ABCB1* was the first human ABC transporter gene cloned and characterized through its ability to confer a multi-drug resistant (MDR) phenotype to cancer cells that had developed resistance to certain chemotherapy drugs [14]. It has been shown to transport a wide range of hydrophobic substrates from diverse therapeutic classes [13], including several anticancer drugs [15]. *ABCB1* is expressed in multiple healthy organs, and is thought to play an important role in removing toxic substances or metabolites from cells. For example, the protein is highly expressed in cells comprising the blood-brain barrier and presumably plays a role in transport of toxic compounds out of the brain, effectively preventing uptake [16]. It is also expressed in many excretory cell types such as kidney, liver, intestine, and adrenal gland, where the normal physiological function is thought to involve the secretion of toxic xenobiotics and their metabolites, in addition to steroids [6, 17, 18]. The expression of *ABCB1* on the apical surface of epithelial cell of the lower gastrointestinal tract (jejunum, ileum, and colon) has been shown to influence intestinal drug absorption and limit oral bioavailability of a wide variety of structurally diverse drugs, including important anticancer agents derived from natural sources, though this is highly substrate dependent [18].

ABCB1 VARIANTS

The first systematic screen of the *ABCB1* gene for the presence of single-nucleotide polymorphisms (SNP) was published in 2001 [19, 20] and to date, over 100 polymorphisms that occur at a frequency of greater than 5% have been identified in Caucasians [21-24]. Several recombinant variants have been generated either by *in vivo* drug selection or by site-directed mutagenesis techniques, which show altered substrate specificity or impaired function of a properly assembled protein [15, 25]. The functional effect of many common polymorphisms in *ABCB1* is unknown. The three most commonly studied exonic variants *in vitro* are 1236C>T, 2677G>A/T and 3435C>T. However, any differences in variant-dependent protein expression and function may be due to other variants that are co-expressed with *ABCB1* variants, such as the *ABCB1* 3435C>T polymorphism. This has led to a number of

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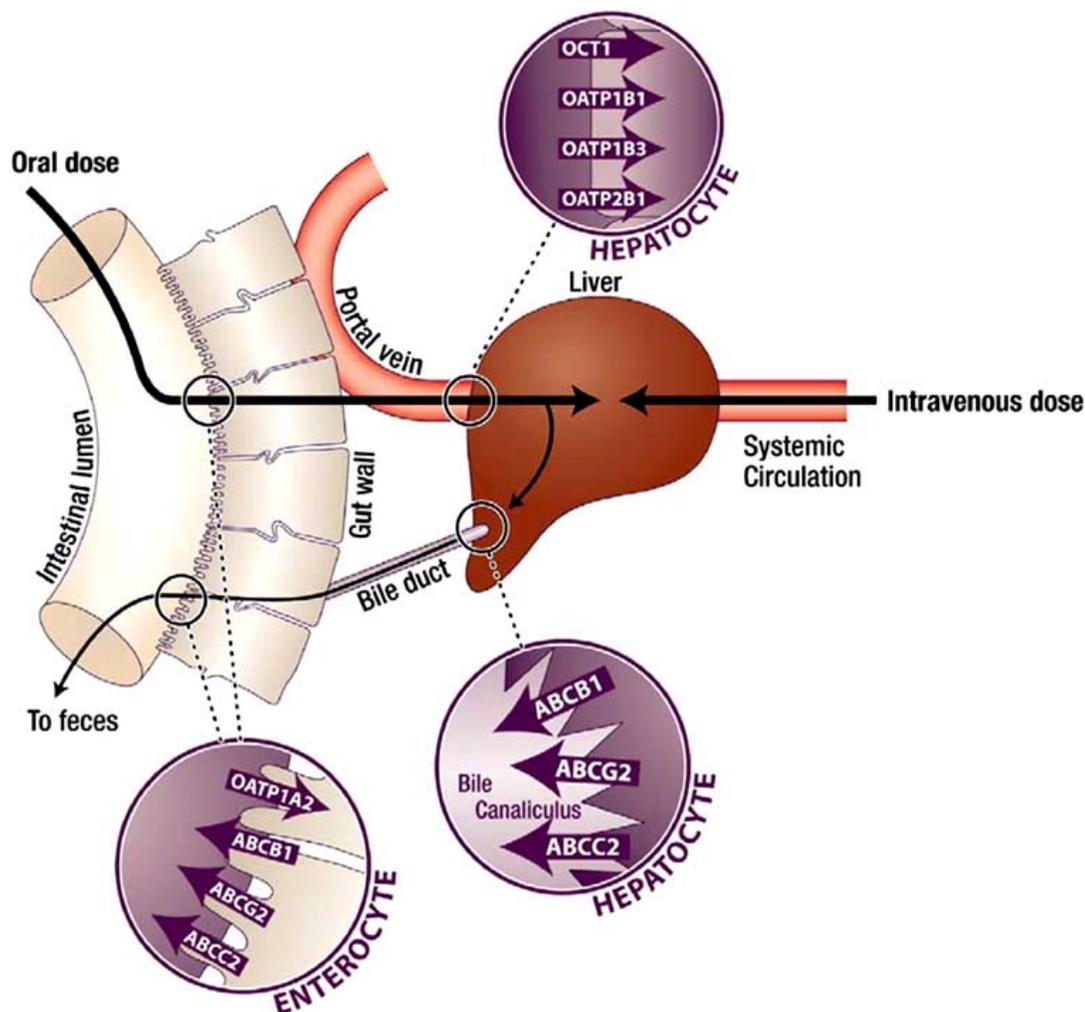


Fig. (1). Schematic showing localization of ABC and SLC transporters involved in pharmacokinetics, specifically oral absorption from the GI tract, hepatic uptake, and elimination in the bile.

haplotypes being identified (see Table 1) that commonly include the 2677G>T/A and/or 1236C>T polymorphisms, which are in strong linkage disequilibrium [24, 26].

IN VITRO EFFECTS OF *ABCB1* VARIANTS

A majority of the *in vitro* studies exploring effects of *ABCB1* variants have focused on individual SNPs, such as the 2677G>T/A variant. This polymorphism contains a tri-allelic polymorphism (with G at nucleotide 2677 found in the reference sequence, and with A or T at that position being the two possible variants), which results in an amino acid change in exon 21 (Ala893Ser/Thr) [27]. The Ser893 substitution has been shown to be associated with altered multi-drug resistance in AdrR MCF-7 cells as well as approximately 2-fold enhanced efflux in stably transduced NIH3T3 GP+E86 cells [28]. In contrast to the 2677G>T/A, the *ABCB1* 3435C>T variant has been most extensively studied *in vitro*, although a clear mechanism has not been elucidated. Although this variant is a silent mutation, there is a 2-fold decrease in protein level for individuals with the homozygous T allele (TT genotype) as compared to those with the wild-type alleles (CC genotype) [19, 29]. Furthermore, using an *ABCB1* substrate, rhodamine 123 fluorescence in CD56⁺ natural killer cells was significantly lower *in vitro* with the CC genotype, as compared to the TT genotype [30], suggesting that the CC genotype had increased efflux of the *ABCB1* substrate.

Currently it is unclear whether the decreased protein expression associated with the 3435C>T variant is due to a secondary polymorphism found in a critical haplotype or due to some mechanism controlled by the variant directly. One possible explanation for changes in protein folding due to this silent mutation is ribosome stalling, resulting in altered transport and substrate specificity [26]. Additionally, expression of *ABCB1* is known to be regulated by the pregnane X receptor (PXR; NR1I2), a ligand-activated, nuclear receptor, which may further obscure any effects of the polymorphism [31, 32]. Novel variants have been identified in the promoter region of the *ABCB1* gene that results in increased transcriptional activity and mRNA expression in the placenta [33]. Furthermore, a recent study has suggested that down regulation of *ABCB1* function by a genetic variant can increase PXR-induced expression of a variety of genes, presumably due to decreased efflux of the PXR activators by *ABCB1* [34]. Regardless of the underlying mechanism for why the 3435C>T variant is associated with decreased *ABCB1* protein there is a need for further studies to determine the *in vivo* effects of these polymorphisms, either alone or in haplotypes.

IN VIVO EFFECTS OF *ABCB1* VARIANTS

As mentioned earlier, distribution of other (unidentified) variation in the same gene and/or other genes relevant to drug disposition linked to the 3435C>T polymorphism might be different among the different human populations studied. In this context, it is

Table 1. Major Haplotypes in the *ABCB1* Gene

Nomenclature	Exonic SNPs				Intronic SNPs				
	61	1236	2677	3435	5.1*	10.1*	13.1*	14.2*	20.2*
<i>ABCB1</i> *1	A	C	G	C	G	A	C	A	G
<i>ABCB1</i> *2	A	C	G	T		A	C	A	G
<i>ABCB1</i> *13	A	T	T	T	G	G	T	G	G
<i>ABCB1</i> *15	A	T	T	C	G	G	T	G	G
<i>ABCB1</i> *11	A	T	G	C		G	T	G	G
<i>ABCB1</i> *14	G	T	T	T	G	G	T	G	G
<i>ABCB1</i> *12	A	T	G	T	G	G	T	G	G
<i>ABCB1</i> *24	A	C	A	C	G	A	C	A	G
<i>ABCB1</i> *26	A	C	G	C	T	A	C	A	A
<i>ABCB1</i> *21	A	T	G	C	T	A	T	G	G

*Denotes variant number by exon [24].

noteworthy that a reduced expression of intestinal *CYP3A4* mRNA was observed in subjects carrying the TT genotype of the 3435C>T polymorphism in a Japanese population [35], although this finding could not be confirmed by others [36]. It has also been suggested that the interindividual variation of protein expression levels in the human intestine might be associated with SNPs in the 5'-regulatory region of the *ABCB1* gene (i.e., at nucleotides -692T>C and -2352G>A) that are possibly in linkage with the 3435C>T polymorphism [37].

Of the ABC transporters, phenotypical consequences of variants have so far been most extensively described for *ABCB1*, and have primarily focused on the 3435C>T and 2677G>T/A SNPs. However, the possible effects of individual polymorphisms on the pharmacokinetics of substrate drugs remain highly controversial. In line with the initial observation of lower duodenal expression of *ABCB1* in individuals homozygous for the T-allele of the 3435C>T SNP, patients with this variant have increased digoxin exposure (as measured by AUC) and maximum concentration (C_{max}) following oral drug administration [19]. Furthermore, it has been reported that the AUC of oral digoxin was significantly higher in subjects with the TT genotype, but there was no difference in AUC after intravenous administration of digoxin [38]. This suggests that although concentrations of oral digoxin are dependent on both absorption and elimination pathways [29], the involvement of *ABCB1* may only be rate-limiting in the intestines.

In a large study evaluating the effects of several polymorphisms, including *ABCB1* 1236C>T and 2677G>T/A on the pharmacology of morphine, SNPs at either location were found to significantly correlate with higher incidence of central side effects, including drowsiness, confusion and hallucinations [39]. Interestingly, *ABCB1* genotype did not correlate with required morphine dose, nor do serum concentrations of morphine or its metabolites, thus highlighting the difficulty in drawing broad conclusions about the role of *ABCB1* in drug disposition. The role of *ABCB1* in drug elimination may be ethnicity- and drug-dependent, and could potentially affect total clearance or tissue distribution.

In a small Asian population of 28 cancer patients, 3435C>T genotyping showed no statistically significant difference in docetaxel clearance [40]. A subsequent study evaluating the effect of *ABCB1* polymorphisms on docetaxel pharmacokinetics in 92 predominantly Caucasian cancer patients found that individuals

carrying the 1236C>T polymorphism had decreased drug clearance, yet no association with haplotype was observed [41]. The inconsistency of findings related to this SNP on pharmacokinetics is not specific to docetaxel. When the relationship between irinotecan disposition and multiple SNPs in several ABC transporter genes was studied in 59 Caucasian patients no statistical associations were found with any of the variants studied, including the *ABCB1* 3435C>T polymorphism [42].

IN VIVO EFFECTS OF *ABCB1* HAPLOTYPES

Overall, the seemingly contradictory findings may indicate that genetic variation of *ABCB1* 3435C>T is not the causal modulator of any of the observed functional differences. Therefore, it is very likely that functional differences arise from SNPs in linkage disequilibrium with other (unidentified) functional polymorphism(s), including the *ABCB1* 2677G>T/A polymorphism, suggesting that functional effects of genetic variants in the *ABCB1* gene should be considered as haplotypes rather than independent SNPs. For example, close linkage of the polymorphisms 1236C>T, 2677G>T, and 3435C>T has been reported [28]. Individuals who are homozygous for the reference allele had approximately a 40% higher AUC value of fexofenadine, an *ABCB1* substrate, compared to those who are homozygous for the variant allele. Recent work also indicates that the use of *ABCB1* haplotypes is superior to unphased SNP analysis to predict the pharmacokinetics of digoxin [43], cyclosporine [44], and fexofenadine [45]. Furthermore, it is suggested that there is a correlation between the haplotype of these three SNPs and intestinal expression of *ABCB1* mRNA [35]. Assessing haplotypes in the *ABCB1* gene and consideration of their interethnic differences in future investigations will likely provide greater power to detect associations with functional differences [24, 44, 46-48]. However, as with the individual polymorphism assessments, many discrepant findings have been observed. A number of clinical haplotype studies have been performed, though many are limited by small sample size, resulting in few patients per haplotype. As such, the large sample sizes required to determine significance of the numerous possible haplotypes has limited studies analyzing any significance of haplotypes on pharmacokinetics.

An additional dilemma for pharmacogenetic research of *ABCB1* variants is that standard nomenclature for the *ABCB1* SNPs and

haplotypes has not been fully defined. However, there has been a comprehensive sequence diversity analysis reported for 33 haplotypes in at least three chromosomes in a collection of 247 ethnically diverse DNA samples [24]. The authors noted two very common haplotypes in the *ABCB1* gene, referred to as *ABCB1*1* for the reference allele and *ABCB1*13*, which contains three common codon polymorphisms (i.e., 1236C>T, 2677G>T, and 3435C>T) as well as three intronic variants (10.1, 13.1, and 14.2; see Table 1) [24]. In line with previously reported data, no functional difference was found in the transport of ABCB1 probe drugs in cells transfected with the *ABCB1*1* or *ABCB1*13* constructs, either in the presence or absence of the ABCB1 inhibitor, GF120918 [24]. The *ABCB1* 1236/2677/3435 haplotype was shown to correlate with both response and drug exposure (as defined by trough concentration) in 90 patients with chronic myeloid leukemia treated with imatinib. Significantly lower trough concentrations and a reduced rate of major molecular response was observed in patients with the “1a” CGC haplotype (also referred to as *ABCB1*1*), as compared to all other haplotypes, the opposite of what might be expected based on studies with other substrates [49].

In contrast to the findings reported on individual SNPs [42], patients with homozygous variant at both 2677 and 3435 had significantly lower exposure to SN-38, the active metabolite of irinotecan, suggesting that the variant haplotype is associated with increased efflux activity [50]. However, in a subsequent multivariate analysis, no correlations with individual *ABCB1* were observed [51]. A correlation was observed between the TTT haplotype (1236T, 2677T and 3435T) and decreased irinotecan clearance in 49 Japanese patients with cancer [48]. Furthermore, both the 2677GG genotype and the 2677G-3435C haplotype had a statistically significant better response to chemotherapy [52]. The 2677G-3435C haplotype was also correlated with significantly better response to vinorelbine, another anticancer ABCB1 substrate [53]. These discrepant findings are perhaps unsurprising, based on preclinical observations in *Abcb1*-deficient mice as well as clinical data that metabolism rather than transport is the prominent elimination pathway for docetaxel [54, 55] and irinotecan [56, 57]. Similarly, several studies have evaluated the possible correlation between loperamide pharmacokinetics with mixed results. The *ABCB1* 2677G/3435T haplotype exhibited the highest plasma concentrations of loperamide [47], although another study found no correlation between 3435 polymorphism or haplotypes with pharmacokinetics [58]. These studies highlight the need for further studies to recruit a very high number of patients in order to conduct more refined analysis with enough statistical power to examine how both individual polymorphisms and haplotypes can impact the pharmacokinetics of drugs.

ABCB1 CONCLUSION

It remains reasonable to assume that genetic variations in *ABCB1* could alter drug disposition of substrates and might have clinical consequences. If the function or expression level of the ABC transporters is altered due to genetic changes, intestinal secretion of substrate drug into the gut lumen may change, as could drug distribution or elimination. It is essential that individual transporters or metabolizing enzymes not be considered in isolation, due to the drug-specific differences in metabolism and excretion for various substrates of ABCB1 [59, 60]. For example, cyclosporine and digoxin are both transported by ABCB1, but only cyclosporine is metabolized by the cytochrome P450 3A4 (CYP3A4) isoform. In the case of cyclosporine, reduced ABCB1 function by possible genetic effects might be compensated for by (inducible) CYP3A4 activity. Despite the inconsistent results and complexities in allele frequency amongst different ethnic groups, *ABCB1* polymorphism-mediated variability could have an impact on drug disposition profiles and thus may provide a mechanistic basis for some of the observed discrepancies among different populations [24, 28, 46, 61-63].

ABCG2 (ABCG2)

The ABCG subfamily consists of several half transporters that are generally thought to form homo- or heterodimers to create the active transporter. The *ABCG2* gene is comprised of 16 exons and 15 introns and is located on chromosome 4q22. The gene encodes a 655 amino-acid ATP binding cassette half transporter (ABCG2, also known as MXR, BCRP, or ABCP) that is comprised of one nucleotide binding fold and one transmembrane region, often referred to as an NBF-TM. Like other cell membrane localized ABC transporters, ABCG2-mediated flux is primarily unidirectional, and it transports substrates from the cytoplasm out of the cell.

The gene product ABCG2 has been shown to be a promiscuous transporter of a large number of hydrophobic substrates, including several prescription drugs. Various high-throughput assays for ABCG2 have been developed recently to screen large libraries of compounds [64], and the application of these screening systems has resulted in an explosion in the identification of novel selective inhibitors of this transporter [65]. Similar to ABCB1, ABCG2 is expressed in apical membranes of multiple healthy organs, including the liver, kidney, intestine, and brain, and is thought to play an important role in removing toxic substances from cells, in preventing excessive accumulation in certain tissues, and in reducing absorption. ABCG2 expression is strongly induced in the mammary gland of various mammals during lactation [66], where it is likely involved in the secretion of certain important nutrients into milk, such as riboflavin (vitamin B2) [67].

Similar to work done on ABCB1, recent re-sequencing of the ABCG2 transporter has revealed a number of allelic variants that may dramatically affect activity of the gene product *in vivo*. Some of these genetic variants may potentially modulate the ABCG2 phenotype in patients and therefore affect their predisposition to toxicity and response to substrate drug treatment. In particular, a SNP in exon 5 of the *ABCG2* gene has been described, in which a 421C>A transversion results in a lysine to glutamine amino acid change at codon 141 (Q141K) [68]. This *ABCG2* variant is associated with altered substrate specificity and function of the mutant protein relative to the reference protein (reviewed in [69]). Several other SNPs have been identified in coding regions of the gene, and at least three additional non-synonymous SNPs have been identified occurring at positions 34 (V12M; exon 2), 616 (I206L, exon 6), and 1768 (N590Y, exon 15). Although these SNPs have not been found to confer an alteration in protein expression or function, some variants can affect the protein stability of ABCG2 [70]. Based on a re-sequencing of the *ABCG2* promoter and intron 1, sequence diversity in the *cis*-regulatory region has been found to be a significant determinant of ABCG2 protein expression [71].

Evidence suggesting that *ABCG2* SNP analysis might be a useful strategy to predict systemic exposure to ABCG2 substrate drugs is becoming increasingly prevalent. Specifically, recent studies have demonstrated that subjects with a reduced ABCG2 activity due to the Q141K variant are at an increased risk for gefitinib-induced diarrhea [72], and altered pharmacokinetics of 9-aminocamptothecin, diflomotecan, irinotecan, rosuvastatin, sulfasalazine, and topotecan [64]. However, contradictory results have been reported for other known ABCG2 substrates, such as doxorubicin, imatinib, nelfinavir, and pitavastatin [64]. It should be pointed out that several studies published to date suffer from small sample sizes in relation to the allelic and genotypic frequencies of the studied variants, as well as from a host of potentially confounding factors that influence their outcome. Most important among these are environmental and physiological factors that may affect expression of the transporter, and links to other genes or variants of putative relevance for drug absorption and disposition pathways. The inclusion of data on other variants in *ABCG2* [73], and/or the use of haplotype profiles as opposed to testing unphased SNPs to predict certain phenotypes may have clinical ramifications.

for agents such as erlotinib [74], but this remains to be clarified for most drugs. In addition, more detailed investigations into the influence of ethnicity on ABCG2 transporter function and expression in relation to substrate specific phenotypes is urgently needed.

SOLUTE CARRIERS

While pharmacogenetic evaluation of the ABC transporters has been extensively studied, only in recent years has the impact of genetic variation in solute carriers (SLCs) been evaluated. In humans, there are more than 300 individual proteins that are organized into 47 families of SLCs [75]. The SLC families encode membrane proteins that have been identified as passive transporters, ion coupled transporters, and exchangers. Particular focus has been applied to the organic anion transporting polypeptides (OATP) and the gene family that encodes them, *SLCO* (previously called *SLC21*) [76]. OATPs mediate the sodium-independent transport of a wide range of amphipathic organic compounds, including steroid conjugates, anionic oligopeptides, thyroid hormones, bile salts, xenobiotics, and pharmaceuticals [77]. OATPs have 12 transmembrane domains, with a large, highly conserved extracellular loop between the 9th and 10th transmembrane domains. *N*-glycosylation sites in extra-cellular loops 2 and 5 are consistent among the various members of the OATP family [78].

OATP1B1 (*SLCO1B1*)

OATP1B1 (OATP2, OATP-C, LST-1) is primarily expressed on the basolateral membrane of hepatocytes in the human liver. Based on its localization and it being an uptake transporter, the primary role of OATP1B1 is believed to be removal of substrates from the blood into the liver [79, 80], presumably for subsequent elimination. A large number of structurally diverse drugs are known substrates for OATP1B1, including pravastatin [80, 81], rosuvastatin [82], atorvastatin [83], pitavastatin [84], cerivastatin [85], fluvastatin [86], atrasentan [87], bosentan [88], benzylpenicillin [78], rifampicin [89], caspofungin [90], enalapril [91], temocapril [81], olmesartan [92], valsartan [81, 93], SN-38 (active metabolite of irinotecan) [94], methotrexate [79], and troglitazone sulphate [95]. OATP1B1 represents a mechanism underlying both drug-drug interactions due to competition at the transporter and pharmacokinetic variation due to genetic polymorphisms in the gene encoding the OATP1B1 protein, *SLCO1B1*.

At least 17 SNPs have been identified in *SLCO1B1* [96, 97]. However, in regards to any possible changes in function only 14 have been studied *in vitro*, and even fewer studied *in vivo*. In humans, the 521T>C variant has consistently been found to cause a functional decrease in OATP1B1 activity based on altered *in vitro* transport of a number of substrates, including estrone-3-sulphate, estradiol-17 β -D-glucuronide, pravastatin, atorvastatin, cerivastatin, rifampicin, and SN-38 [83, 94, 97-99]. This variant is relatively common in non-African populations with 8-20% of Caucasians, 9-16% of Chinese, and 10-16% of Japanese populations. These studies also identified another SNP that has a possible impact on OATP1B1 function at the 388 A>G locus, but it should be noted that there is some inconsistencies with the reported *in vitro* data. Interestingly the 521T>C and 288A>G variants are in linkage disequilibrium and exist in several haplotypes together (Table 2).

Traditionally the *SLCO1B1**1A, *SLCO1B1**1B, *SLCO1B1**5, and *SLCO1B1**15 haplotypes have been identified in patient populations. Furthermore, individuals of European ancestry are further divided into additional haplotype groups based on presence or absence of two variants found in the promoter region of the *SLCO1B1* gene, namely -11187G>A and -10499A>C. Europeans with the -11187G>A variant are classified as *16 (~7.9% of population) and those with the -10499A>C variant are classified as *17 (~6.9% of population) [100]. Several drugs have been studied *in vivo* for any possible associations of *SLCO1B1* SNPs or

Table 2. Major Haplotypes in the *SLCO1B1* Gene

Nomenclature	SNPs			
	-11187	-10499	388	521
<i>SLCO1B1</i> *1A	G	A	A	T
<i>SLCO1B1</i> *1B	G	A	G	T
<i>SLCO1B1</i> *5	G	A	A	C
<i>SLCO1B1</i> *15	G	A	G	C
<i>SLCO1B1</i> *16	G	C	G	C
<i>SLCO1B1</i> *17	A	A	G	C

haplotypes with systemic exposure to substrates or drug-induced toxicity, such as repaglinide, fexofenadine, and a wide range of statins [83, 94, 97-99]. Generally, there is a variant-dependent change in pharmacokinetics, such that individuals that are homozygous for the 521 T>C variant (CC) have the highest plasma concentration, which is in line with *in vitro* data suggesting that this variant leads to a decrease in function of OATP1B1.

Statins (HMG-CoA reductase inhibitors) are widely used as prophylactic treatment for the risk of cardiovascular events and mortality. Several of the statins, including simvastatin, rosuvastatin, and pravastatin, are well tolerated and appear to have a wide safety margin [101, 102]. While statins have relatively low-to-medium bioavailability (≤ 5 up to 30%), they are generally associated with high inter-individual pharmacokinetic variability, even up to 10-fold or more [100, 103-106]. One possible cause of this variability could be genetic variation in the genes encoding OATPs. Since statins are primarily metabolized in the liver, the hepatic uptake of these drugs could be a critically important rate-limiting step in their clearance, which gives the importance of OATPs further weight [107]. Several members of the OATP family have been identified as capable of transporting statins, including OATP1B1, OATP1B3, OATP2B1, and OATP1A2 [82, 108-110]. Of these transporters, OATP1B1 has been the most extensively characterized in regards to an association between genetic variants and statin pharmacokinetics.

Using single SNP analysis, the area under the curve (AUC) and peak concentration (C_{max}) of pravastatin were 232% and 274% increased in individuals that carried the *SLCO1B1* 521CC genotype [103]. The 521T>C variant was also associated with a 221% increase in the AUC, a 200% increase in C_{max} for simvastatin acid, although no associations were noted for clearance or half-life [100]. Individuals that are homozygous variant at the 521 locus also demonstrate increased AUC and C_{max} for atorvastatin and rosuvastatin, with the increase for atorvastatin being more pronounced (144% vs. 65% increase) [111].

Studies that included haplotype analyses have also confirmed the importance of the 521T>C variant in their populations. For example, the plasma concentrations of pravastatin were highest in volunteers that had the *17 haplotype, which includes the -11187G>A, 388A>G, and 521T>C variants [96]. There is some evidence that, independent of the 521T>C SNP, the 388A>G variant may be associated with an increased activity of OATP1B1, since patients carrying the *SLCO1B1**1B haplotype (388G, but 521T) had decreased systemic exposure to pravastatin [81, 112]. However this is possibly inconsistent with the previously mentioned *in vitro* studies.

Since the mechanism of action of statins is dependent on inhibiting HMG-CoA reductase in hepatocytes, any decrease in the uptake of these drugs into the liver could reduce their efficacy and

increase the risk of systemic toxicity, especially statin-induced myopathy [108, 113]. The ability of pravastatin to reduce plasma cholesterol and lathosterol is significantly impaired in individuals carrying the *SLCO1B1**17 haplotype [114]. Furthermore, an impaired efficacy of pravastatin, simvastatin, and atorvastatin on cholesterol reduction was found in Japanese patients expressing variants in the 521 T>C SNP [115].

Several other *SLCO1B1* SNPs have been identified *in vitro* as leading to a change in OATP1B1 function; however many of these have not been evaluated *in vivo*. While a lot of interesting associations have been found between *SLCO1B1* variants and pharmacokinetics, especially for statins like pravastatin, more work needs to be done in the field of *SLCO1B1* pharmacogenetics. In particular, many other compounds that have been identified as substrates for OATP1B1 should be examined for any possible impacts of variants, including antibiotics, chemotherapeutics, targeted cancer agents, bilirubin, and circulating hormones, such as prostaglandin, estradiols, and androgens. Furthermore, the majority of studies have focused on a handful of SNPs that may not represent critical variants yet to be studied or identified. While there is a substantial amount of evidence that genetic variation in the gene encoding OATP1B1 contributes to interindividual pharmacokinetic and pharmacodynamic variability, future studies should expand upon this knowledge and further the field of pharmacogenetics.

OATP1B3 (*SLCO1B3*)

Like OATP1B1, OATP1B3 (OATP8, LST-2) is predominantly expressed in the basolateral membrane of hepatocytes in humans [116], and transports a wide range of structurally diverse compounds, with a certain degree of overlap in substrate specificity between the two transporters. However, it should be noted that according to currently published findings OATP1B3 appears to be unique in transporting digoxin, and possibly also the taxanes docetaxel and paclitaxel [117-119]. While *in vitro* studies are either lacking or contradicting about common SNPs in the gene encoding OATP1B3, *SLCO1B3*, there has been some work evaluating the effect of these variants on pharmacokinetics of OATP1B3 substrates.

Patients with end-stage renal failure are often prescribed digoxin to combat the congestive heart failure from undergoing hemodialysis. Under the conditions of normal renal function, digoxin is primarily excreted unchanged in the urine (~80% of the drug), with the remainder eliminated by bile excretion via the liver [120]. The hepatic contribution to digoxin elimination in patients undergoing hemodialysis is increased by 75% [121], and may be even further increased with end-stage renal failure. In a Japanese population associations between trough concentration-to-dose ratios and 4 *SLCO1B3* variants were noted; these variants included 2 deletions in exon 1 (-28 to -11 and -7 to -4) and 2 SNPs (334T>G and 699G>A) [122]. The 2 deletion variants were found to be in linkage disequilibrium and the 2 SNPs were also found to be in linkage disequilibrium [123]. In this study, the ratio of concentration-to-dose was significantly lower in those patients that expressed the deletion allele, and a similar trend was seen in patients expressing the reference SNP alleles. These findings suggest that the inter-individual variation in digoxin clearance is partly explained by variants in *SLCO1B3*, and that genotyping may allow for dosage adjustments to decrease this variability.

In a recent study, several polymorphisms in *SLCO1B3* were evaluated for an effect on the pharmacokinetics of docetaxel [124]. A total of 92 adult Caucasian cancer patients were treated with docetaxel and genotyped for 6 variants in *SLCO1B3*. These included the 334T>G (*2), 439A>G (*3), 699G>A (*4), 767G>C (*5), 1559A>C (*6), and 1679T>C (*7) polymorphisms. Haplotype analysis revealed 12 haplotypes of minor frequency, with the exception of one that was present in 64% of the patients (334G,

439A, 699A, 767G, 1559A, and 1679T). It should be noted that this haplotype contains the reference allele for all of the variants except 334T>G and 699G>A, which are in high linkage disequilibrium ($D'=0.86$). Unfortunately, this study failed to find a significant association between any *SLCO1B3* SNPs or haplotypes and docetaxel clearance. Another study did find a highly significant association between the risk of docetaxel-induced leucopenia/neutropenia and SNPs in *SLCO1B3* [125]. Out of 23 variants analyzed 4 (334T>G, 699G>A, an A>G change in intron 12, and a C>T change in an undefined region) were identified as having a significant correlation with docetaxel toxicity. The A>G intronic polymorphism was able to correctly predict 69.2% of the severe docetaxel-induced leucopenia/neutropenia seen in their population. Although this positive association was only performed in a relatively small Japanese population it supports the growing hypothesis that pharmacogenetics might some day be used to reduce inter-patient variability or to predict drug-induced toxicities.

Another OATP1B3 substrate that has not been extensively tested for pharmacogenetic alterations is the related chemotherapeutic agent, paclitaxel. The clearance of paclitaxel was measured in a cohort of 90 cancer patients, but was not associated with either the 334T>G or the 699G>A SNPs [119]. These studies on digoxin, docetaxel, and paclitaxel demonstrate that more research is necessary to fully understand how genetic variation in *SLCO1B3* may impact the pharmacokinetics and/or toxicity of substrates for OATP1B3.

Recently, the role of uptake transporters, such as OATP1B3, has been evaluated for compounds classically thought of as being specific markers of cytochrome P450 (CYP) activity [126]. This study focused on the role of SLCs on the non-invasive CYP3A phenotype probes midazolam and erythromycin. Even though these two CYP3A substrates are both used as a marker for metabolic activity they do not correlate with each other when both are administered in patients. Midazolam was not identified as a substrate for any of the transporters tested *in vitro*, while erythromycin was found to be a very good substrate for OATP1B3. Furthermore, metabolism of erythromycin, as measured by the erythromycin breath test, was significantly faster in patients that expressed the 334G variant. The *in vitro* uptake of erythromycin was significantly increased in cells expression of this variant, suggesting that altered erythromycin breath test seen in those patients with the 334G polymorphism may be due to an increased functional change in OATP1B3 caused by the SNP. These studies taken together strongly suggest that future studies should evaluate the impact of genetic variation on drugs that are substrates for OATP1B3 and that by better understanding the role of pharmacogenetics we can possibly improve drug efficacy and reduce toxicity.

OATP1A2 (*SLCO1A2*), OATP2B1 (*SLCO2B1*), AND OTHER OATPS

OATP1A2 (OATP, OATP-A) is expressed in a wide variety of tissues, including the duodenal section of the intestine [127], cholangiocytes of the bile duct [128], blood-brain-barrier [128, 129], brain [129], and kidneys [128]. Similar to other OATPs, a wide range of drugs and endogenous compounds have been found to be either substrates for or inhibitors of OATP1A2 [130]. While several genetic variants in the gene encoding OATP1A2, namely *SLCO1A2*, have been identified in humans and several of these variants have been shown to cause functional changes *in vitro*, no studies have yet evaluated any role that *SLCO1A2* variants may have *in vivo* on drug pharmacokinetics, efficacy, or toxicity.

Similar to OATP1A2, OATP2B1 (OATP-B), encoded by *SLCO2B1*, is expressed in a variety of tissues, including liver, intestine, placenta, heart, and skin [78, 117, 131-134]. Several *SLCO2B1* variants have been identified and have been associated with reduced function *in vitro*, but no data is publicly available on any associations between these variants and drug effects *in vivo*.

Furthermore, while tissue distribution, substrates, and functional variants have been identified for other OATPs, such as OATP1C1, OATP2A1, OATP3A1, OATP4A1, OATP4C1, OATP5A1, and OATP6A1, to date there have been no *in vivo* studies to evaluate any effect these variants may have on drugs used in humans. Despite a wealth of knowledge that has been generated over the past few years on the pharmacogenetics of a variety of drugs that are substrates for OATPs, they illuminate the real need for more studies to evaluate the impact of genetic polymorphisms on therapeutic drugs.

OCT1 (*SLC22A1*)

The SLC, organic cation transporter 1 (OCT1) is encoded by the *SLC22A1* gene. Similar to OATP1B1 and OATP1B3, OCT1 is primarily expressed on the basolateral membrane of hepatocytes [135, 136]. Due to its location, it is also believed to play a role in liver-mediated metabolism and excretion of substrate drugs. Currently several polymorphisms have been identified in the *SLC22A1* gene, which have been characterized for function *in vitro* and ethnic distribution [137-141]. In an earlier study, the 1393G>A polymorphism was found to reduce the localization of OCT1 to the surface of the basolateral membrane of hepatocytes [141]. The *SLC22A1* variants 41C>T, 566C>T, 1201G>A, and 1256delATG (a deletion variant) were all associated with decreased uptake activity of metformin, an OCT1 substrate [142], independent of changes in *SLC22A1* mRNA expression [137]. Furthermore, these 4 variants were found to significantly decrease metformin's ability to lower glucose levels in a small population of healthy volunteers. Within this same population these 4 variants were found to be associated with an increase in AUC and C_{max} , and a lower apparent volume of distribution (Vd/F) of metformin [143]. This *in vitro* and *in vivo* data combined strongly suggests that variants in the gene encoding OCT1 can directly impact the pharmacokinetics and liver-mediated effects of metformin. However, a separate study looked at associations between *SLC22A1* variants and chronic metformin treatment response and did not see a significant prevalence of variants between patients grouped as responder or nonresponder [144]. Several possible explanations could exist for the discrepancy between these studies. While it is not explicitly reported by both groups, it is likely that different ethnic groups were studied and may lead to a difference in prevalence of key variants. Another possibility is that genetic alteration in an important renal transporter, OCT2, may have altered expression/function in the populations of these two patients or that the relatively small population sizes failed to have adequate statistical power. Furthermore, genetic effects could have been reduced or masked in the patient population by other concomitant medications or treatments, as compared to the healthy volunteers. The discrepancies between these two studies emphasize the need for larger, more robust studies into possible effects *SLC22A1* polymorphisms may have on therapeutic drugs.

CONCLUSIONS

Variation in the pharmacokinetic profile of a therapeutic drug in a patient population is the net result of many complex interactions between genetic, physiological, and environmental factors. A number of theories have been put forward to explain the observed inconsistencies between the various substrate drugs evaluated, including environmental factors, exogenous chemicals, food constituents, herbal preparations, and/or therapeutic drug use that may induce or inhibit the function or expression of these protein (e.g., rifampin [145] and St. John's wort [146]), thus affecting the phenotypical activity of ABC and/or SLC transporters. This is particularly important for patients treated with a wide variety of medications concomitantly with their therapeutic regimen [147]. In order to understand and reduce inter-individual pharmacokinetic and pharmacodynamic variability, a better understanding of how drugs are transported in the body is needed. These transporters offer possible mechanisms underlying changes in drug resistance,

absorption, distribution, metabolism, excretion, as well as toxicity and efficacy. Larger studies are needed to properly study these polymorphisms and any significant haplotypes, especially in light of how all of these transporters work in a very complex orchestra that together impact the drugs that we use in the clinic.

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