Pharmacogenetics And Pharmacogenomics of Drug Transport

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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 (Pglycoprotein), ABCC2 (MRP2), and ABCG2 (BCRP), more studies have been conducted in recent years evaluating genes encoding solute ccarriers (SLC) that mediate the cellular uptake of drugs, such as SLCO1B1 (OATP1B1) and SLC22A1 (OCT1).*

Most drug responses are determined by the interplay of several gene products that influence pharmacokinetics and pharmacodynamics, i.e., drug metabolising enzymes, drug transporters, and drug targets.

I. INTRODUCTION

Phatmacogenetics 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 sufficientl 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 .

Pharmacogenomics is a rapidly growing field of research into the ways in which genetic variation affects drug response-

- Identifying genetic markers for differences in the way people metabolise drugs
- Developing genetic tests that predict how individual patients will respond to drugs (i.e. statins, cancer therapies)

Goal

- To develop precisely targeted, optimal drug therapy
- Minimising drug related adverse events.

Pharmacogenetics of Drug Transporters

TP-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 thereb yaffect toxicity and response to drug treatment or predisposition to disease.

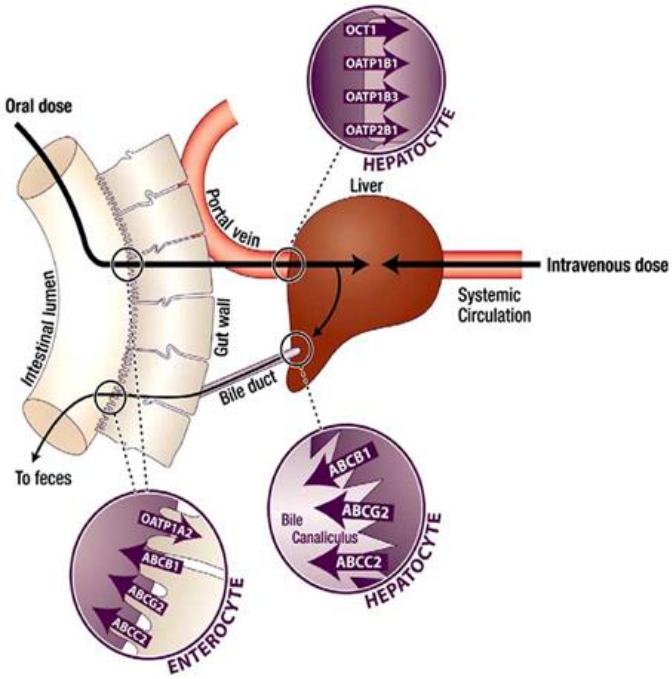


Fig. (1). Schematic showing localization of ABC and SLC transporters involved in pharmacokinetics, specifically oral absorption from the GI tract, hepatic uptake, and elimination in the bile.

Table 1. Major Haplotypes in the *ABCB1* Gene

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

*Denotes variant number by exon [14]

HEPATOCYTE

- OCT1
- OATP181
- OATP183
- OATP281
- ABCB1
- ABCG2
- ABCC2

ENTEROCYTE

- OATP1A2
- ABCB1
- OCT1
- ABCG2
- ABCC2

Table 2. Major Haplotypes in the *SLCO1B1* Gene

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

ABCB1 (ABCB1)

The ABCB1 gene, the first ABC transporter identified and the best characterised, 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 characterised through its ability to confer a multidrug 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.

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 localised 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 [16], and the application of these screening systems has resulted in an explosion in the identification of novel selective inhibitors of this transporter [17]. 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 [18], where it is likely involved in the secretion of certain important nutrients into milk, such as riboflavin (vitamin B2) [19].

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 [20,21], presumably for subsequent elimination. A large number of structurally diverse drugs are known substrates for OATP1B1, including pravastatin [22, 23], rosuvastatin [24], atorvastatin [25], pitavastatin [26], cerivastatin [27], fluvastatin [28], atrasentan [29], bosentan [30], benzyl-penicillin [20], rifampicin [31], caspofungin [32], enalapril [33], temocapril [23], olmesartan [34], valsartan [23, 35], SN-38 (active metabolite of irinotecan) [36], methotrexate [21], and troglitazone sulphate [37]. 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.

OATP1B3 (SLCO1B3)

Like OATP1B1, OATP1B3 (OATP8, LST-2) is predominantly expressed in the basolateral membrane of hepatocytes in humans [38], 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 [39-40]. 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 [41]. The hepatic contribution to digoxin elimination in patients undergoing hemodialysis is increased by 75% [42], 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) [43]. The 2 deletion variants were found to be in linkage disequilibrium and the 2 SNPs were also found to be in linkage disequilibrium [44]. 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 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.

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 [45], cholangiocytes of the bile duct [46], blood-brain-barrier [46, 47], brain [47], and kidneys [46]. Similar to other OATPs, a wide range of drugs and endogenous compounds have been found to be either substrates for or inhibitors of OATP1A2 [48]. 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.

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 . 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 characterised for function in vitro and ethnic distribution . 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 . 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, independent of changes in SLC22A1 mRNA expression . 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 Cmax, and a lower apparent volume of distribution (Vd/F) of metformin .

Pharmacogenomics of Drug Transport

Individual Transporters of Pharmacogenomic Interest.

ABC Transporters

ATP-binding cassette (ABC) transporters are present in cellular and intracellular membranes and can be responsible for either importing or removing (efflux) of substances from cells and tissues. They often transport substances against a concentration gradient by using the hydrolysis of ATP to drive the transport. There are at least 49 ABC transporter genes, which are divided into seven different families (A-G) based on sequence similarity. Three of these seven gene families are particularly important for drug transport and multiple drug resistance in tumor cells7: [49] the ABCB1 gene, encoding MDR1 (also known as P-glycoprotein); [50] ABCG2 (breast cancer resistance protein); and [51] the ABCC family (ABCC1 through ABCC6) or multidrug resistance proteins (MRP).

ABC transporters are characterised as such by the homology of their ATP binding regions. All families but one (ABCG2) contain two ATP binding regions and two transmembrane domains. The transmembrane domains contain multiple alpha helices, which span the lipid bilayer. The number of alpha helices in a transmembrane domain differs depending on the family. The ATP binding regions are located on the cytoplasmic side of the membrane. As well as being important mediators of resistance in human chemotherapy, ABC transporters are also found in bacteria and can contribute to the development of resistance to multiple antibiotics. The localization of the proteins depends on the cell type, such as hepatocyte, enterocyte, and renal proximal tubule. The majority of ABC transporters move compounds from the cytoplasm to the outside of a cell, although some move compounds into an intracellular compartment such as the endoplasmic reticulum, mitochondria, or peroxisome.

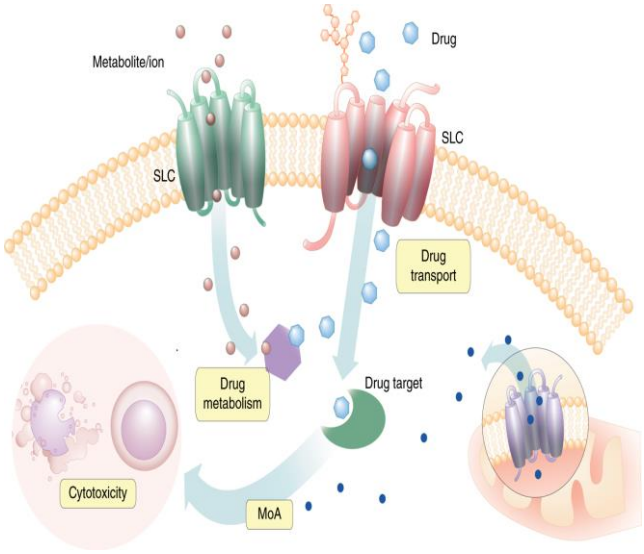
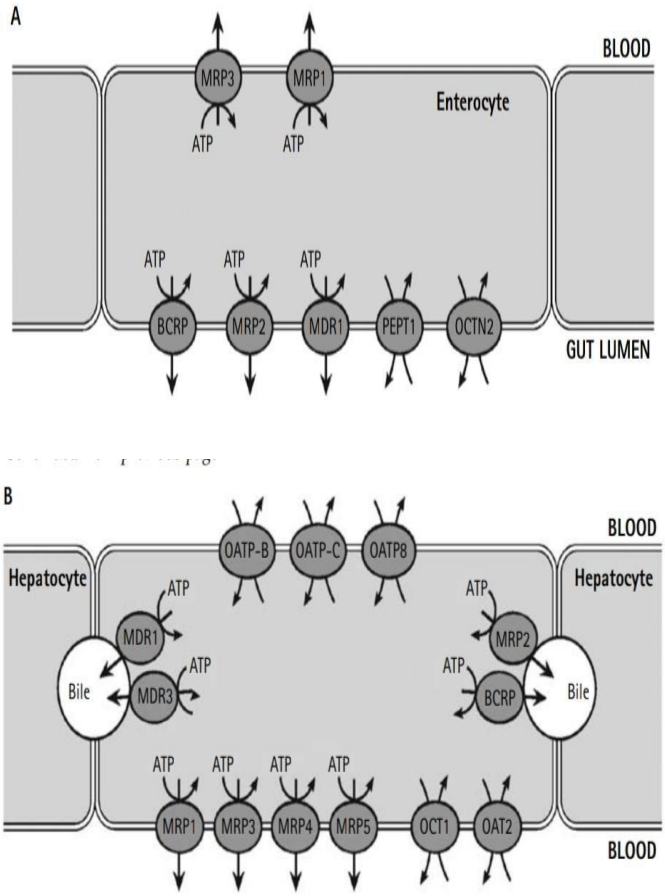


Fig (2). Mechanisms of action



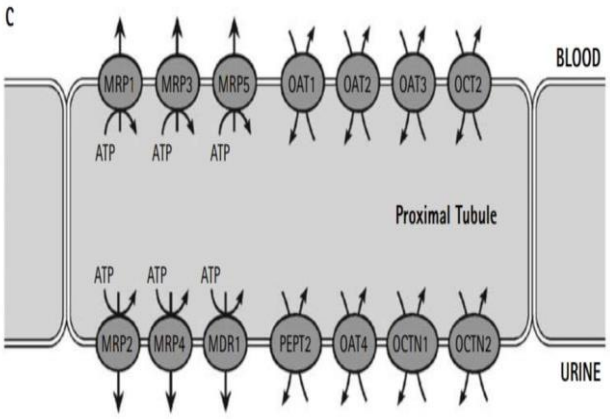


Fig . Localization of transporters in differing cell types. A) small intestine enterocyte, B) hepatocyte with canaliculi, and C) renal proximal tubule. In addition to those transporters discussed in the text, other transport proteins with protective and possible pharmacogenomic relevance are shown. OCTN1 and OCTN2: novel organic cation transporters-1 and 2 (SLC22A4, SLC22A5), OATP-B: organic anion transporting polypeptide-B (SLCO2B1), OATP-C (SLCO1B1), OATP8 (SLCO1B3), OCT1 (SLC22A1), OAT2 (SLC22A7). Figure adapted from reference [52]

Table based on MOA[54]

Transporter (common name)	**Gene Name (systematic protein name)**	**Tissue Localization and Position in Polarized Cells**	**Representative Substrates**	**Example Polymorphisms and Phenotype Effect**
MDR1, P-gp	ABCB1	Apical: kidney, liver, brain, intestine, placenta	Anthracyclines, cyclosporine, taxanes, vinca alkaloids, doxorubicin	3435C>T (↓ intestinal expression, ↓ substrate bioavailability) 2677G>T/A (↑ response to docetaxel/cisplatin)
MRP1	ABCC1	Lung, ubiquitous on basolateral membrane epithelial: e.g., choroid plexus (blood-cerebrospinal fluid barrier), testes	Anthracyclines, vinca alkaloids, methotrexate, glutathione conjugates, leukotriene C4, bilirubin, glutathione, saquinavir, ritonavir, difloxacin	Arg433Ser (↑ doxorubicin resistance) Cys433Ser (↓ vincristine resistance)
MRP2, cMOAT	ABCC2	Apical: liver, proximal tubule, small intestine, placenta	Bilirubin conjugates, glucuronide, sulphate & glutathione conjugates of various drugs, unconjugated anionic drugs (e.g., methotrexate): broad substrate specificity	↑ cisplatin resistance 2302C>T, 2439T>C (Dubin-Johnson syndrome) c.3972C>T (↑ hepatocellular carcinoma)

MRP3	ABCC 3	Basolateral: liver, kidneys, intestines	Glucuronidated substrates (acetaminophen, morphine, estradiol, bilirubin)	211C>T (↓ expression),47 (worsen prognosis: lung cancer) Arg1381Ser, Ser346Phe, & Ser607Asn (↓ transport activity)
MRP4 and MRP5	ABCC 4 and ABCC 5	Prostate (asolateral), kidney, lung, brain, pancreas, lymphocytes, platelets , heart (MRP5)	Azidothymidine, mercaptopurine, thioguanine, cladribine, abacavir	MRP4: rs3765534 (↑ thiopurine sensitivity), Gly187Trp, Gly487Glu (↓ azidothymidine transport),97 A3463G (↓ tenofovir efflux)
MRP6	ABCC 6	Basolateral: liver, kidney	Glutathione conjugates, leukotriene C4	Many: e.g., c.3421C>T (pseudoxanthoma elasticum)
BCRP, MXR, ABCP	ABCG 2	Placenta syncytiotrophoblasts, hepatocyte canalicular, apical intestinal epithelia, vascular endothelial	Doxorubicin, daunorubicin, mitoxantrone, topotecan, prazosin, uric acid	↑ anthracyclines, mitoxantrone, SN-38 resistance 421C>A (worsen prognosis: lung cancer & cisplatin), (↑ gefitinib-induced diarrhea) Gln141Lys (↑ chemotherapy-induced diarrhea)
Serotonin transporter	SLC6 A4	Neurons, heart valve, intestine (apical)	Serotonin	"l" allele (↑ psychopathology) "s" allele (↓ antidepressant efficacy, citalopram-induced diarrhea)
Reduced folate carrier (RFC-1)	SLC19 A1	Apical: kidney, leukemic cells, wide distribution	Methotrexate, leucovorin, pemetrexed	80AA (↑ methotrexate polyglutamation)
OATP 1B1	SLCO 1B1	Basolateral: liver, brain	Pravastatin, atorvastatin, lovastatin, cerivastatin, bilirubin, digoxin, estradiol, thyroid hormones, mycophenolate	521T>C (↓ pravastatin AUC)
OATP 1B3	SLCO 1B3	Basolateral: liver	Methotrexate, glucuronidated estradiol, mycophenolate	334T>G (GG ↑ mycophenolate AUC)

PEPT 1 and PEPT 2	SLC15 A1, SLC15 A2	PEPT1: small in-testine, duode-num (apical) PEPT2: broad dis-tribution	Cephalexi n, other β-lactam antibiotics , ACE inhibitors (?), valacyclo vir, peptides	Arg57His (transport function loss)
RFC-1	SLC19 A1	Broad distributi on	Methotrex ate	80A>G (AA ↑ plasma folate)77(↑ remission of rheumatoid ar-thritis with metho-trexate)
CNT1 , CNT2 , CNT3	SLC28 A1, SLC28 A2, SLC28 A3	Intestinal /renal epithelia, liver, macroph ages, leukemic cells	Didanosin e, idoxuri-dine, zidovudin e, cladribine , fludara-bine, gemcitabi ne, capecitabi ne	Unclear relevance for polymorphisms
ENT1, ENT2, ENT3, ENT4	SLC29 A1, SLC29 A2, SLC29 A3, SLC28 A4	Intestine, liver, kid-ney, placenta	Pyrimidin e and/or purine nucleosid es, adenosine , gemcit-abine, cladribine , fludarabin e	Unclear relevance for polymorphisms

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