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PharmGKB very important pharmacogene: *SLCO1B1*

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Introduction

The solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene encodes for a membrane-bound sodium-independent organic anion transporter protein (OATP1B1) that is involved in active cellular influx of many endogenous and xenobiotic compounds. *SLCO1B1*, formerly known by several other names including organic anion transporter 2 (OATP2), OATPC, liver-specific transporter 1 (LST1), and *SLC21A6*, is located on chromosome 12 and encodes a 691 amino acid protein with 12 transmembrane helices [1,2]. The gene is a member of the family of SLC21 (human: OATP, rodent: Oatp) transporters [3,4]. OATP1B1 is expressed predominantly on the basolateral membrane of hepatocytes [5,6], where it mediates active intracellular hepatic transport of various anionic compounds [5,6].

The protein sequence of OATB1B1 is similar to those of other organic anion transporters. The human protein shares 64% sequence identity with rOatp4 and 65% sequence identity with mOatp4 and 44–47% with other rodent Oatps [3]. Compared with other members of the human organic anion transporters, OATP1B1 is the most similar to OATP1B3 (*SLCO1B3*, previously known as *SLC21A8*). These two proteins share 80% amino acid sequence identity, are expressed predominantly in the liver, and have similar substrate selectivity [1]. Functionality between these two human transporters in the *SLC21* family can be distinguished using estrone-3-sulfate, an OATP1B1-selective ligand, and cholecystokinin octapeptide, an OATP1B3-selective ligand [7]. Note that the selectivity for estrone sulfate applies only in distinguishing the transport between OATP1B1 versus OATP1B3; estrone sulfate is an excellent substrate for other organic anion transporters, such as OAT3 (*SLC22A9*)[8].

Recent reviews describe the role of OATP1B1 in general drug disposition [2] and, specifically, in 3-hydroxy-3-methyl-glutaryl-CoEnzyme A reductase reductase inhibitor (statin) pharmacokinetics [9]. As OATP1B1 mediates intrahepatic transport of pharmaceutical agents, *SLCO1B1* is an important pharmacokinetic gene – and, as described below, an important pharmacogene.

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SLCO1B1 substrates and inhibitors

OATP1B1 mediates active transport of many endogenous substrates, such as bile acids, xenobiotic compounds, and a wide panel of pharmaceutical compounds. Table 1 lists endogenous ligands and Table 2 lists drugs and xenobiotics that have been reported to be substrates for this transporter. Several molecules have been excluded from the table because of conflicting reports. These include fexofenadine, an H1 receptor antagonist, the active metabolite of terfenadine [7,33], simvastatin, the 3-hydroxy-3-methyl-glutaryl-CoEnzyme A reductase inhibitor [11,14], and bilirubin [34,35]. For the case of bilirubin, conflicting reports may be because of the difficulty in working with bilirubin because of its photolabiity [36,37].

OATP1B1-dependent transport is an important step in mediating drug hepatic clearance. We would like to highlight one class of drugs, the statins, because statins are widely prescribed for cardiovascular disease (CVD) risk reduction [9,38]. OATP1B1 transport is particularly important for hepatic accessibility of pravastatin, as this compound is too hydrophilic to gain significant hepto-cellular entry through passive transport [39]. OATP1B1-dependent transport may also be important for the acid (active) form of simvastatin, a lactone, (and other statins less hydrophobic than pravastatin) as *SLCO1B1* variants were recently associated with simvastatin-induced myopathies [40], implying that OATP1B1 was involved with simvastatin transport.

In addition to substrates transported by OATP1B1, there are many pharmaceutical compounds known to inhibit OATP1B1 transport activity. Owing to the nature of these experiments, it is known that these compounds interact with *SLCO1B1* but it is not known (except for the case of repaglinide) whether these compounds are actively transported by the transporter. This list of molecules is given in Table 3. All inhibitors listed were identified by in-vitro experiments in cells expressing *SLCO1B1*. We include the half maximal inhibitory concentration or Ki values, where available in the manuscripts.

These data indicate the wide substrate selectivity of OATP1B1 and show that sequence variation at the *SLCO1B1* locus may have a sizable impact on pharmaceutical response to many a broad range of drugs.

SLCO1B1 variants and their functional consequences

The *SLCO1B1* gene spans 15 exons and 190 common variants with minor allele frequency greater than 5% have been identified within this gene (www.hapmap.org). Of these, two common nonsynonymous *SLCO1B1* variants have been well characterized: rs2306283 (*SLCO1B1*:492A > G on reference sequence NM_006446.4, previously referred to as 388A > G; encoding OATP1B1:N130D) and rs4149056 (*SLCO1B1*: 625T > C on reference sequence NM_006446.4; commonly referred to as T521C, encoding OATP1B1:V174A). These two variants are in partial linkage disequilibrium. Consequently, there are four important haplotypes: *SLCO1B1**1A, containing neither variant, *SLCO1B1**1B (rs2306238), *SLCO1B1**5 (rs4149056) and *SLCO1B1**15 (both) [43].

In cellular studies, OATP1B1-Ala174 and associated haplotypes, particularly *SLCO1B1**15, have shown reduced transport activity in comparison with OATP1B1-Val174 [11,14,22,43-45]. This may be a result of intracellular protein sequestration and reduced surface expression [11]. Several studies suggest that the OATP1B1:N130D protein had increased transporter function but these reports have been inconsistent [11,14,22,43-45]. *SLCO1B1* single nucleotide polymorphisms and haplotypes have been implicated in altered pharmacokinetic handling and pharmacodynamic response for several major drug classes.

As mentioned previously, OATP1B1-dependent transport is an important step in mediating hepatic clearance of statins. The minor allele of *SLCO1B1* T521C (present in *5, *15, *16, *17 haplotypes) has been consistently associated with elevated circulating concentrations of statins, as measured by plasma area under the curve (AUC) values or Cmax [38,46-50], implying reduced hepatic access. Because statins act primarily through hepatic mechanisms, reduced hepatic statin availability associated with *SLCO1B1* T521C may also influence statin efficacy. However, studies describing a relationship of this variant with either statin-mediated LDL-cholesterol lowering or CVD risk reduction are conflicting and the evidence remains weak [51-56]. Collectively, these data suggest that any effect of *SLCO1B1* T521C on statin efficacy is minor. In contrast, reduced transporter function may promote adverse drug responses through prolonged systemic statin exposure. This theory is supported by a recent genome-wide association study that identified this same *SLCO1B1* variant (rs4149056) as the genotype most predictive of simvastatin-induced myotoxicity [40].

Associations have also been observed between *SLCO1B1* T521C and pharmacokinetic handling and drug efficacy for other classes of drugs. Repaglinide is an antidiabetic agent and OATP1B1 substrate. Repaglinide plasma AUC was increased in *SLCO1B1*:T521C carriers in several studies across a range of dosages [20,57,58]. Furthermore, increased repaglinide efficacy, as measured by plasma glucose AUC reductions, was also observed in these studies [20,57]. Notably, *SLCO1B1*:A388G (rs2306283) was associated with decreased repaglinide plasma AUC and reduced efficacy [20]. No association was observed between these variants and pharmacokinetic handling of a second meglitinide family member, nateglinide [20]. *SLCO1B1*: T521C, as observed in the *5 and *15 haplotypes, has also been associated with increased irinotecan plasma AUC, an anticancer agent, and, in two studies, was predictive of irinotecan-induced neutropenia [59-62]. This variant has also been associated with altered steady state concentrations of the antihypertensive agent, torasemide [63].

SLCO1B1:T521C has also been associated with increased serum bilirubin levels. Bilirubin is an endogenous heme metabolite; low plasma bilirubin concentrations have been associated with elevated CVD risk [64]. *SLCO1B1*: T521C carriers exhibited increased serum bilirubin (as well as estrone sulfate) concentrations in two Caucasian populations [44,65]. These results are further supported by the results of a recent genome-wide association study meta-analysis that identified rs4149056 as the major genetic predictor of serum bilirubin levels in a combined population of approximately 9500 Caucasians [66].

Population frequencies

The genotypic frequencies for the single nucleotide polymorphisms s and variants identified seem to be dependent on ethnicity. Summary is given in Table 4.

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Table 1

Endogenous ligands reported to be transported by OATP1B1

Endogenous substrates	Ligand class	Test system	Measurement	Km (μmol/l)	References
Taurocholic acid	Bile acid	293c18 cells	Transport	33.8	[6]
		Xenopus oocytes	Transport	13.6	[10]
		HeLa cells	Transport		[11]
Dehydroepiandrosterone sulfate	Conjugated steroid	293c18 cells	Transport		[6]
		Xenopus oocytes	Transport		[10]
		HEK 293	Transport		[5]
Estradiol-17beta-glucuronide	Conjugated steroid	Xenopus oocytes	Transport		[10]
		HeLa cells	Transport	5.1	[11]
		HEK 293	Transport		[12]
		HEK 293	Transport		[5]
		CHO cells	Transport	5.4	[13]
Estrone-3-sulfate	Conjugated steroid	Xenopus oocytes	Transport		[10]
		HeLa cells	Transport	0.54	[11]
		CHO cells	Transport	2.4	[13]
Prostaglandin E2	Eicosanoid	Xenopus oocytes	Transport		[10]
		HEK 293	Transport		[12]
Thromboxane B2	Eicosanoid	Xenopus oocytes	Transport		[10]
Leukotriene C4	Eicosanoid	Xenopus oocytes	Transport		[10]
Leukotriene E4	Eicosanoid	Xenopus oocytes	Transport		[10]
Thyroxine (T4)	Thyroid hormones	Xenopus oocytes	Transport	3	[10]
		293c18 cells	Transport	3	[6]
Triiodothyronine (T3)	Thyroid hormones	Xenopus oocytes	Transport	2.7	[10]

Columns are, in order: endogenous substrate; ligand class; test system, that is, cell system for in-vitro experiment versus in-vivo experiment; experimental measurement; Km, where available, and finally, references. Several ligands were studied by different investigators and these data are listed in separate rows. Data organized by ligand class.

Table 2

Drugs and xenobiotics reported to be transported by OATP1B1

Drug/xenobiotic substrates	Indication	Test system	Measurement	Km (μmol/l)	References
Pravastatin	HMG CoA reductase inhibitor	293c18 cells	Transport	30	[6]
		HEK 293	Transport		[14]
		Human hepatocytes, Xenopus oocytes	Transport	11.5	[15]
Atorvastatin	HMG CoA reductase inhibitor	HEK 293	Transport		[14]
		293c18 cells	Inhibition of pravastatin transport		[6]
	HMG CoA reductase inhibitor	HEK 293	Inhibition of Estradiol 17ß-D-Glucuronide transport		[16]
Lovastatin	HMG CoA reductase inhibitor	293c18 cells	Inhibition of pravastatin transport		[6]
Lovastatin (acid)	HMG CoA reductase inhibitor	HEK 293	Inhibition of Estradiol 17ß-D-Glucuronide transport		[16]
Cerivastatin	HMG CoA reductase inhibitor	HEK 293	Transport		[14]
Pitavastatin	HMG CoA reductase inhibitor	HEK 293	Transport	3	[17]
		Human hepatocytes	Inhibition of E217ßG and E1S		[18]
Rosuvastatin	HMG CoA reductase inhibitor	HeLa cells	Transport	4.0–7	[19]
Repaglinide	Antidiabetic agent	In-vivo	Patients with different *SLCO1B1* variants have different plasma concentrations		[20]
		In-vivo	Patients with different *SLCO1B1* variants have different plasma concentrations		[21]
7-ethyl-10-hydroxycamptothecin (SN-38)	Irinotecan (anticancer agent) active metabolite	HEK 293	Transport		[22]
Benzylpenicillin	Antibiotic	HEK 293	Transport		[12]
Bosentan	Endothelin receptor antagonists	CHO cells	Transport and inhibition by cyclosporin A, rifampicin		[23]
Atrasentan	Endothelin receptor antagonists	HeLa cells	Transport		[24]
Enalaprilat	ACE inhibitor	HEK 293	Transport	262	[25]

Drug/xenobiotic substrates	Indication	Test system	Measurement	Km (μmol/l)	References
Temocapril	ACE inhibitor	In-vivo	Patients with different *SLCO1B1* variants have different plasma concentrations		[26]
Valsartan	ACE inhibitor	In-vivo	Patients with different *SLCO1B1* variants have different plasma concentrations		[26]
		HEK 293 and human hepatocytes	Transport		[27]
Olmesartan	ACE inhibitor	In-vivo	Patients with different *SLCO1B1*variants have different plasma concentrations		[28]
		HEK 293	Transport		[29]
Caspofungin	Anti-fungal agent	HeLa cells	Transport		[30]
Troglitazone sulfate	Thiazolidinediones	oocytes	Transport		[31]
Methotrexate	Chemotherapeutic agent	HeLa cells	Transport		[11]
Arsenic	Exogenous toxin	HEK 293	Transport		[32]

Columns are, in order: drug or xenobiotic substrate; indication (how drug is used for disease treatment); test system, that is, cell system for in-vitro experiment versus in-vivo experiment; experimental measurement performed; Km, where available, and finally, reference. Several ligands were studied by different investigators and these data are listed in separate rows. Data organized by drug class.

ACE, angiotensin-converting enzyme; HMG CoA, 3-hydroxy-3-methyl-glutaryl-CoEnzyme A reductase.

Table 3

Inhibitors of OATP1B1 identified from in-vitro transport experiments

Drug	Indication	Test cell system	Substrate whose transport was inhibited	Ki or IC_{50} (μmol/l)	References
Rosiglitazone	Thiazolidinedione PPARγ agonist	Xenopus oocytes	Estrone-3-sulfate		[31]
		HEK 293	Sulfobromophthalein	IC_{50}, 6.0	[41]
Pioglitazone	Thiazolidinedione PPARγ agonist	Xenopus oocytes	Estrone-3-sulfate		[31]
Troglitazone	Thiazolidinedione PPARγ agonist	Xenopus oocytes	Estrone-3-sulfate		[31]
		CHO cells	Estradiol-17β-glucuronide	K_i, 1.2	[13]
Cyclosporine A	Immunosupressant	HEK 293	Pitavastatin	K_i, 0.24	[18]
		CHO cells	Bosentan	IC_{50}, 0.3	[23]
Tacrolimus	Immunosupressant	HEK 293	Pitavastatin	K_i, 0.61	[18]
Rifampicin	Antibiotic	HEK 293	Pitavastatin	K_i, 0.48	[18]
		CHO cells	Bosentan	IC_{50}, 3.2	[23]
Rifamycin SV	Antibiotic	HEK 293	Pitavastatin	K_i, 0.17	[18]
		Xenopus laevis oocytes	Sulfobromophthalein	K_i, 2.0	[42]
Glibenclamide	Antidiabetic agent	HEK 293	Pitavastatin	K_i, 0.75	[18]
Ritonavir	HIV protease inhibitor	HEK 293	Pitavastatin	K_i, 0.78	[18]
Paclitaxel	Anticancer agent	CHO cells	Estradiol-17β-glucuronide	K_i, 0.03	[13]
Mifepristone	Synthetic steroid	CHO cells	Estradiol-17β-glucuronide	K_i, 3.3	[13]
Lithocholate	Bile acid	CHO cells	Estradiol-17β-glucuronide	K_i, 0.7	[13]
Clotrimazole	Antifungal agent	CHO cells	Estradiol-17β-glucuronide	K_i, 9.0	[13]
Repaglinide	Antidiabetic	HEK 293	Sulfobromophthalein	IC_{50}, 2.2	[41]

Columns are, in order: Drug that is identified as inhibitor, Indication (how drug is used for disease treatment); cell system used in in-vitro experiment; substrate whose transport was inhibited in the study; Ki or IC50, where available and reference. Several drugs were studied by different investigators and these data are listed in separate rows.

IC_{50}, half maximal inhibitory concentration.

Table 4

Population frequencies of variants described in the text

Common name	rsID	Protein change	Haplotype	African–American [11,67] (%)	Japanese [43] (%)	Asian (includes Japanese) [46,68] (%)	Caucasian [11,67,69,70] (%)
T521C	rs4149056	Val174Ala	*5	1–4	0.7	6–19	12–20
G388A	rs2306283	Asn130Asp	*1b	74–78	54	56–81	37–46
T521C + G388A		Val174Ala + Asn130Asp	*15		10		