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Pharmacogenetics of the organic anion transporting polypeptide 1A2

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Abstract

The solute carrier, human organic anion transporting polypeptide 1A2 (OATP1A2, OATP-A, OATP1 and OATP) is highly expressed in the intestine, kidney, cholangiocytes and the blood–brain barrier. This localization suggests that OATP1A2 may be vitally important in the absorption, distribution and excretion of a broad array of clinically important drugs. Several nonsynonymous polymorphisms have been identified in the gene encoding OATP1A2, *SLCO1A2* (*SLC21A3*), with some of these variants demonstrating functional changes in the transport of OATP1A2 substrates.

Keywords

genetic variant; inhibitor; OATP1A2; pharmacogenetics; SLCO1A2; SNP; substrate; transporter

Human organic anion transporting polypeptide 1A2 (OATP1A2)

In humans the solute carrier (SLC) family of membrane transport proteins is comprised of approximately 300 individual proteins and is organized into 43 families [1,101]. The SLC families encode proteins for passive transporters, ion-coupled transporters and exchangers. The genes found in the *SLCO* family (previously called *SLC21*) encode the organic anion transporting polypeptides (OATPs) [2]. OATPs mediate the transport of a wide range of amphipathic organic compounds in a sodium- independent manner, including bile salts, anionic oliopepties, steroid conjugates and thyroid hormones, in addition to several xenobiotics and pharmaceuticals [3]. OATPs have 12 transmembrane domains, with a large, highly conserved extracellular loop between the 9th and 10th transmembrane domains (Figure 1). *N*-glycosylation sites in extracellular loops 2 and 5 are consistent among the various members of the OATP family [4]. The *SLCO1A2* gene is comprised of 16 exons and 15 introns and is located on chromosome 12p12. The gene encodes OATP1A2 (OATP, OATP1 and OATP-A), a 670 amino acid glycoprotein that shares between 67–73% amino

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acid sequence with its rodent orthologs, rOatp1a1, rOatp1a4, rOatp1a5 [5]. Similar to other OATPs, OATP1A2 is primarily involved in the uptake of substrates into the cell.

OATP1A2 has been shown to transport a broad spectrum of substrates, including both endogenous compounds and clinically relevant pharmaceuticals (Table 1). As with the other human OATP transporters, OATP1A2 transports more amphipathic substrates, including bile salts, thyroid hormones, steroid conjugates, organic dyes and anionic oligopepties, as well as several pharmaceuticals and xenobiotics [5-19]. There is a wide variety of inhibitors for OATP1A2-mediated uptake, including some compounds that are also classified as substrates for the transporter [9-11,13,14,19-23]. Similar to other OATP transporters, the tissue distribution of OATP1A2 appears ubiquitous, although there is some discrepancy between studies. Using northern blot analysis, OATP1A2 has been localized to the liver, intestine, kidney, lung and testes, with the highest expression being found in the brain [9,10].

Western blots of human brain tissue confirmed the presence of OATP1A2 in the frontal cortex of the brain, with immunoflourescence localizing the transporter to human brain microvessels and brain capillary endothelial cells [11,16,24]. The abundance of OATP1A2 at the blood–brain barrier suggests a strong role of this transporter on brain penetration of therapeutic drugs. In the kidney OATP1A2 is localized to the apical domains of the distal tubule, where it is most likely involved in the reabsorption of compounds [16]. While studies have found expression of *SLCO1A2* in the liver, the localization of the transporter within this organ is controversial. Earlier studies have hypothesized that since the transporter was cloned from human liver banks it would be found on the basolateral membrane of hepatocytes, implying a role in the hepatic uptake of compounds from the blood [9]. However, immunohistochemical staining of proteins did not find any OATP1A2 transporters in the hepatocytes, but rather in the cholangiocytes of the liver [16]. There are also conflicting studies on the presence of OATP1A2 in the intestine. When using real-time PCR to detect the presence of *SLCO1A2* mRNA in the intestine, it was found that, based on their criteria, there was no detectable levels in any of the intestinal regions tested [25,26]. Again, however, the use of immunohistochemical staining for proteins found abundant expression of OATP1A2 in the duodenum of the intestine, co-localized with the efflux transporter ABCB1 at the apical membrane of the intestinal villi [20]. The presence of OATP1A2 protein in the intestine suggests that the transporter may be important for the oral absorption of drugs that are substrates for the transporter. It is important to note that the expression of *SLOC1A2* mRNA may not directly reflect the amount of OATP1A2 protein or functional activity.

Recently, the expression of OATP1A2 has been detected in human breast tissue and human breast carcinoma [27]. However, the expression of OATP1A2 in normal tissue is considerably lower, as compared with other members of the OATP family [28]. The expression of OATP1A2 is up to ten-times higher in cancerous breast tissue than it is in adjacent normal cells [29]. Furthermore, there is evidence to suggest that the pregnane X receptor, a ligand-activated transcription factor, may be involved in the elevated expression of OATP1A2 in human breast carcinoma [29]. Considering that OATP1A2 is known to uptake hormones into the cell it is interesting to contemplate OATP1A2 playing a significant roll in the hormone-induced progression of breast cancer in humans.

Genetic variants in the *SLCO1A2* gene

One major dilemma in treating patients in the clinic is the impact of interindividual variability in the pharmacokinetics and therapeutic effect of pharmaceuticals. This inter-individual variability is the result of complex interactions between morphometric, demographic, physiological, genetic and environmental factors [30]. While the vast majority of recent studies have focused on the impact of genetic variation in metabolic enzymes and efflux transporters on interindividual pharmacokinetic variability, it is only more recently that research has begun to address genetic variation in solute carriers [31]. Given its tissue distribution and ability to transport xenobiotic substances, it is reasonable to assume that genetic variations in the *SLCO1A2* gene may also contribute to differences in drug disposition and might have critical consequences for the therapeutic effects and toxicity of drugs. Within the 5′-flanking regions of the *SLCO1A2* gene there have been several SNPs identified [32].

Recently, six SNPs in the exonic regions have been identified from a mixed ethnic background and the associated variant proteins have been functionally characterized *in vitro* [16]. Functional variants found in this study consist of three SNPs that lead to a decreased uptake of substrates. In exon 4, a 404A>T variant results in an asparagine to isoleucine amino acid change, that reduces the uptake of estrone sulfate, deltonorphin II and (D-Pen2,D-Pen5)-enkephalin [DPDPE]). In exon 5, a 516A>C variant causes a glutamic acid to aspartic acid amino acid change that also reduced uptake of the three substrates, while a 559G>A variant causes an alanine to tyrosine amino acid change that decreases the uptake of deltonorphin II only. The 516A>C variant had an allele frequency of 5.3% of patients with European background and 2.1% with an African or Hispanic background. The 559G>A variant had an allele frequency of 0.5% of patients with a Hispanic background. None of the ethnic groups appeared to possess the 404A>T variant in the population studied. The presence of these functional variants in different ethnic groups strongly suggests that the clinical impact of these *SLCO1A2* variants on drug pharmacokinetics and therapeutic outcome needs to be urgently evaluated in future studies.

A subsequent study identified 11 SNPs in their mixed ethnic population and also functionally characterized these SNPs *in vitro* [33]. This study found that the 38T>C variant in exon 1 that causes a isoleucine to threonine amino acid change increased the uptake of estrone sulfate and methotrexate. Similar to the previous study, the 516C>T (exon 5) variant also demonstrated decreased uptake of estrone sulfate and methotrexate. An additional variant in exon 5 (502C>T) that results in an arginine to cysteine amino acid change also caused a functional decrease in the uptake of these substrates. One functional variant not previously studied is the 833A>– in exon 7 that causes a deletion of the asparagine amino acid, which was found to be associated with decreased function. The frequency of these variants was also ethnically divergent. The 38T>C variant had an allele frequency of 16.3% in European Americans and 2.5% in African–Americans. The 502C>T variant was relatively minor with an allele frequency of only 0.6% in European Americans, while the 516A>C variant had a frequency of 1.9% in European Americans. Finally, the 833A>– deletion variant was only found in African–Americans with a frequency of 0.6%.

While there is some overlap in the SNPs analyzed by these two studies, their functional studies resulted in differences for three of the six SNPs studied by both groups (Table 2) [16,33]. The 38T>C variant in exon 1 had no effect on the uptake of estrone sulfate in the study by Lee *et al.* [16], but demonstrated a significant increase in uptake by Badagnani *et al.* [33]. Furthermore, the 449G>A variant demonstrated a significant decrease in the uptake of estrone sulfate for Badagnani *et al.* that was not seen in the previous study. The 404A>T variant was found to cause a functional decrease in uptake, but only in the study by Lee *et al.* One possible explanation for these discrepancies is that the *in vitro* work was performed in different cell models. The study by Lee *et al.* overexpressed the various *SLCO1A2* SNPs in HeLa cells using transient transfection. However, Badagnani *et al.*, primarily used *Xenopous laevis* oocytes that were injected with the respective variant copy RNAs (cRNAs). However, Badagnani *et al.* also tested the uptake of estrone sulfate in a Human Embryonic Kidney (HEK)293 cell model transiently tranfected with the 38T>C variant. They found that the functional change in uptake seen in oocytes was also observed in the mammalian cell line. While the reasons behind these differences between the two studies are not fully understood, both studies demonstrate that several of the known SNPs for *SLCO1A2* can lead to functional changes in OATP1A2 mediated uptake of substrates.

Future perspective

While little is known regarding the consequences of genetic alterations in *SLCO1A2* on pharmacokinetics and therapeutic effects of clinically used drugs, there is strong evidence suggesting that a better understanding of the effects of these functional variants is needed. With better diagnostic tests and clinical studies on the effects of these variants in patients, it is anticipated that future studies may be able to link genetic variability in *SLCO1A2* with the interindividual variability seen with so many drugs that are substrates for the OATP1A2 transporter. Future directions in this field will be mainly concerned with better understanding the known functional SNPs, how they impact the toxicity, pharmacokinetics and therapeutic effect of pharmaceuticals, and with the development of genomic and proteomic tools for evaluating OATP1A2 function in patients.

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Highlights

- The human organic anion transporting polypeptide 1A2 (OATP1A2) is involved in the uptake of several endogenous substances, as well as clinically used drugs.
- The presence of OATP1A2 transporters in several tissues key to drug pharmacokinetics suggests an important role in absorption, distribution and excretion of drugs.
- Many inhibitors of OATP1A2-mediated uptake have been identified and suggest a possible mechanism for some drug–drug interactions.
- SNPs for the gene encoding OATP1A2, *SLCO1A2*, have been identified in human populations and have ethnically-dependent allelic frequencies.
- Cellular *in vitro* studies have demonstrated that several of these SNPs cause functional changes in the uptake of both endogenous compounds and clinical pharmaceuticals.
- Variants in *SLCO1A2* may impact the efficacy of several clinically relevant drugs and could be one strategy for predicting systemic exposure to drugs that are OATP1A2 substrates.
- Future studies are needed to critically evaluate the usefulness of *SLCO1A2* genotyping as a tool to predict treatment outcome.

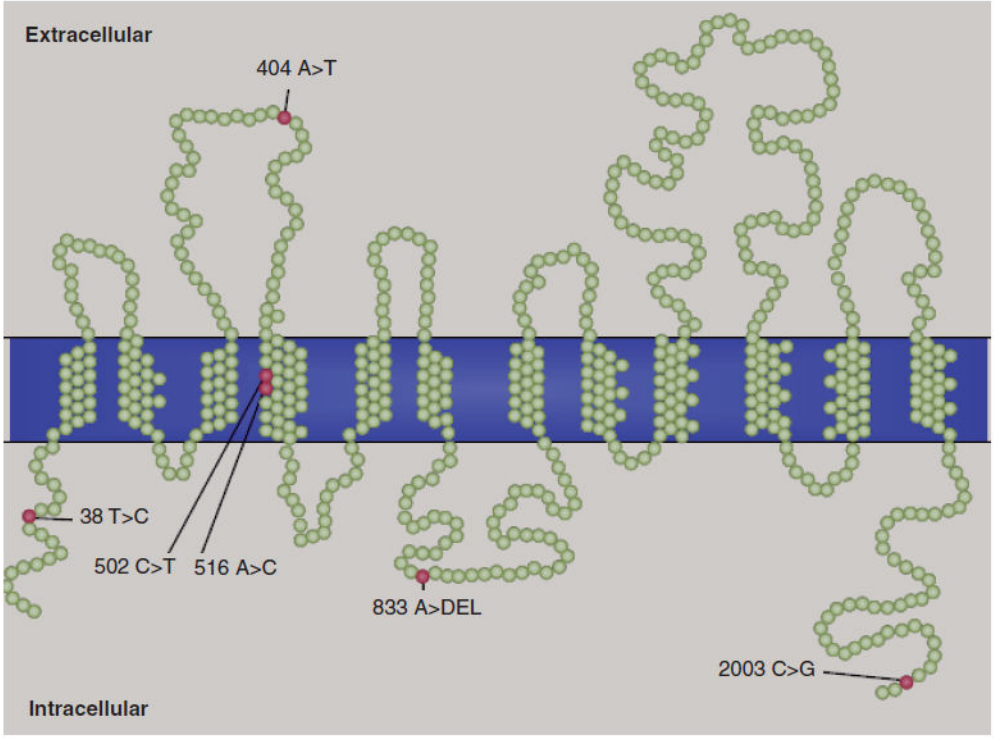

Figure 1. Structure of OATP1A2

Includes major functional variants found in the *SLCO1A2* gene. Variants expressed as base pair changes. Adapted from [16].

Table 1

Substrates and inhibitors of OATP1A2.

Category	Substrate	Inhibitor	Model	Ref.
Bile salts	Taurocholate	Ursodeoxycholate, tauroursodeoxycholate, aurochenodeoxycholate, ursodeoxycholate, indocyanine green, glycocholate, cholate, chenodeoxycholate	Oocyte	[9]
	Cholate, glycocholate, TCDCA, TUDCA		Oocyte	[5,9]
Hormones	DHEAS	Tauroursodeoxycholate, taurochenodeoxycholate, E-3-S, dexamethasone	Oocyte	[10]
	$E_2$17βG	Bilirubin	Oocyte	[5,23]
	Unconjugated bilirubin	$E_2$17βG	Oocyte	[23]
	E-3-S, T_4, T_3, rT_3		Oocyte	[7,16,33]
Peptides	Deltorphin II	Naltrindole, naloxone, Leu-enkephalin, E-3-S, DPDPE	Oocyte	[11,16]
	BQ-123, CRC-220, DPDPE		Oocyte	[5,11,16]
Organic anions	BSP	Rifampin, rifamycin SV, oubain, tauroursodeoxycholate, ursodeoxycholate, taurocholate, taurochenodeoxycholate, indocyanine green, glycocholate, cholate, chenodeoxycholate	Oocyte	[9,22]
Organic cations	APD-ajmalinium, *N*-methylquinine, *N*-methylquinidine, rocuronium		Oocyte	[15]
Drugs	Fexofenadine	Grapefruit juice (naringin), orange juice (hesperidin), apple juice, verapamil, saquinavir, ritonavir, quinidine, PSC-833, nelfinavir, lovastatin, ketoconazole, indinavir, erythromycin	HeLa	[13,20,21]
	Ouabain	Taurochenodeoxycholate	Oocyte	[5,12]
	Imatinib	Uremic toxins (CMPF)	Oocyte	[19]
	Rocuronium	Taurocholate, quinidine, *N*-methylquinidine, K-strophantoside, Azidoprocainamide methiodide	Oocyte	[14,15]
	Chlorambuciltaurocholate, Gd-B 20790, erythromycin, levofloxacin, pitavastatin, pravastatin, rosuvastatin, saquinavir, D-penicillamine, bamet-UD2, bamet-R2, bromosulfophthalein, unprostone, methotrexate		Oocyte	[17,33]
Toxins	Microcystin		Oocyte	[6]
Eicosanoids	Prostaglandin E_2		Oocyte	[5]

BSP: Sulfobromophthalein; CMPF: 3-carboxy-4-methyl-5-propyl-2-furan-propanoic acid; CRC-220: 4-methoxy-2,3,6-trimethylphenylsulfonyl-L-aspartyl-D-4-amidino-phenylalanyl-piperidide; DPDPE: (D-Pen2,D-Pen5)-enkephalin; TCDCA: Taurochenodeoxycholate; TUDCA: Tauroursodeoxycholic acid.

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Table 2

SLCO1A2 genetic polymorphisms.

Exon	Position	Base pair change	AA position	AA change	dbSNP Id	Nomenclature/function	
						Lee* et al. [16] *(ES, Delt II, DPDPE)	***Badagnani* et al. [33] *(ES, MTX)***
1	38	T>C	13	I>T	rs10841795	**2*	1.1 (↑ both)
	51	C>T	S	S	rs11568572		
	186	T>C	S	S	rs2306227		
4	382	A>T	128	N>Y	rs11568567	**5*	4.1
4	404	A>T	135	N>I	rs45502302	**6* (↓ all)	4.2
5	502	C>T	168	R>C	rs11568564		5.1 (↓ both)
5	516	A>C	172	E>D	rs11568563	**3* (↓ all)	5.2 (↓ both)
5	559	G>A	187	A>Y	NA	**4* (↓ Delt II only)	
	726	C>T	S	S	rs11045953		
	768	C>T	S	S	NA		
7	830	C>A	277	T>N	NA		7.3
7	833	A>–	278	N>del	NA		7.4 (↓ both)
	837	T>G	S	S	NA		
7	841	A>G	281	I>V	rs11568551		7.6
8	968	T>C	323	L>P	rs11568579		8.2
8	1063	A>G	355	I>V	rs45628437		8.3
	1380	A>G	S	S	rs3764044		
	1662	C>T	S	S	rs2417971		
14	2003	C>G	668	T>S	rs11568557	**7*	14.2

↑: Increased function; ↓: Decreased function; AA: Amino acid; Delt II: Deltorphin II; dbSNP: SNP database; DPDPE: (D-Pen2,D-Pen5)-Enkephalin; ES: Estrone Sulfate; MTX: Methotrexate; NA: Not currently available; S: Synonymous.