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Genetic Polymorphisms and Function of the Organic Anion-Transporting Polypeptide 1A2 and Its Clinical Relevance in Drug Disposition

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Key Words

Organic anion-transporting polypeptide 1A2 · Drug transport · Polymorphism · Single nucleotide polymorphism

Abstract

The solute carrier organic anion-transporting polypeptides (OATPs) are a family of transporter proteins that have been extensively recognized as key determinants of absorption, distribution, metabolism and excretion of various drugs because of their broad substrate specificity and wide tissue distribution as well as the involvement of drug-drug interaction. Human OATP1A2 is a drug uptake transporter known for its broad substrate specificity, including many drugs in clinical use. OATP1A2 expression has been detected in the intestine, liver, brain and kidney. A considerable number of single nucleotide polymorphisms have been found for the OATP1A2 gene. A number of studies have shown that the cellular uptake and pharmacokinetic behavior of some drugs may be impaired in the case of certain OATP1A2 variants. Interestingly, some studies show that the mRNA expression of OATP1A2 is nearly 10-fold higher in breast cancer compared with adjacent healthy breast tissues. This review is, therefore, focused on the genetic polymorphisms, function and clinical relevance of OATP1A2 as well as on the substrates transported by it.

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Introduction

The two major superfamilies of membrane transport proteins influencing drug absorption, distribution and elimination are the solute carrier (SLC) uptake and the ATP-binding cassette efflux transporter. In humans, the SLC family of membrane transport proteins is composed of approximately 300 individual proteins and is organized into 43 families [1]. The SLC families encode proteins for passive transporters, ion-coupled transporters and exchangers. Organic anion-transporting polypeptides (OATPs) are coded by the gene SLCO.

Human OATPs represent a family of membrane SLC proteins that are expressed in a variety of organs important for drug disposition. They have been extensively recognized as key determinants of absorption, distribution, metabolism and excretion of various drugs, xenobiotics and toxins. So far, 40 members of the OATP/SLCO su-

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perfamily have been identified in humans, rats and mice. Most OATPs are expressed in multiple tissues including the blood-brain barrier (BBB), choroid plexus, lung, heart, intestine, kidneys, placenta and testes. The different proteins are named OATP followed by the family number (e.g. OATP1, OATP2), the subfamily letter (e.g. OATP1A, OATP1B) and then a consecutive number identifying the individual members within the family based on the historical order in which they have been identified (e.g. OATP2B1).

Within this family, OATP1A2 (SLCO1A2, also known as human OATP-A or OATP1) is the first human OATP to be cloned and characterized [2]. OATP1A2 has the highest mRNA expression in the brain and is also observed in the liver, intestine, kidneys, lung and testes. OATP1A2 has a broad spectrum of substrates including endogenous compounds (such as bile acids, steroid hormones and their conjugates, thyroid hormones) and various drugs (such as fexofenadine, ouabain and the cyanobacterial toxin microcystin).

The presence of OATP1A2 in the distal tubules of the nephrons suggests a potentially important role for this transporter in the reabsorption of drugs that are filtered or secreted at the level of the proximal tubule. Some findings suggest that OATP1A2 may play a role in the active tubular reabsorption of methotrexate (MTX) and in MTX-induced toxicities; furthermore, genetic variation in OATP1A2 may contribute to variation in MTX disposition and response. Its expression at the level of the BBB is of particular clinical relevance given the broad substrate specificity for this transporter, including opioid peptide analogues such as deltorphin II and DPDPE. Human OATP1A2 could be a determinant of the intestinal absorption of fexofenadine, a histamine H_1 receptor antagonist [3–5]. The results of one study strongly indicate that OATP1A2 contribute to the intestinal absorption of pravastatin in humans [6].

The present paper aims to summarize and update the current knowledge about the structure, function, genetic polymorphisms and regulation of OATP1A2 as well as the associated clinical implications.

Features of OATP1A2

Tissue Distribution and Localization

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 brain, liver, intestine, kidneys, lung and testes, with the highest expression being found in the brain [7].

OATP1A2 protein has been localized to the brush border membrane of enterocytes in the duodenum, where it may mediate the absorption of xenobiotics. 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 blood [2]. However, immunohistochemical staining of proteins did not show any OATP1A2 transporters in the hepatocytes, but rather in the cholangiocytes of the liver [8]. This suggests that OATP1A2 may be involved in the reabsorption of xenobiotics excreted into the bile. In the kidney, OATP1A2 is expressed at the apical membrane of the distal nephron, where it could be responsible for either the reabsorption of xenobiotics from or their secretion into urine. Western blots of human brain tissue confirmed the presence of OATP1A2 in the frontal cortex of the brain, with immunofluorescence localizing the transporter to human brain microvessels and brain capillary endothelial cells [8–10]. Another study found by immunohistochemical staining that OATP1A2 was exclusively expressed in human brain microvessels but not in astrocytes and neurons and was thought to be part of the BBB. The abundance of OATP1A2 at the BBB suggests an important role of this transporter in brain penetration of therapeutic drugs.

OATP1A2 expression in normal nonmalignant breast tissue is low as compared with that of other members of the OATP family such as OATP-B (OATP2B1), OATP-E (OATP4A1) and OATP-D (OATP3A1). However, OATP1A2 expression in lactating mammary epithelium cells is significantly greater than in nonlactating mammary epithelium cells, suggesting a regulated physiological function of this transporter in breast tissue [11, 12].

Structure and Activity

OATP1A2 is a glycoprotein of 670 amino acids and shares between 66 and 77% amino acid sequence identity with its rodent orthologues [12]. Like all human OATPs, OATP1A2 possesses a secondary structure of 12 transmembrane (TM) domains (fig. 1), with common structural features such as a large extracellular domain between TMs 9 and 10 (extracellular loop 5), which contains many conserved cysteine residues, the N-glycosylation sites in extracellular loops 2 and 5 and the consensus superfamily signature D-X-RW-(I,V)-GAWW-X-G-(F,L)-L at the border between extracellular loop 3 and TM 6 [13].

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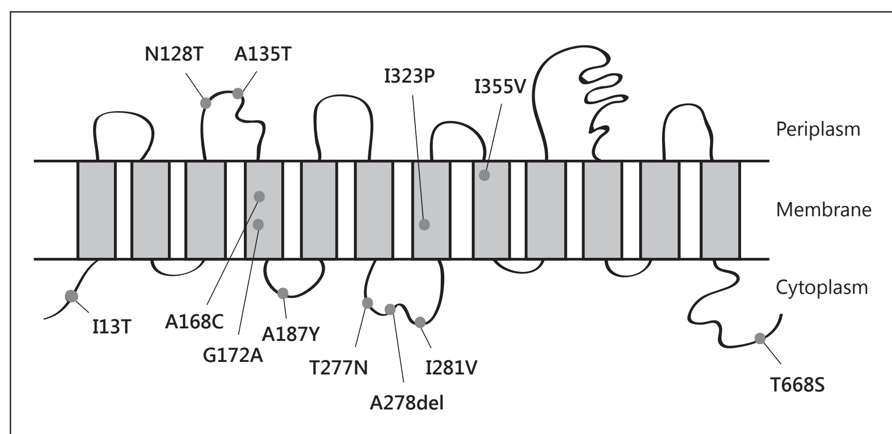

Fig. 1. Predicted structural model of OATP1A2. Two-dimensional depiction of the structure showing the corresponding helices. Rectangular bars indicate TM helices. Gray dots show the location of amino acid residues encoded by the nonsynonymous SNPs.

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Several conserved structural features are believed to be important for the transport function of OATPs/Oatps. These features include the number of TM helices, the so-called superfamily signature and the large extracellular region between TM helices 9 and 10 [14]. N-glycosylation of membrane-bound proteins has been demonstrated to play a number of important roles including modulation of biological activity, regulation of intracellular targeting, protein folding and maintenance of protein stability. In the most straightforward arrangement of the transporter structures, the 12 helices were arranged as a pair of 6 distinct helix bundles using the glycerol-3-phosphate transporter from the *Escherichia coli* template [15].

It has been suggested that TM domain helices control membrane targeting, protein stability and substrate binding in SLC transporters [16–19]. While the residues threonine (polar amino acid) and alanine (small, hydrophobic amino acid) sustain transporter function and stability, the larger or more rigid histidine, tyrosine, phenylalanine, proline and tryptophan strongly disrupt transport function, perhaps by altering the conformation of the protein. Study of the structure-activity relationship showed that the position of the positively charged basic amine atom played an important role in altering the OATP1A2-mediated triptan uptake rate, in the following order: tertiary > secondary > primary [20].

Polymorphisms and Function of OATP1A2 and Drug Pharmacokinetics

One major dilemma in treating patients in the clinic is the impact of interindividual variability in the pharmacokinetics and therapeutic effect of pharmaceuticals. Interindividual variability is the result of a complex interaction between morphometric, demographic, physiological, genetic and environmental factors. 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.

Significant genetic and functional variation in drug uptake transporters exists and may contribute to variation in drug disposition. Genetic variants of SLCO1A2 were identified as part of a large study, the Pharmacogenetics of Membrane Transporters Project, which entails identifying variants in membrane transporter genes that may lead to differences in drug response and disposition. The 14 coding exons of SLCO1A2 and 50–200 bp of flanking intronic sequence were screened in a collection of 270 ethnically diverse genomic DNA samples [21]. This study identified 11 single nucleotide polymorphisms (SNPs) in mixed ethnic populations and also functionally characterized these SNPs in vitro. According to this study, the 516C>T (exon 5) variant showed a decreased uptake of estrone sulfate and MTX, while a 559G>A variant caused an alanine-to-tyrosine amino acid change that decreased the uptake of deltorphin II only. An additional variant in exon 5 (502C>T) that induced an arginine-to-cysteine amino acid change also caused a functional decrease in the uptake of these substrates. This study found that the 38T>C variant in exon 1 which caused an isoleucine-to-threonine amino acid change increased the uptake of estrone sulfate and MTX. One functional variant not previously studied was 833A>– in exon 7, which could cause a deletion of the asparagine amino acid, which was found to be associated with decreased function.

An in vitro study showed that imatinib uptake was completely abolished in HeLa cells expressing the

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Table 1. SLCO1A2 genetic polymorphisms

Exon	Position	Base pair change	AA position	AA change	dbSNP IP
1	38	T>C	13	I>T	rs10841795
	51	C>T	S	S	rs11568572
	186	T>C	S	S	rs2306227
4	382	A>T	128	N>Y	rs11568567
4	404	A>T	135	N>Y	rs45502302
5	502	C>T	168	R>C	rs11568564
5	516	A>C	172	E>D	rs11568563
5	559	G>A	187	A>Y	NA
	726	C>T	S	S	rs11045953
	768	C>T	S	S	NA
7	830	C>A	277	T>N	NA
7	833	A>–	278	N>del	NA
	837	T>G	S	S	NA
7	841	A>G	281	I>V	rs11568551
8	968	T>C	323	I>P	rs11568579
8	1,063	A>G	355	I>V	rs45628437
	1,380	A>G	S	S	rs3764044
	1,662	C>T	S	S	rs2417971
14	2,003	C>G	668	T>S	rs11568557
7	550	G>A	184	E>K	NA
7	553	G>A	185	D>N	NA
9	763	G>A	255	V>I	NA
9	775	A>C	259	T>P	NA
9	862	G>A	288	D>N	NA

AA = Amino acid; dbSNP = SNP database; NA = not currently available; S = synonymous.

Table 2. Allelic frequencies of SLCO1A2 variants in different ethnic groups

Exon	Position	Base pair change	Allele frequency, %			
			AA	EA	AS	ME
1	38	T>C	2.5	16.3	0	5.0
4	382	A>T	1.3	0	0	1.0
4	404	A>T	1.3	0	0	0
5	502	C>T	0	0.6	0	0
5	516	A>C	0	1.9	0	2.0
7	830	C>A	0.6	0	0	0
7	833	A>–	0.6	0	0	0
7	841	A>G	0	0	0.8	0
8	968	T>C	0	0.6	0	0
8	1,063	A>G	0	1.9	0	0
14	2,003	C>G	4.4	0	0	1.0

Allele frequencies were calculated from actual DNA samples sequenced. AA = African American; EA = European American; AS = Asian American; ME = Mexican American.

OATP1A2 variants (516A>C, 382A>T and 404A>T), and the variant 2003C>G decreased imatinib uptake in a pH-dependent manner, with a 77% reduction at pH 7.4 and a 46% reduction at pH 5, compared with that in the wild type at these respective pH values [22]. Another investigation found that the SLCO1A2 –1105G>A/–1032G>A genotype and the SLCO1A2 –361GG genotype affected imatinib uptake in chronic myeloid leukemia patients [23].

SNPs of OATP1A2

The SLCO1A2 gene is located on chromosome 12 at q12, with 16 exons and 15 introns. One study identified 11 SNPs in their mixed ethnic population and also functionally characterized these SNPs in vitro. Recently, 6 SNPs in the exonic regions have been identified from a mixed ethnic background, and the associated variant proteins have been functionally characterized in vitro [21]. 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 16.3% in European Americans. Finally, the 833A>– deletion variant was not found in African Americans with a frequency of 0.6%. The variant c.516A>C was present exclusively in the European American (1.9%) and Mexican American (2%) samples. Only one protein-altering variant, c.841A>G, was observed in Asian Americans. The allelic frequencies of SLCO1A2 and variants in different ethnic groups are summarized in tables 1 and 2, respectively.

Zhou et al. [24] identified 5 novel SNPs in coding exons of the SLCO1A2 gene in a cohort of subjects: G550A, G553A, G673A, A775C and G862A, which encoded the OATP1A2 variants E184K, D185N, V255I, T259P and D288N, respectively. Within the 5′-flanking regions of the SLCO1A2 gene, several SNPs have been identified [25]. Five SNPs in the promoter region of SLCO1A2 (–1105G>A, –1032G>A, –715T>C, –361G>A and –189_–188insA) were analyzed in 100 healthy subjects [23].

Substrate Specificity of OATP1A2

OATP1A2 is a drug uptake transporter with broad substrate specificity that includes endogenous amphipathic substrates as well as pharmacological drugs and xenobiotics. Endogenous substrates of OATP1A2 include bile acids and steroid and thyroid hormones as well as their conjugates. Important drug substrates include imatinib, fexofenadine, MTX, HIV protease inhibitors, HMG-CoA reductase inhibitors and certain peptides

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Table 3. Substrates of human OATP1A2

	K_m, μmol/l
Atenolol	
Acebutolol	
Atrasentan	
APD-ajmalinium	
BQ-123	
Bamet-R2	24
Bilirubin	
Bamet-UD2	14
Bromosulfophthalein	20
Cholate	93
Celiprolol	20.5
CRC 220	
Ciprofloxacin	
Chlorambucil-taurocholate	
Darunavir	
Deltorphin II	330
[D-penicillamine 2,5]enkephalin	202
Dehydroepiandrosterone-3-sulfate	7
Enoxacin	
Erythromycin	
E3S	16
Epicatechin gallate	10
Epigallocatechin gallate	19
Ouabain	5,500
Fexofenadine	6
Gatifloxacin	
Gd-B20790	
Glycocholate	
Hydroxyurea	
Imatinib	
Labetalol	
Levofloxacin	136
Lomefloxacin	
Lopinavir	
MTX	457
Microcystin	20
Nadolol	
Norfloxacin	
N-methylquinine	5
N-methylquinidine	26
Pitavastatin	3
Prostadin E2	
Pravastatin	
Prostaglandins	
Rocuronium	
Rosuvastatin	3
Saquinavir	36
Sotalol	
Steroid	
Talinolol	714
Taurocholate	60
Taurochenodeoxycholate	
Tauroursodeoxycholate	19
Thyroxine	8
Tebipenem pivoxil	41
TR-14035	
Triiodothyronine	7
Unoprostone metabolite	93

Bamet-R2 = *cis*-diammine-chloro-cholylglycinateplatinum(II); Bamet-UD2 = *cis*-diammine-bisursodeoxycholateplatinum(II); BQ-123 = cyclic pentapeptide endothelin receptor antagonist; CRC 220 = peptidomimetic thrombin inhibitor; TR-14035 = a4b1/a4b7 integrin dual antagonist.

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[21]. As with the other human OATP transporters, OATP1A2 transports more amphipathic substrates, including bile salts, thyroid hormones, steroid conjugates, organic dyes and anionic oligopeptides, as well as several pharmaceuticals and xenobiotics. In addition to amphiphilic anionic substances such as these conjugates, OATP1A2 can transport certain neutral or cationic compounds. All substrates of OATP1A2 are shown in table 3.

The mechanism of OATP-mediated transport remains controversial. It is well established that transport is ATP and sodium independent, but the driving force for transport is still under investigation. OATP1A2-mediated transport can be affected by pH, as demonstrated by Badagnani et al. [21], who found that uptake of MTX is increased as much as 7-fold at pH 5.0 compared with pH 7.4. The transport activities of OATP1A2 and their mechanisms have been examined in several different expression systems, including transfected mammalian cells and *Xenopus laevis* oocytes [26, 27].

Inhibitor of OATP1A2

Inhibition of OATP transporters likely results in adverse drug-drug or drug-food interactions. Treatment with cyclosporin, an inhibitor of OATP, is associated with increased plasma concentrations of statins [28]. Cyclosporin and rifampicin also increase the plasma concentration of bosentan by inhibiting OATP-mediated bosentan uptake at clinically relevant concentrations [29]. Both

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Table 4. Distribution of OATP1A2 in normal and malignant tissues

Normal tissue	Malignant tissue
BBB	Expressed in bone cancer tissues and cell lines
Apical membrane of the distal nephrons	Reduced in colon polyps and cancer
Cholangiocytes of the liver	High expression levels in benign bone tumors
Brush border membrane of enterocytes	Increased in breast carcinoma cells and malignant breast tissue

rifamycin SV and rifampicin reduce bromosulfophthalein elimination in humans and inhibit the uptake of bromosulfophthalein by OATP1A2 in vitro [30]. OATP1A2 transports the fluoroquinolone antibiotic levofloxacin, and this transport is inhibited by other quinolones.

There are also reports on potential OATP-mediated drug-food interactions, particularly with OATP1A2 and OATP2B1, which are expressed at the luminal membrane of enterocytes. Fruit juices decrease the oral bioavailability of fexofenadine in humans, at least in part, by inhibition of OATP1A2 [31]. Uptake of this OATP1A2 substrate is inhibited by naringin, a component of grapefruit and orange juice (at 5% soft drink strength) in vitro. In healthy subjects, the AUC of fexofenadine has been decreased by 25% after ingestion of naringin and by 40–70% after ingestion of grapefruit or orange juice, which is consistent with an inhibition of OATP1A2 at the apical membrane of enterocytes [26]. Rebello et al. [32] showed that grapefruit juice decreased exposure of aliskiren partially via inhibition of intestinal OATP1A2. Another study showed that green tea markedly decreased the C_{max} and AUC_{0-48} of nadolol by 85.3 and 85.0%, respectively ($p < 0.01$) [33].

In addition, many flavonoids affect OATP-mediated uptake of the model substrates estrone-3-sulfate (E3S), estradiol-17β-glucuronide and dehydroepiandrosterone-3-sulfate (DHEAS), suggesting that possible drug-food interactions could occur especially in patients taking over-the-counter dietary supplements in addition to prescribed medications. Modification of OATP1A2 and OATP2B1 transport activity by the ginkgo flavonoids apigenin, kaempferol and quercetin can also result in clinically relevant food-drug or drug-drug interactions [34]. Interestingly, this study also indicated that quercetin is more abundant than kaempferol in vegetables and fruits such as onions, lettuce, French beans and apples.

Role of OATP1A2 in Tumors

In normal nonmalignant breast tissue, OATP1A2 expression has been shown to be very low, especially compared with that of other members of the OATP family such as OATP2B1, OATP4A1 and OATP3A1. Meyer zu Schwabedissen et al. [35] showed that mRNA expression of OATP1A2, which is capable of mediating the cellular uptake of estrogen metabolites, was nearly 10-fold higher in breast cancer than in adjacent healthy breast tissues. E3S, a substrate for OATP1A2, is a predominant source of tumor estrogen in postmenopausal, hormone-dependent patients with breast cancer. In vitro, exposure of breast cancer cells to E3S has been shown to result in increased cellular proliferation. These data suggest a potential role of OATP1A2 in hormone-dependent breast cancer proliferation by facilitating E3S cellular uptake [36].

OATP-mediated DHEAS transport plays a major role in the survival and proliferation of androgen receptor-positive prostate cancer cells under conditions of androgen depletion. In other words, the enhanced import of DHEAS mediated by the increased expression of OATPs, most likely predominantly OATP1A2, can be utilized to provide an alternative source of androgen under conditions of androgen depletion, allowing prostate cancer cells to acquire castration resistance because the high serum concentration of DHEAS is altered little during the course of androgen deprivation therapy. An experiment yielded the result that knockdown of OATP1A2 in LNCaP cells resulted in a loss of the cell growth response to DHEAS [37].

Through RT-PCR, OATP1A2 expression was detected in healthy colon tissue; however, its expression was decreased in polyps and in colon cancer tissue [38]. Some data revealed that 8 out of 11 OATPs (OATP1A2, 1C1, 2A1, 2B1, 3A1, 4A1, 4C1 and 5A1) are expressed in human bone tumors, with differences in their expression levels between osteosarcomas, bone metastases and benign bone tumors [39]. High OATP expression levels, particularly in benign bone tumors, suggest an important role of these transporters in providing hormones, their conjugates, prostaglandins and drugs to bone cells. The distribution of OATP1A2 in some normal and malignant tissues is shown in table 4.

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Conclusions and Perspectives

OATP1A2 has been extensively recognized as a key determinant of absorption, distribution, metabolism, and excretion of various drugs because of its broad substrate specificity and wide tissue distribution as well as the involvement of drug-drug interaction. Genetic variants of SLCO1A2 may lead to differences in drug response and disposition. At present, there is growing interest in drug-drug and drug-food interactions that occur on the transporter level, since they can lead to either increased toxicity or subtherapeutic drug levels. In addition, the relationship between tumors and transporters will contribute to its treatment.

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