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REVIEW

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Pharmacogenomics of human OATP transporters

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Abstract Organic anion transporting polypeptides (OATPs) mediate the uptake of a broad range of compounds into cells. Substrates for members of the OATP family include bile salts, hormones, and steroid conjugates as well as drugs like the HMG-CoA-reductase inhibitors (statins), cardiac glycosides, anticancer agents like methotrexate, and antibiotics like rifampicin. OATPs are expressed in a variety of different tissues, including intestine, liver, kidney, and brain, suggesting that they play a critical role in drug absorption, distribution, and excretion. The identification and functional characterisation of naturally occurring variations in genes encoding human OATP (SLCO) family members is in the focus of transporter research. As a result of their broad substrate spectrum and their wide tissue distribution, altered transport characteristics or protein localisation can contribute significantly to interindividual variations of drug effects. The analysis of the consequences of genetic variations in genes encoding transport proteins may, therefore, contribute to a better understanding of interindividual differences in drug effects and to individualise treatment regimens with drugs that are substrates for human OATP proteins. In this review, we summarise the current knowledge on genetic variations in transporter genes encoding human OATP family members and their functional consequences analysed by in vitro and in vivo studies.

Keywords Drug transport · Haplotypes · OATPs · Pharmacogenomics · Polymorphisms

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The OATP family of uptake transporters

Uptake transporters belonging to the superfamily of solute carriers (SLC) (Hagenbuch and Meier 2004; Hediger et al. 2004), and efflux pumps belonging to the ATP-binding cassette transporter (ABC transporter) superfamily (Borst and Elferink 2002; Fromm 2004; König et al. 1999; Kruh and Belinsky 2003), have an impact on the absorption, distribution and elimination of drugs. Genes encoding organic anion transporting polypeptides form a large family within this superfamily of solute carriers. Their genes are classified within the solute carrier family SLCO (Hagenbuch and Meier 2004). OATP1A2 (formerly termed OATP or OATP-A) was described in 1995 (Kullak-Ublick et al. 1995) and followed by the discovery of the second member OATP1B1 (formerly termed OATP2, OATP-C, or LST1) (Abe et al. 1999; Hsiang et al. 1999; König et al. 2000a). Today, the human OATP family consists of 11 members (Hagenbuch and Meier 2003; Mikkaichi et al. 2004a) including 10 OATPs and the prostaglandin transporter OATP2A1 (formerly termed PGT). Due to the fact that trivial names for individual proteins do not correspond to the continuous numbering based on the chronology of protein identification, and because many mouse/rat Oatps have no direct human orthologue, Hagenbuch and Meier (Hagenbuch and Meier 2004) introduced a new nomenclature for the OATP family. In this review, we will follow this new nomenclature and designate all proteins and genes according to this denomination.

According to computer based hydropathy analysis, all OATPs share a very similar transmembrane domain organisation, with 12 predicted transmembrane domains and a large 5th extracellular loop (Hagenbuch and Meier 2003). Additional conserved features of all OATP proteins are N-glycosylation sites in the extracellular loops 2 and 5 and the OATP 'superfamily signature' at the border between the extracellular loop 3 and transmembrane domain 6 (Hagenbuch and Meier 2003). While most of the OATP proteins are expressed in multiple tissues, OATP1B1 (OATP2 / OATP-C) and OATP1B3 (OATP8)

are predominantly if not exclusively expressed in liver (Hsiang et al. 1999; König et al. 2000a,b). OATP1A2 shows highest expression in brain and testis (Kullak-Ublick et al. 1995), whereas OATP2B1 (OATP-B) and OATP4A1 (OATP-E) are ubiquitously expressed in all tissues investigated so far (Hagenbuch and Meier 2003). Almost all OATP family members are localised to the basolateral membrane of polarised cells. OATP1B1, OATP1B3 and OATP2B1 have been localised to the basolateral membrane of human hepatocytes (Hsiang et al. 1999; König et al. 2000a,b), whereas OATP2A1 has been localised to the basolateral membrane of brain endothelial cells (Lee et al. 2005a). Interestingly, in addition to its basolateral localisation in liver and placenta (St-Pierre et al. 2002), OATP2B1 has been detected in the apical membrane of enterocytes (Kobayashi et al. 2003). OATP4A1 (formerly termed OATP-E) is predominantly expressed at the apical surface of the syncytiotrophoblast in placenta (Sato et al. 2003) and, together with OATP1C1 (formerly termed OATP-F) and OATP3A1 (formerly termed OATP-D), in the basolateral plasma membrane of the non-pigmented human ciliary body epithelium (Gao et al. 2005). OATP4C1 has been found to be highly expressed at mRNA level in human kidney (Mikkaichi et al. 2004b) and the rat Oatp4c1 protein has been localised to the basolateral membrane of kidney proximal tubular cells (Mikkaichi et al. 2004b). The expression and subcellular localisation of human OATP5A1 and OATP6A1 remains to be clarified.

Originally, human OATP1A2 was cloned based on its homology to rat Oatp1a1 (Jacquemin et al. 1994) as a sodium-independent transporter for bile salts and bromosulfophthalein in human liver (Kullak-Ublick et al. 1995). Further studies investigating the substrate spectrum in more detail have shown that OATP1A2 is capable of transporting a wide range of amphipathic organic anions (Table 1), including bile salts (Kullak-Ublick et al. 1995; Meier et al. 1997), thyroid hormones (Friesema et al. 1999), steroid hormones and their conjugates (Bossuyt et al. 1996a), as well as organic cations like N-methyl-quinidine and others (van Montfoort et al. 1999).

Determining the substrate spectrum of other human OATP family members demonstrated that most of them have a similarly broad substrate spectrum partially overlapping with the substrate spectrum defined for OATP1A2 (Table 1). In addition to endogenous compounds, OATPs are capable of transporting various xenobiotics and drugs and, therefore, play an important role in drug absorption, disposition, and excretion. Especially OATP1B1 and OATP1B3, both highly expressed in human liver and involved in the uptake of endogenous substances and of xenobiotics into hepatocytes, are able to transport various drugs, including HMG-CoA-reductase inhibitors like pravastatin (Hsiang et al. 1999; Nakai et al. 2001) and pitavastatin (Hirano et al. 2004), the endothelin receptor antagonist BQ123 (Kullak-Ublick et al. 2001), and the antibiotic rifampicin (Tirona et al. 2003; Vavricka et al. 2002) (Table 1). Since expression and substrates for all human OATP family members have not been completely characterised, additional functional studies and investiga-

Table 1 Substrates for human OATP family members

Substrate	K_m value (μM)	References
OATP1A2 (OATP-A)		
APD-ajmalinium		Bossuyt et al. (1996b)
BQ123		Kullak-Ublick et al. (2001)
Bromosulfophthalein	20	Kullak-Ublick et al. (2001)
Chlorambuciltaurocholate		Kullak-Ublick et al. (1997)
Cholate	93	Kullak-Ublick et al. (1995)
Bamet-UD	14	Briz et al. (2002)
Bamet-R2	24	Briz et al. (2002)
Dehydroepiandrosterone-3-sulfate	7	Kullak-Ublick et al. (1998)
Deltorphin II	330	Gao et al. (2000)
DPDPE	202	Briz et al. (2003)
Estradiol-17β-glucuronide		Briz et al. (2003)
Estrone-3-sulfate	59	Bossuyt et al. (1996b)
Fexofenadine	6	Cvetkovic et al. (1999)
Gd-B20790	92	Pascolo et al. (1999)
Glycocholate		Kullak-Ublick et al. (1995)
Microcystin-LR	20	Fischer et al. (2005)
N-Methyl-quinidine	26	van Montfoort et al. (1999)
N-Methyl-quinidine	5	van Montfoort et al. (1999)
Ouabain	5.5	Bossuyt et al. (1996b)
Prostaglandin E_2		Kullak-Ublick et al. (2001)
Reverse Triiodothyronine (rT3)		van Montfoort et al. (1999)
Rocuronium		van Montfoort et al. (1999)
Taurocholate	60	Kullak-Ublick et al. (1995)
Taurochenodeoxycholate		Kullak-Ublick et al. (1995)
Thyroxin (T4)	8	Fujiwara et al. (2001)
Triiodothyronine (T3)	7	Fujiwara et al. (2001)
Tauroursodeoxycholate	19	Kullak-Ublick et al. (1995)
OATP1B1 (OATP-C/OATP2)		
DADLE		Nozawa et al. (2003)
ACU-154		Takada et al. (2004)
Atorvastatin		Kameyama et al. (2005)
Benzylpenicillin		Tamai et al. (2000)
Bilirubin	8	Cui et al. (2001)
Bisglucuronosyl bilirubin	0.3	Cui et al. (2001)
BQ-123		Kullak-Ublick et al. (2001)
Bromosulfophthalein	0.1	Cui et al. (2001)

Table 1 (continued)

Substrate	K_m value (μM)	References
Capsofungin		Sandhu et al. (2005)
Cerivastatin		Shitara et al. (2004)
Cholate	11	Cui et al. (2001)
Bamet-UD2	10	Briz et al. (2002)
Bamet-R2	10	Briz et al. (2002)
Dehydroepiandrosterone-3-sulfate	22	Cui et al. (2001)
Demethylphalloin	17	Meier–Abt et al. (2004)
DPDPE		Abe et al. (2001)
Estradiol-17β-glucuronide	8	König et al. (2000a)
Estrone-3-sulfate	0.2	Tamai et al. (2000)
	13	Cui et al. (2001)
Fluvastatin		Kopplow et al. (2005)
Glycocholate		Kullak-Ublick et al. (2001)
Leukotriene C_4		Abe et al. (1999)
Leukotriene E_4		Abe et al. (1999)
Methotrexate		Abe et al. (1999)
Microcystein-LR	7	Fischer et al. (2005)
Monoglucuronosyl bilirubin	0.1	Cui et al. (2001)
Phalloidin	39	Fehrenbach et al. (2003)
Pitavastatin	3	Hirano et al. (2004)
Pravastatin	35	Hsiang et al. (1999)
Prostaglandin E_2		Tamai et al. (2000)
Repaglinide		Niemi et al. (2005a)
Rifampicin	2	Tirona et al. (2003)
	13	Vavricka et al. (2002)
Rosuvastatin		Schneck et al. (2004)
SN-38		Nozawa et al. (2005)
Taurocholate	10	Cui et al. (2001)
	14	Abe et al. (1999)
	34	Hsiang et al. (1999)
Thromboxane B_2		Abe et al. (1999)
Thyroxine (T4)	3	Abe et al. (1999)
Triiodothyronine (T3)	3	Abe et al. (1999)
Troglitazone metabolite M1		Nozawa et al. (2004c)
OATP1B3 (OATP8)		
Bilirubin	39	Briz et al. (2003)
BQ-123		Kullak-Ublick et al. (2001)
Bromosulfophthalein	3.3	König et al. (2000b)
	6	Letschert et al. (2004)
CCK-8	11	Ismair et al. (2001)
Dehydroepiandrosterone-3-sulfate	>30	Cui et al. (2001)
Deltorphin II		Kullak-Ublick et al. (2001)
Demethlyphalloin	8	Meier–Abt et al. (2004)
Digoxin		Kullak-Ublick et al. (2001)
Docetaxel		Smith et al. (2005)
DPDPE		Abe et al. (2001)

Table 1 (continued)

Substrate	K_m value (μM)	References
Estradiol-17β-glucuronide	5.4	König et al. (2000b)
Estrone-3-sulfate		Nozawa et al. (2004c)
Fexofenadine	108	Shimizu et al. (2005)
Fluvastatin		Kopplow et al. (2005)
Fluo-3		Cui et al. (2001)
Glycocholate		Kullak-Ublick et al. (2001)
Leukotriene C_4		Kullak-Ublick et al. (2001)
Methotrexate	25	Abe et al. (2001)
Microcystin-LR	9	Fischer et al. (2005)
Monoglucuronosyl bilirubin	0.5	Cui et al. (2001)
Ouabain		Kullak-Ublick et al. (2001)
Paclitaxel	7	Smith et al. (2005)
Pitavastatin		Hirano et al. (2004)
Rifampicin	2	Vavricka et al. (2002)
Taurocholate	6	Abe et al. (2001)
	112	Letschert et al. (2004)
Thyroxine (T4)		Kullak-Ublick et al. (2001)
Triiodothyronine (T3)	6	Abe et al. (2001)
OATP1C1 (OATP-F)		
Bromosulfophthalein		Pizzagalli et al. (2002)
Estradiol-17β-glucuronide		Pizzagalli et al. (2002)
Estrone-3-sulfate		Pizzagalli et al. (2002)
reverse Triiodothyronine (rT3)	0.1	Fujiwara et al. (2001)
Thyroxin (T4)	0.1	Pizzagalli et al. (2002)
Triiodothyronin (T3)		Pizzagalli et al. (2002)
OATP2B1 (OATP-B)		
Benzylpenicillin		Tamai et al. (2000)
Bromosulfophthalein	0.7	Kullak-Ublick et al. (2001)
Dehydroepiandrosterone-3-sulfate		Kullak-Ublick et al. (2001)
Estrone-3-sulfate	5	Tamai et al. (2000)
Fexofenadine		Nozawa et al. (2003)
Fluvastatin		Kopplow et al. (2005)
Prostaglandin E_2		Tamai et al. (2000)
OATP3A1 (OATP-D)		
Benzylpenicillin		Tamai et al. (2000)
Estrone-3-sulfate		Tamai et al. (2000)
Prostaglandin E_2		Tamai et al. (2000)
OATP4A1 (OATP-E)		
Benzylpenicillin		Tamai et al. (2000)
Estradiol-17β-glucuronide		Tamai et al. (2000)
Estrone-3-sulfate		Tamai et al. (2000)
Prostaglandin E_2		Tamai et al. (2000)
Reverse Triiodothyronine (rT3)		Fujiwara et al. (2001)
Taurocholate	15	Fujiwara et al. (2001)
Thyroxin (T4)		Fujiwara et al. (2001)

Table 1 (continued)

Substrate	K_m value (μM)	References
Triiodothyronine (T3)	1	Fujiwara et al. (2001)
OATP4C1 (OATP-H)		
cAMP		Mikkaichi et al. (2004b)
Digoxin	8	Mikkaichi et al. (2004b)
Methotrexate		Mikkaichi et al. (2004b)
Ouabain	0.4	Mikkaichi et al. (2004b)
Thyroxine (T4)		Mikkaichi et al. (2004b)
Triidothyronine (T3)	6	Mikkaichi et al. (2004b)
OATP5A1 (OATP-J) and OATP6A1 (OATP-I)		
Substrates not yet determined		

Abbreviations:ACU-154, *O*-glucuronide of PKI166 (inhibitor of the tyrosine kinase activity, Novartis Basel); APD ajmalinium, N-(4,4-Azo-n-pentyl)-21-deoxy[21-3H]ajmalinium; Bamet-R2, Cis-diammineplatinum(II)-chlorocholylglycinate; Bamet-UD2, Cis-diamminebisursodeoxycholateplatinum(II); BQ-123, cyclic pentapeptide (cyclo[D-Trp-D-Asp-L-Pro-D-Val-L-Leu]); cAMP, cyclic adenosine monophosphate; CCK-8, L-aspartyl-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalaninamide hydrogen sulfate ester); CRC 220, thrombin inhibitor, 4-methoxy-2,3,6-trimethylphenylsulfonyl-L-aspartyl-D-4-amidinophenylalanyl- piperidide; DADLE, (D-Ala[2],D-Leu[5])-enkephalin;DPDPE, [D-penicillamine-2,5] enkephalin; Fluo-3, 1-[2-Amino-5-(2,7-dichloro-6-hydroxy-3-oxo-3H-xanthen-9-yl)]-2-(2′-amino-5′ methyl-phenoxyl)-ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid penta-ammonium salt; Gd-B20790, MRI contrast agent, gadolinium complex of 18-[[3-(2-carboxybutyl)-2,4,6-triiodophenyl] amino]-3,6,9-tris(carboxymethyl)-11,18-dioxo-3,6,9,12-tetraazaoctadecanoic acid; SN-38, 7-ethyl-10-hydroxycamptothecin

tions of protein localisations are required to determine the specific role of each OATP family member in drug disposition.

Pharmacogenomics of OATP1B1

In vitro analysis of polymorphisms and haplotypes

Polymorphisms in genes encoding transport proteins may play an important role in the interindividual variability of drug disposition and drug response. A considerable effort has been made to identify single nucleotide polymorphisms (SNPs) or haplotypes, to determine their frequency, and to establish their potential functional consequences on protein localisation and transport function. A summary of so far reported non-synonymous SLCO polymorphisms, haplotypes, alleles, and their allelic frequencies is shown in Table 2 and the localisation of the respective amino acid exchanges is indicated in Fig. 1.

Tirona et al. (2001) investigated 14 non-synonymous polymorphisms in the *SLCO1B1* gene identified in a population of African and European Americans and discovered that some polymorphisms or haplotypes can affect localisation or transport function of the respective protein. In particular, the exchange 217T>C (OATP1B1*2; see Table 2), alone or together with the exchange 1964A>G (haplotype OATP1B1*12), increased the K_m value for [^{3}H] estrone-3-sulfate from 0.54 μM to 5.9 and 8.1 μM, respectively. Furthermore, reduced transport of the substrates estrone-3-sulfate, rifampicin, and estradiol-17β-glucuronide was observed for the variants OATP1B1*3, *5, *6, *9, and *13. Interestingly, many of these amino acid exchanges are located within the transmembrane-spanning domains or in the 2nd and 5th extracellular loop (Fig. 1). These results suggest that these protein regions are involved in substrate recognition and transport.

Michalski et al. (2002) analysed 81 human liver samples originating from Caucasians and identified one haplotype containing 5 base pair exchanges resulting in 3 amino acid substitutions. Two of them corresponded to the previously analysed, frequent polymorphisms OATP1B1*1b and OATP1B1*4 (Tirona et al. 2001). The third exchange could be analysed as the first naturally occurring, rare mutation (OATP1B1-Leu193Arg) within the *SLCO1B1* gene with a frequency below 0.3%. Using stably transfected MDCKII cells and bromosulfophthalein, estradiol-17β-glucuronide, and taurocholate as substrates, the functional consequences of these 3 exchanges have been analysed (Michalski et al. 2002). Whereas bromosulfophthalein was transported from OATP1B1*1b and OATP1B1*4 according to transport rates determined for the OATP1B1 protein, transport of estradiol-17β-glucuronide was significantly reduced by OATP1B1*4. Using taurocholate as substrate, the transport by OATP1B1*1b was reduced and totally abolished by OATP1B1*4. Furthermore, none of the tested substrates was transported by a protein containing the mutation Leu193Arg. In addition, a pronounced change in protein localisation was observed after expression of the mutant OATP1B1-Leu193Arg protein, which was hardly detectable in the lateral membrane of MDCKII cells and mainly retained intracellularly. These investigations demonstrated that alterations in the extracellular loop 2, where the polymorphisms OATP1B1*1b and OATP1B1*4 are localised (Fig. 1), could influence the substrate spectrum whereas the mutation OATP1B1-Leu193Arg totally abolishes the transport function of the protein.

Nozawa et al. (2002) investigated several polymorphisms in the Japanese population and found that the previously identified OATP1B1*1c allele could not be detected in 267 healthy Japanese subjects, whereas OATP1B1*1b and OATP1B1*5 were present with 54% and 0.7%, respectively. In addition, they identified a novel allele, termed OATP1B1*15 (Table 2), possessing the two SNPs Asn130Asp and Val174Ala simultaneously. The allelic frequency of OATP1B1*15 in the investigated population was 3.0%. Using transfected HEK293 cells, they also investigated the functional consequences of these polymorphisms and found no significant alteration in K_m or V_{max}values of the [^{3}H]estrone-3-sulfate uptake. These results were confirmed in a second study investigating the

Table 2 Non-synonymous polymorphisms, alleles, amino acid exchanges, and allelic frequencies in *SLCO* genes encoding human OATP family members

	Polymorphism or Haplotype	Alleles	Amino acid exchange	Allellic frequency [%]						Reference
				AA	EA	CA	HA	Cau	JP	
OATP1A2	NM_134431	OATP1A2*1								
	38T>C	OATP1A2*2	Ile13Thr	2.1	11.1	0	5.7			Lee et al. (2005a)
	516A>C	OATP1A2*3	Glu172Asp	2.1	5.3	0	2.1			Lee et al. (2005a)
	559G>A	OATP1A2*4	Ala187Thr	0	0	0	0.5			Lee et al. (2005a)
	382A>T	OATP1A2*5	Asn128Tyr	1	0	0	0			Lee et al. (2005a)
	404A>T	OATP1A2*6	Asn135Ile	0*	0*	0*	0*			Lee et al. (2005a)
	2003C>G	OATP1A2*7	Thr668Ser	3.7	0	0	1			Lee et al. (2005a)
OATP1B1	AB026257; AJ132573	OATP1B1*1a								König et al. (2000a);
									35.2	Nozawa et al. (2002)
	388A>G	OATP1B1*1b	Asn130Asp	74	30				53.7	Hsiang et al. (1999); Tirona et al. (2001); Nozawa et al. (2002)
	388A>G + 1007C>G	OATP1B1*1b +1007C>G	Asn130Asp + Pro336Arg							Kameyama et al. (2005)
	455G>A + 721G>A	OATP1B1*1c	Arg152Lys + Asp241Asn						0	Abe et al. (1999); Nozawa et al. (2002)
	−11110T>G	OATP1B1*1e	Promoter							Niemi et al. (2004)
	217T>C	OATP1B1*2	Phe73Leu	0	2				0	Tirona et al. (2001); Nishizato et al. (2003)
	245T>C + 467A>G	OATP1B1*3	Val82Ala + Glu156Gly							Tirona et al. (2001)
	463C>A	OATP1B1*4	Pro155Thr	2	16				0	Tirona et al. (2001); Nishizato et al. (2003)
	521T>C	OATP1B1*5	Val174Ala	2	14				0.7	Tamai et al. (2000); Tirona et al. (2001); Nozawa et al. (2002)
	521T>C + 1007C>G	OATP1B1*5 +1007C>G	Val174Ala + Pro336Arg							Kameyama et al. (2005)
	1058T>C	OATP1B1*6	Ile353Thr	0	2					Tirona et al. (2001)
	1294A>G	OATP1B1*7	Asn432Asp	0	1					Tirona et al. (2001)
	1385A>G	OATP1B1*8	Asp462Gly	0	1					Tirona et al. (2001)
	1463G>C	OATP1B1*9	Gly488Ala	9	0					Tirona et al. (2001)
	1964A>G	OATP1B1*10	Asp655Gly	0	2					Tirona et al. (2001)
	2000A>G	OATP1B1*11	Glu667Gly	34	2					Tirona et al. (2001)
	217T>C + 1964A>G	OATP1B1*12	Phe73Leu + Asp655Gly							Tirona et al. (2001)
	245T>C + 467A>G + 2000A>G	OATP1B1*13	Val82Ala + Glu156Gly + Glu667Gly							Tirona et al. (2001)
	388A>G + 463C>A	OATP1B1*14	Asn130Asp + Pro155Thr							Tirona et al. (2001)
	388A>G + 512T>C	OATP1B1*15	Asn130Asp + Val174Ala						10.3	Nozawa et al. (2002)
	388A>G + 521T>C + 1007C>G	OATP1B1*15 +1007C>G	Asn130Asp + Val174Ala + Pro336Arg							Kameyama et al. (2005)
	452A>G	OATP1B1*16	Asn151Ser						3.7	Iida et al. (2001); Nishizato et al. (2003)

Table 2 (continued)

	Polymorphism or Haplotype	Alleles	Amino acid exchange	Allelic frequency [%]						Reference
				AA	EA	CA	HA	Cau	JP	
	−11187G>A + 388A>G + 521T>C	OATP1B1*17	Asn130Asp + Val174Ala							Niemi et al. (2004)
	388A>G + (411G>A) + 463C>A + (571T>C) + 578T>G	OATP1B1*18	Asn130Asp + Pro155Thr + Leu193Arg							Niemi et al. (2004)
	(571T>C) + 1929A>C	OATP1B1*19	Leu643Phe							Niemi et al. (2004)
	388A>G + (597C>T) + 1929A>C	OATP1B1*20	Asn130Asp + Leu643Phe							Niemi et al. (2004)
	−11187G>A + 388A>G + (597C>T) + 1929A>C	OATP1B1*21	Asn130Asp + Leu643Phe							Niemi et al. (2004)
	245T>C		Val82Ala	0	2				0	Tirona et al. (2001); Nishizato et al. (2003)
	467A>G		Glu156Gly	0	2				0	Tirona et al. (2001); Nishizato et al. (2003)
	578T>G		Leu193Arg							Michalski et al. (2002)
	1007C>G		Pro336Arg						1.2	Nishizato et al. (2003)
	1454G>T		Cys485Phe						0.8	Nishizato et al. (2003)
	1628T>G		Leu543Trp							Morimoto et al. (2004)
	1929A>C		Leu643Phe							Niemi et al. (2004)
	−11187G>A		promoter					7.1		Niemi et al. (2004)
OATP1B3	NM_019844									König et al. (2000b)
	334T>G		Ser112Ala					74		Iida et al. (2001); Letschert et al. (2004)
	699G>A		Met233Ile					71		Letschert et al. (2004)
	1564G>T		Gly522Cys					1.9		Letschert et al. (2004)
OATP2B1	NM_007256	OATP2B1*1							69.1	Tamai et al. (2000); Nozawa et al. (2002)
	1175C>T	OATP2B1*2	Thr392Ile					0*	0*	Nozawa et al. (2002); Niemi et al. (2004)
	1457C>T	OATP2B1*3	Ser486Phe					1.2	30.9	Tamai et al. (2000); Nozawa et al. (2002); Niemi et al. (2004)

( ): synonymous mutation; *AA*: African-American; *EA*: European-American; *CA*: Chinese-American; *HA*: Hispanic-American; *Cau*: Caucasian; *JP*: Japanese; * found only in SNP-database

same haplotypes (Iwai et al. 2004) and estradiol-17ß-glucuronide as substrate. Interestingly, the authors did not find a change in K_m values for any of the three haplotypes. However, the V_{max} value for OATP1B1*15 was decreased to less than 30% compared with OATP1 B1*1a. Furthermore, Nozawa et al. (2004b) demonstrated that this haplotype exhibits decreased transport activities for SN-38, the active metabolite of the topoisomerase inhibitor topotecan as well as for the HMG-CoA-reductase inhibitor pravastatin. Therefore, the haplotype OATP1B1*15 could contribute to the known interindividual variability in disposition of these two drugs.

OATP1B1 polymorphisms and drug disposition and effects in humans

Based on the in vitro findings described above, various groups tested the hypothesis whether polymorphisms in the *SLCO1B1* gene have an impact on pharmacokinetics and the effects of drugs in humans. The data currently available on this issue are summarised in Table 3. In spite of the fact that the HMG-CoA-reductase inhibitor pravastatin is not significantly metabolised in humans, pharmacokinetic studies in humans reported a large interindividual variability in pravastatin plasma concentrations (Neuvonen et al. 1998). Kobayashi et al. (2003) reported a pH-dependent OATP2B1-mediated transport of pravastatin. In addition,

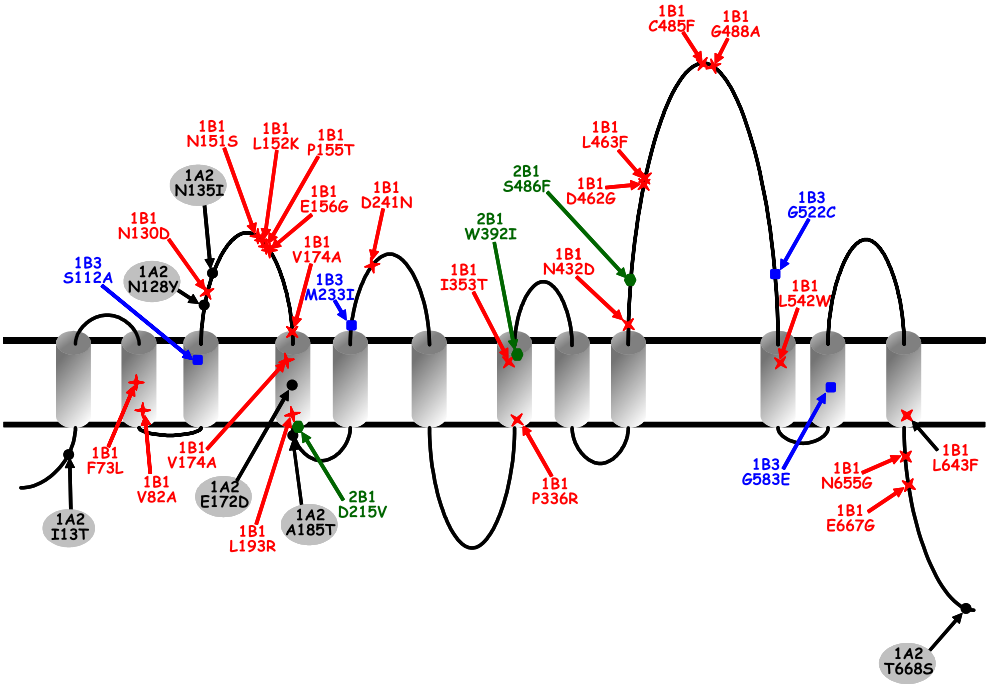

Fig. 1 Localisation of amino acid exchanges caused by mutations and polymorphisms in genes encoding human members of the OATP family. A two-dimensional model of human OATP proteins is shown based on several transmembrane analysis programs. Amino acid exchanges caused by mutations in the *SLCO1A2* gene encoding human OATP1A2 are shown in *grey*, by mutations in the *SLCO1B1* gene encoding human OATP1B1 are shown in *red*, by mutations in the *SLCO1B3* gene encoding human OATP1B3 are shown in *blue*, and by mutations in the *SLCO2B1* geneencoding human OATP2B1 are shown in *green*

in vitro data indicate that pravastatin is also a substrate of OATP1B1 (Hsiang et al. 1999; Nakai et al. 2001), thereby mediating pravastatin uptake into hepatocytes. One would expect that genetic variations or haplotypes associated with a reduced OATP1B1 function would limit the access of pravastatin into the hepatocytes and thereby result in increased systemic exposure to pravastatin. Indeed, several publications highlight the relevance of genetic variations in the *SLCO1B1* gene for pravastatin disposition (Table 3, Fig. 2) (Mwinyi et al. 2004; Niemi et al. 2004; Nishizato et al. 2003). For example, Niemi et al. (2004) reported that individuals with the 521TC genotype have on average a

Table 3 Impact of *SLCO1B1* polymorphisms on drug disposition and effects in humans

Drug	Subjects / study design	Result	Reference
Pravastatin	41 healthy Caucasians / 1×40 mg p.o.	AUC: −11187GG<GA; AUC: 521TT<TC; AUC: *15B non-carriers<carriers; AUC: *17 non-carriers<carriers	Niemi et al. (2004)
Pravastatin	30 healthy Caucasians / 1×40 mg p.o.	AUC: *1a/*1b or *1b/1b<*1a/*1a<*1a/*5	Mwinyi et al. (2004)
Pravastatin	23 healthy Japanese / 1×10 mg p.o.	CLnr: *1b/*15<*1b/*1b	Nishizato et al. (2003)
Pravastatin	41 healthy Caucasians / 1×40 mg p.o.	effect of pravastatin on rate of cholesterol synthesis: *17 carriers<non-carriers	Niemi et al. (2005c)
Pravastatin/ atorvastatin	10 Japanese patients with plasma creatinine kinase elevation or severe muscle complaints vs control patients, who received statins	risk for pravastatin- or atrovastatin induced myopathy: *15 non-carriers<carriers	Morimoto et al. (2004)
Fexofenadine	20 healthy Caucasians / 1×180 mg p.o.	AUC: 521TT<TC< CC	Niemi et al. (2005b)
Repaglinide	56 healthy volunteers / 1×0.25 mg p.o.	AUC: 521TT<TC< CC (+ CYP2C8 genotype) change in blood glucose concentration: −11187GG<GA	Niemi et al. (2005a)
Repaglinide	12 healthy volunteers / 1×0.25 mg p.o.	Increase in repeglinide AUC caused by cyclosporine: 521TT>TC	Kajosaari et al. (2005)
Pitavastatin	24 healthy Koreans / 1×1–8 mg p.o.	AUC: *1b/*1b<*1a/*1a or *1a/*1b<*1a/*15 or *1b/*15	Chung et al. (2005)
Rosuvastatin	36 white, 36 Chinese, 35 Malay and 35 Asian-Indians / 1×40 mg p.o	Whites AUC: 521TT<TC<CC; other ethnic groups AUC: no effect of 521 polymorphism	Lee et al. (2005b)

AUC: area under the plasma-concentration-time curve; CL_{nr}: non-renal clearance

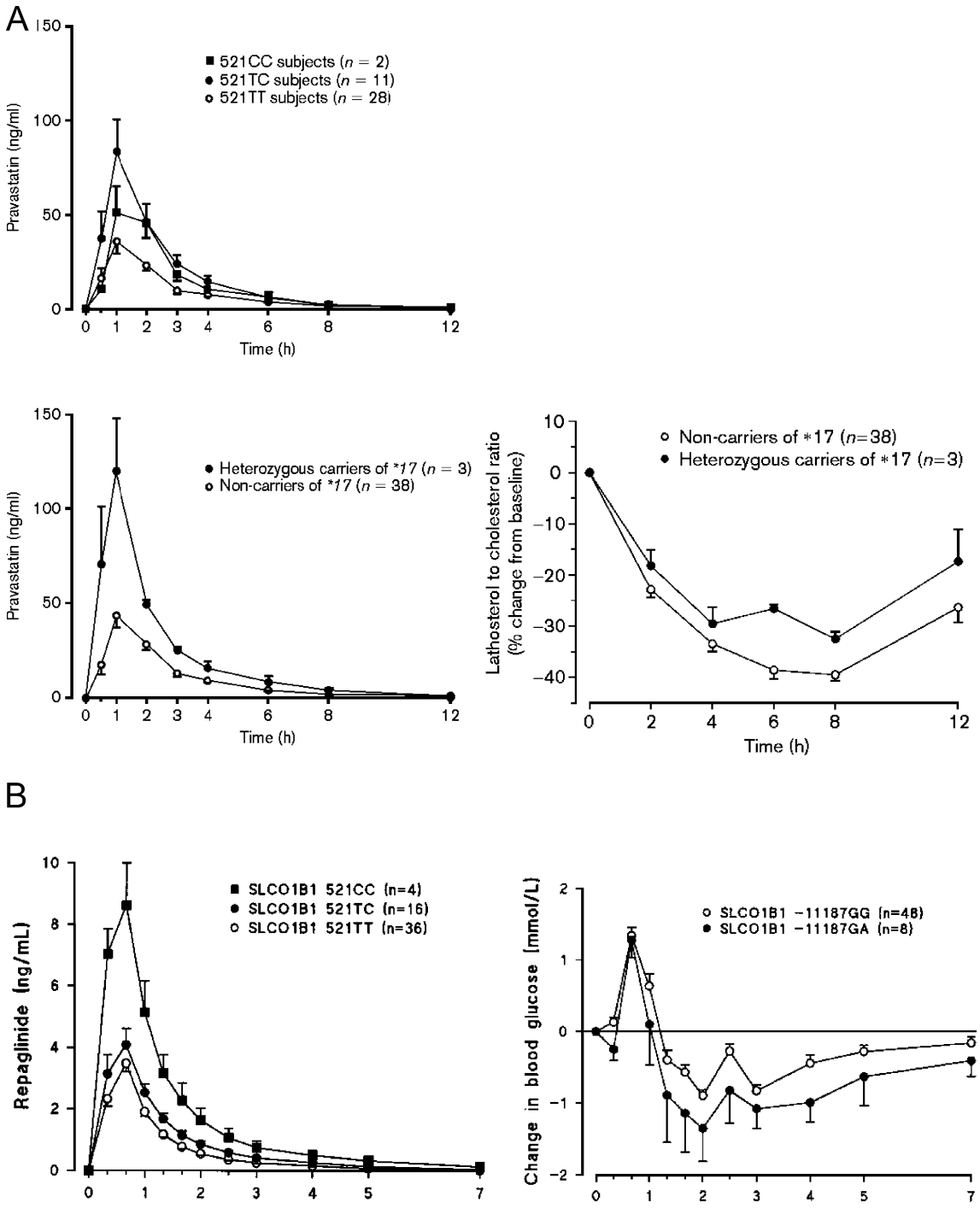

Fig. 2 Impact of *SLCO1B1* polymorphisms and haplotypes on the disposition and effects of pravastatin and repaglinide. **a** *Left panels*: effect of *SLCO1B1* polymorphism 521 and of haplotype OATP1B1*17 on pharmacokinetics of orally administered pravastatin (1×40 mg) to healthy volunteers of both genders (with permission from Niemi et al. 2004); *right panel*: reduced pravastatin effect on cholesterol synthesis in carriers with haplotype OATP1B1*17 (with permission from Niemi et al. 2005c). **b** Effect of *SLCO1B1* polymorphisms 521 and -11187 on repaglinide pharmacokinetics and effects on blood glucose studied in healthy volunteers of both genders (1×0.25 mg p. o.). (With permission from Niemi et al. 2005a; American Society for Clinical Pharmacology and Therapeutics)

106% higher pravastatin plasma concentration compared to the 521TT group (Fig. 2a), which is in accordance with previous in vitro studies showing reduced transport activity for 521T>C (OATP1B1*5; see Table 2) (Tirona et al. 2001, 2003). Based on these pharmacokinetic findings, it was tempting to speculate whether the pravastatin effect on hepatic HMG-CoA-reductase is reduced in individuals with the 521C genotype. In accordance with the underlying hypothesis, Niemi et al. (2005c) reported significantly smaller effects of pravastatin on cholesterol synthesis

(determined by plasma lathosterol concentration and lathosterol to cholesterol concentration ratio) in heterozygous carriers of the *SCLO1B1**17 (containing -11187G, 388A and 521C) haplotype compared with non-carriers (Fig. 2a) (Niemi et al. 2005c).

Recently, the effect of OATP variant alleles on the pharmacokinetic of pitavastatin, another HMG-CoA-reductase inhibitor, has been analysed in healthy Korean subjects (Chung et al. 2005). This group characterised the effect of the alleles OATP1B1*1a, *1b, and *15 (Table 2) and found that the OATP1B1*15 allele is associated with increased pitavastatin plasma concentrations. Similar to pravastatin, the H_1-receptor antagonist fexofenadine is not metabolised in humans and is excreted mainly via the biliary route. In a study with healthy volunteers, fexofenadine plasma concentrations were (similar to the observations with pravastatin) highest in individuals with the 521CC genotype, intermediate in the 521TC group and lowest in the 521TT group (Table 3) (Niemi et al. 2005b). Interestingly, fexofenadine has been established to be a substrate for P-glycoprotein and several OATP transporters (OATP1A2, OATP1B3, OATP2B1) (Cvetkovic et al. 1999; Nozawa et al. 2004a; Shimizu et al. 2005). However, one recent in vitro study reported no significant fexofenadine transport by OATP1B1 (Shimizu et al. 2005). This discrepancy between in vivo and in vitro findings deserves further studies.

Finally, there are recently published data indicating a relevance of polymorphisms in the *SLCO1B1* gene for pharmacokinetics and effects of a drug which is eliminated completely by metabolism, namely for the antidiabetic drug repaglinide. Similar to the in vivo findings with pravastatin and fexofenadine, the AUC for repaglinide in subjects with the 521CC genotype was 107% and 188% higher, respectively, than in individuals with 521TC and 521CC genotype (Table 3, Fig. 2b) (Niemi et al. 2005a). Accordingly, the 521CC group had the largest changes in blood glucose levels, which were, however, not statistically significant (Niemi et al. 2005a). In addition, the effect of repaglinide on blood glucose was significantly associated with the *SCLO1B1* polymorphism - 11187G>A (Fig. 2b).

In addition to this data on the influence of OATP1B1 polymorphisms on drug disposition and effects, Huang et al. (2005) reported an increased risk for unconjugated hyperbilirubinemia in Taiwanese patients with the two frequent polymorphisms at nucleotide position 388 and 521.

Pharmacogenomics of OATP1A2, OATP1B3, and OATP2B1

OATP1A2 (also known as OATP-A) was the first human OATP family member to be cloned and characterised (Kullak-Ublick et al. 1995). Substrates for this uptake transporter include endogenous compounds like steroid hormones and bile salts, but also drugs such as fexofenadine (Table 1). *SLCO1A2* mRNA has been detected in various tissues with a high expression in brain (Kullak-Ublick et al. 1995). There, the protein has been localised to the capillary endothelium (Lee et al. 2005a) suggesting that OATP1A2 may play a critical role in the constitution of the blood-brain barrier. Thus, genetic variations in the *SLCO1A2* gene encoding human OATP1A2 may have significant pharmacological consequences. Lee et al. (2005a) identified and analysed 6 non-synonymous polymorphisms in the *SLCO1A2* gene and found that the allelic frequencies appear to be ethnicity-dependent (Table 2). To investigate the functional consequences of these polymorphisms, they used transiently transfected HeLa cells expressing the respective mutant OATP1A2 protein. They found that the two alleles OATP1A2*3 (516A>C; Glu172Asp) and OATP1A2*6 (404A>T; Asn135Ile) had a markedly reduced transport capacity for deltorphin II and for estrone-3-sulfate. The reason for this reduced transport could be due to an altered plasma membrane localisation of mutated OATP1A2 proteins as demonstrated by surface biotinylation experiments. Furthermore, the authors found that the variants OATP1A2*4 (559G>A; Ala185Thr) and OATP1A2*7 (2003C>G; Thr668Ser) exhibit a substrate-dependent change in transport activity as shown by altered V_{max} values only for selected substrates.

Besides OATP1B1, OATP1B3 seems to be the second liver-specific member of the human OATP family (König et al. 2000b). OATP1B3 has 80% amino acid identity with OATP1B1 and both have an overlapping substrate spectrum. Interestingly, literature on the pharmacogenetics of OATP1B3 is relatively sparse in comparison with OATP1B1. The first identification of SNPs in the *SLCO1B3* gene was published by Iida et al. (2001) without analysing the functional consequences of the base pair alterations. They found several SNPs in the noncoding region of the *SLCO1B3* gene and the non-synonymous SNP 334T>G resulting in the amino acid exchange Ser112Ala. This exchange, as well as one additional frequent polymorphism (699G>A; Met233Ile; allelic frequency of 71%), one rare polymorphism (1564C>T; Gly522Cys; allelic frequency of 1.9%) and the artificial mutation 1748G>A (Gly583Glu), have been analysed in detail by Letschert et al. (2004) with respect to functional consequences on protein localisation and transport characteristics. These investigations demonstrated that both frequent polymorphisms showed localisation and transport properties corresponding to the protein encoded by the reference sequence. In contrast, the rare polymorphism and the artificial mutation abolish the transport function of the protein for the bile salt taurocholate, whereas other substrates like estradiol-17β-glucuronide and estrone-3-sulfate were transported with transport rates according to the protein encoded by the reference sequence. These results support the hypothesis that the 5th extracellular loop of the OATP1B3 protein is involved in substrate recognition, as has also been suggested for the OATP1B1 protein (Tirona et al. 2001). Interestingly, depending on the cell system used for analysis, the rare polymorphism and the mutation showed different glycosylation patterns as demonstrated by immunoblot analysis.

Like OATP1B1 and OATP1B3, OATP2B1 is also expressed in human liver and, therefore, may contribute

to the hepatic elimination of endogenous substances and drugs. In addition, OATP2B1 is expressed in various other tissues including placenta (St-Pierre et al. 2002) and small intestine (Kobayashi et al. 2003). As for OATP1A2 and OATP1B3, the knowledge of the functional consequences of variations in the *SLCO2B1* gene is limited. Nozawa et al. (2002) described the two variants OATP2B1*2 (1175C>T; Thr392Ile) and OATP2B1*3 (1457C>T; Ser486Phe) (Table 2) with an allelic frequency of 30.9% for OATP2B1*3, whereas the OATP2B1*2 allele could not be detected in additional 267 Japanese subjects. The functional consequences of both variations compared to the OATP2B1*1 protein have been analysed in HEK293 cells. These experiments demonstrated that the K_m values for estrone-3-sulfate used as model substrate are in a comparable range for all three OATP2B1 proteins. In addition, no change in the cellular distribution of all different OATP2B1 proteins could be detected (Nozawa et al. 2002).

In conclusion, uptake transporters are increasingly recognised as important factors in the absorption of drugs into the body, the distribution of drugs, and the directed elimination out of the body. In addition, modification of transport rates by drug competition is a new, additional mechanism of drug-drug interactions. Variations in genes encoding uptake transporters can cause interindividual variations of drug effects. Studies regarding the detailed analysis of the consequences of genetic variations, not only limited to single polymorphisms but also to frequent haplotypes of allelic variants, may be of importance to further individualise and optimise treatment regimens involving drugs that are substrates for the respective uptake transporter. Many drugs, however, are substrates for drug metabolising enzymes and efflux transporters in addition to uptake transporters, highlighting the need to characterise the importance of each component for overall drug elimination.

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