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Organic anion transporting polypeptides of the OATP/SLC21 family: phylogenetic classification as OATP/SLCO superfamily, new nomenclature and molecular/functional properties

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Abstract The organic anion transporting polypeptides (rodents: Oatps, human: OATPs) form a superfamily of sodium-independent transport systems that mediate the transmembrane transport of a wide range of amphipathic endogenous and exogenous organic compounds. Since the traditional *SLC21* gene classification does not permit an unequivocal and species-independent identification of genes and gene products, all Oatps/OATPs are newly classified within the OATP/SLCO superfamily and subdivided into families ($\geq 40\%$ amino acid sequence identity), subfamilies ($\geq 60\%$ amino acid sequence identity) and individual genes and gene products according to their phylogenetic relationships and chronology of identification. Implementation of this new classification and nomenclature system occurs in agreement with the HUGO Gene Nomenclature Committee (HGNC). Among 52 members of the OATP/SLCO superfamily, 36 members have been identified so far in humans, rat and mouse. The latter are clustered within 6 (out of 12) families (OATP1–OATP6) and 13 subfamilies. Oatps/OATPs represent 12 transmembrane domain proteins and contain the superfamily signature D-X-RW-(I,V)-GAWW-X-G-(F,L)-L. Although species divergence, multispecificity and wide tissue distribution are common characteristics of many Oatps/OATPs, some members of the OATP/SLCO superfamily are highly conserved during evolution, have a high substrate specificity and exhibit unique cellular expression in distinct organs. Hence, while Oatps/OATPs with broad substrate specificity appear to play an important role in the bioavailability, distribution and excretion of numerous exogenous amphipathic organic anionic compounds, Oatps/OATPs with a narrow spec-

trum of transport substrates may exhibit more specific physiological functions in distinct organs.

Keywords Bile salt · Drug transporter · Xenobiotic elimination

Introduction

Organic anion transporting polypeptides (rodents: Oatps, human: OATPs) are important membrane transport proteins that mediate the sodium-independent transport of a wide range of amphipathic organic compounds including bile salts, organic dyes, steroid conjugates, thyroid hormones, anionic oligopeptides, numerous drugs and other xenobiotic substances [1]. Although some Oatps/OATPs are selectively involved in the hepatic clearance of albumin-bound compounds from portal blood plasma [2], most Oatps/OATPs are expressed in multiple tissues including the blood-brain barrier (BBB), choroid plexus, lung, heart, intestine, kidney, placenta and testis [3]. Unfortunately, the rapid and independent identification of new Oatps/OATPs has led to the assignment of either different names for identical proteins or similar names for non-orthologous gene products [1]. Furthermore, the current classification within the solute carrier family 21 (rodents: *Slc21*; human: *SLC21*) does not permit an unequivocal and species-independent identification of the various *Oatp/OATP*-genes [1]. To solve these problems and to avoid further confusions in future scientific discussions, we have proposed a new species-independent classification and nomenclature system that is based on divergent evolution and defines an *Oatp/OATP*-gene superfamily, which can be divided further into families, subfamilies and individual genes and gene products according to the evolutionary relationships and the degree of amino acid sequence identities [1]. Meanwhile, the principle of this evolutionary-based new *Oatp/OATP* classification and nomenclature system has been welcomed and accepted by several experts in the field and, most importantly, also by the HUGO Gene Nomenclature

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Committee (HGNC). Since the current *Slc21/SLC21* classification does not permit the sub-classification of the *Oatp/OATP*-gene superfamily into families and sub-families as suggested in analogy to the cytochrome P450 superfamily [1, 4], and since the HGNC suggested to keep the root gene symbol “*SLC*”, it has been agreed to create the new “*SLCO*” symbol for gene classification and to keep the “*OATP*” symbol for corresponding protein nomenclature. It is the main purpose of this overview to present the definite principles, rules and naming of the new *OATP/SLCO* classification and nomenclature system. Furthermore, comparative tables and figures are provided to help in the translation of the old into the new system. And finally, the history of discovery and the molecular and physiological properties of individual *Oatps/OATPs* will be summarized. Further details about the molecular and functional properties of this transporter superfamily can be found in our previous review [1].

New classification and nomenclature

So far 36 *Oatps/OATPs* have been identified in humans, rat and mouse (Fig. 1). As indicated in Table 1, most *Oatps/OATPs* have been given several different trivial names, and sometimes similar names have been used for different gene products in different species (e.g. rat *Oatp1*/human *OATP1*; rat *Oatp2*/mouse *Oatp2*/human *OATP2*). Furthermore, organ-specific rather than a functionally based nomenclature has been used despite incomplete knowledge about the organ topology of individual *Oatps/OATPs* (Table 1). Although the provisional use of continuous numbering of rodent *Oatps*, alphabetic ordering of human *OATPs* and gene classification within the *Slc21/SLC21* system has helped in the clear-cut identification of a specific gene product in the past, this system permits neither unequivocal and species-independent protein and gene identifications nor the classification of the various *Oatp/OATP* genes within a separate transporter superfamily [1]. That all *Oatps/OATPs* do indeed form a transporter gene superfamily is evidenced by the phylogenetic tree (Fig. 1) and its underlying amino acid sequence identities [1]. This *OATP* superfamily can be further subdivided into families and subfamilies in close analogy to the classification of drug-metabolizing enzymes [4, 5]. Hence, *Oatps/OATPs* within the same family share $\geq 40\%$ amino acid sequence identities and are designated by Arabic numbering, e.g. families *OATP1*, *OATP2*, *OATP3*, *OATP4*, *OATP5* and *OATP6* (Fig. 2). Individual subfamilies include *Oatps/OATPs* with amino acid sequence identities $\geq 60\%$ and are designated by letters, e.g. subfamilies *OATP1A*, *OATP1B*, *OATP1C*, *OATP2A*, *OATP2B*, *OATP3A* etc. If there are several individual gene products (proteins) within the same subfamily, additional continuous Arabic numbering based on the chronology of identification should be used, e.g. *Oatp1a1*, *OATP1A2*, *Oatp1a3*, etc. (Fig. 2).

While the above outlined classification principle has been accepted by several experts in the field (number of experts contacted: 16; positive responses: 8; negative responses: 0; no responses: 8) and by the HGNC, the latter suggested to keep the “*SLC*” symbol for gene identification and to use the functional “*OATP*” symbol for protein nomenclature. To follow this recommendation it was necessary to introduce a new *gene* symbol, since the *SLC21* stem is not compatible with an unambiguous family designation, e.g. the gene of the *OATP1* family member *OATP1A2* would become *SLC21IA2*, which could be confused with a member of the (hypothetical) *SLC21I* gene family. This problem was solved by changing *SLC21* into the new gene symbol “*SLCO*” (O = initial letter of *OATP*), which classifies for example the gene of *OATP1A2* unambiguously as *SLCO1A2* (Figs. 2, 3). By this adaptation it is possible to use the same phylogenetically based, species-independent and open-ended classification/nomenclature system at both the protein and gene levels for all members of the *OATP/SLCO* superfamily [1], to stay within the *SLC* transporter gene classification of the HUGO (<http://www.gene.ucl.ac.uk/nomenclature/>) and mouse (<http://www.informatics.jax.org>) gene nomenclature committees, and to keep the original and well-accepted functional *OATP* designation at the protein level.

The principles and consequences of the new *OATP/SLCO* classification and nomenclature system are further illustrated in Figs. 2 and 3 {Please note the change introduced in Fig. 3 (see legend) with respect to the classification of the families *OATP6* and *OATP10* as compared to our previous suggestion [1]}. Furthermore, the old and new protein and *gene* nomenclatures are compared in Table 2 and Fig. 3 to help in the translation from the old into the new system. Unambiguous and species-independent classification and naming of newly identified proteins (*genes*) of the *OATP/SLCO* superfamily according to the new system must include: (1) the superfamily designation *OATP (SLCO)* (human members) or *Oatp (Slco)* (rodent members), (2) the family number, (3) the subfamily letter (capital letters for human members, small letters for rodent members), and (4) continuous Arabic numbering according to the chronology of protein (*gene*) identification. Human proteins (*genes*) are given in capitals [e.g. *OATP1A2 (SLCO1A2)*] (<http://www.gene.ucl.ac.uk/nomenclature/>), while rat and mouse proteins (*genes*) are indicated by an initial capital followed by small letters [e.g. *Oatp1a1 (Slco1a1)*, *Oatp7a1 (Slco7a1)*] (<http://www.informatics.jax.org>). For other animal species (e.g. farm animals such as cow, pig, cat, dog, chicken) the exact writing styles should follow the recommendations of the respective nomenclature committees (e.g. <http://www.thearkdb.org/nomenclature.html>; for further links see <http://www.gene.ucl.ac.uk/nomenclature/>). Furthermore, if several splice variants of a given *Slco/SLCO* gene are known, the names of the resulting *Oatps/OATPs* should be followed by an underscore, the lower case letter “v” and

Fig. 1 Phylogenetic tree of the human and rodent members of the OATP/*SLCO* superfamily using the traditional (old) protein nomenclature. Human OATPs are given in *capitals* (exception: OAT-K1 represents a rat protein). Rodent Oatps are written with an *initial capital* followed by *small letters*. To distinguish between rat and mouse proteins, all mouse Oatps are indicated by “m”. The tree was calculated using the ClustalW program (<http://www.ebi.ac.uk/clustalw/>) and visualized using the program TREEVIEW [54]

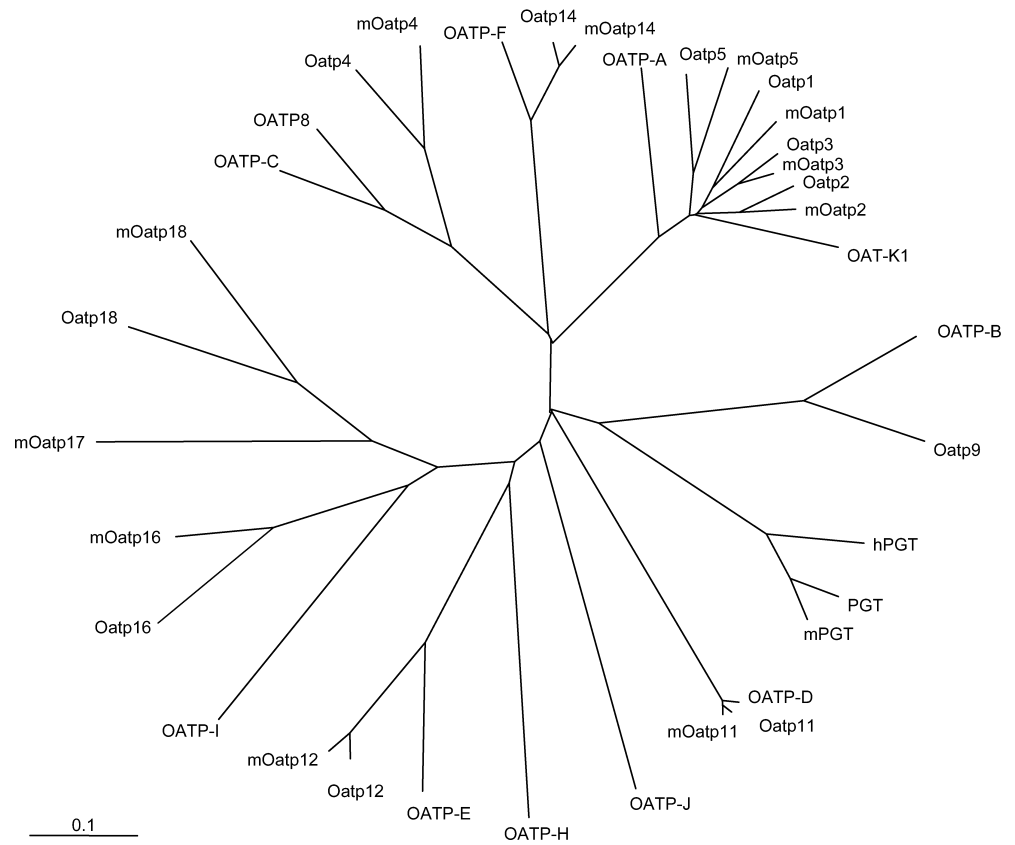


Table 1 Current Oatp/OATP protein and *gene* nomenclature and classification. Ambiguous protein names (e.g. similar names for distinct proteins, tissue specific names) are highlighted in **bold**. Abbreviations: *BSAT*, brain specific anion transporter; *GST*, gonad

specific transporter; *lst/LST*, liver specific transporter; *MJAM*, derived from the researchers initials; *Oatp/OATP*, organic anion transporting polypeptide; *PGT*, prostaglandin transporter; *Slc/SLC*, solute carrier; *TST*, testis-specific transporter

Protein name	Alias	Human gene symbol	Rat gene symbol	Mouse Gene Symbol
Oatp1	Oatp	–	<i>Slc21a1</i>	<i>Slc21a1</i>
PGT	hPGT (human), rPGT (rat), mPGT (mouse)	<i>SLC21A2</i>	<i>Slc21a2</i>	<i>Slc21a2</i>
OATP-A	OATP, OATP1	<i>SLC21A3</i>	–	–
OAT-K1		–	<i>Slc21a4</i>	–
Oatp2		–	<i>Slc21a5</i>	<i>Slc21a5</i>
OATP-C	LST-1, OATP2 , OATP6	<i>SLC21A6</i>	–	–
Oatp3		–	<i>Slc21a7</i>	<i>Slc21a7</i>
OATP8	LST-2	<i>SLC21A8</i>	–	–
OATP-B	OATP-RP2 (human), moat1 (rat), Oatp9	<i>SLC21A9</i>	<i>Slc21a9</i>	–
Oatp4	rlst-1 (rat), mlst-1 (mouse)	–	<i>Slc21a10</i>	<i>Slc21a10</i>
OATP-D	OATP-RP3 (human), Pgt2 (rat), MJAM (mouse), Oatp11	<i>SLC21A11</i>	<i>Slc21a11</i>	<i>Slc21a11</i>
OATP-E	OATP-RP1 (human), oatpE (rat), Oatp12	<i>SLC21A12</i>	<i>Slc21a12</i>	–
Oatp5		–	<i>Slc21a13</i>	<i>Slc21a13</i>
OATP-F	OATP-RP5 (human), BSAT1 (rat), Oatp2 (mouse), Oatp14	<i>SLC21A14</i>	<i>Slc21a14</i>	<i>Slc21a14</i>
OATP-J	OATP-RP4	<i>SLC21A15</i>	–	–
Oatp16	TST-1, GST-1	–	<i>Slc21a16</i>	<i>Slc21a16</i>
Oatp17		–	–	<i>Slc21a17</i>
Oatp18	TST-2, GST-2	–	<i>Slc21a18</i>	<i>Slc21a18</i>
OATP-I	GST	<i>SLC21A19</i>	–	–
OATP-H		<i>SLC21A20</i>	–	–

the consecutive numbering of the variants (e.g. Oatp1a3_v1, Oatp1a3_v2; Table 2).

The above outlined new classification system takes into account the molecular and phylogenetic relationships

between individual genes and proteins, is easy to follow and provides an unambiguous open-ended species-independent nomenclature for all members of the OATP/*SLCO* superfamily. Implementation of the new classifi-

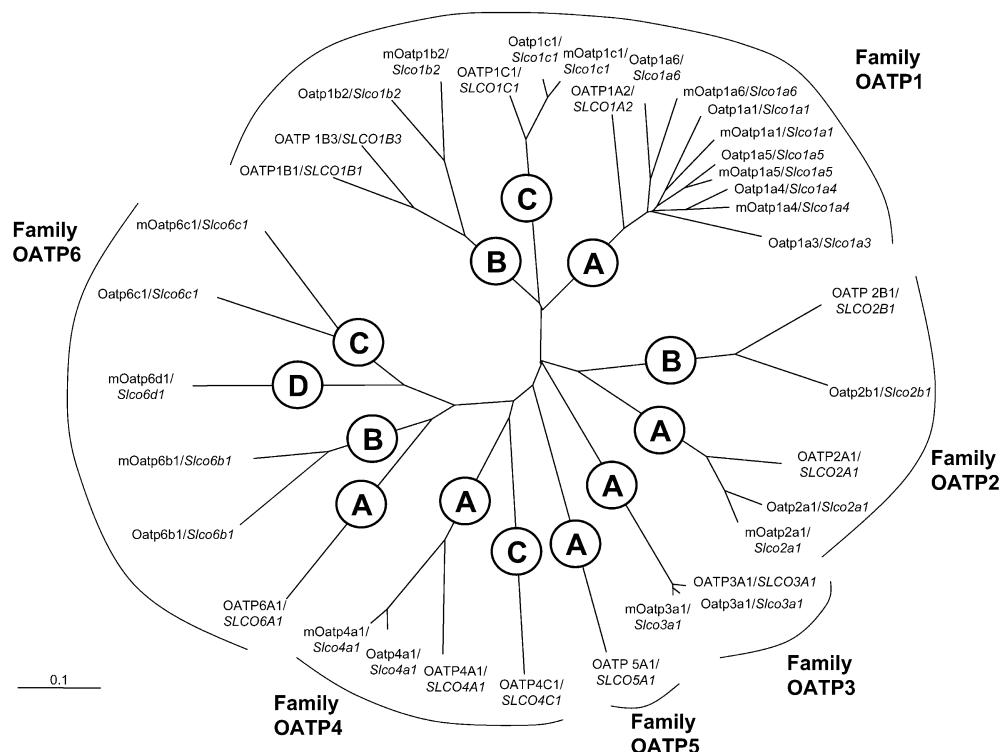


Fig. 2 Phylogenetic classification and new nomenclature of human and rodent (rat, mouse) members of the OATP/SLCO superfamily of membrane transporters. Oatps/OATPs with amino acid sequence identities $\geq 40\%$ among each other belong to the same OATP family (e.g. OATP1, OATP2, OATP3, OATP4, OATP5, OATP6). Proteins with amino acid sequence identities $\geq 60\%$ are grouped into subfamilies and denoted with a capital letter after the family number (e.g. OATP1A, OATP1B, OATP1C, OATP2A, OATP2B, etc.). Individual proteins (*genes*) are continuously numbered

according to the chronology of their identification. The “Oatp” (rodents)/“OATP” (human) symbols denote proteins, while the “Slco”/“SLCO” symbols indicate the respective *genes*. Mouse Oatps are indicated by “m”. The tree was calculated using the ClustalW program (<http://www.ebi.ac.uk/clustalw/>) and visualized using the program TREVIEW [54]. Only the families OATP1 to OATP6 are indicated, since only these six families contain human OATPs (see also Fig. 3)

cation/nomenclature system will be supported by the creation of an OATP/SLCO web site (<http://www.kpt.unizh.ch/oatp/>) and by the corresponding adaptation of the human (<http://www.gene.ucl.ac.uk/nomenclature/>) and mouse (<http://www.informatics.jax.org>) genome nomenclature databases as soon as possible. Furthermore, an expert committee, the members of which will be indicated on the OATP/SLCO web site, shall be created to help and supervise the future classification and nomenclature of newly identified members of the OATP/SLCO superfamily. We suggest starting with the new classification and nomenclature of the OATP/SLCO superfamily immediately and in close coordination with the adaptations of the human and mouse genome nomenclature databases. During the transition period, where the traditional (old) protein and gene names are still familiar to most investigators in the field, the new nomenclature should be supplemented by the familiar old names, which should be given in parentheses at the first occurrence in the text {e.g. OATP1A2 [previously called OATP-A (SLC21A3)]}. This principle will also be adhered to in the following sections of this manuscript.

History of discovery

Rat Oatp1a1 [previously called Oatp1 (*Slc21a1*)] was the first member of the OATP/SLCO gene superfamily to be identified by expression cloning using the *Xenopus laevis* oocyte system [6]. Subsequently Oatp2a1 [previously called PGT (*Slc21a2*)] was identified by Kanai et al. [7]. OATP1A2 [previously called OATP-A (*SLC21A3*)] was the first human superfamily member isolated by hybridization screening from human liver [8]. Subsequently, additional Oatps/OATPs were identified and characterized from various species using homology screening either by hybridization experiments or in silico (Figs. 2, 3, Table 2).

Molecular and phylogenetic relationships

Oatps/OATPs represent 12 transmembrane domain (TM) proteins with common structural features such as (1) a large extracellular domain between TMs 9 and 10 (extracellular loop 5), which contains many conserved cysteine residues, (2) the *N*-glycosylation sites in extracellular loops 2 and 5, and (3) the consensus superfamily

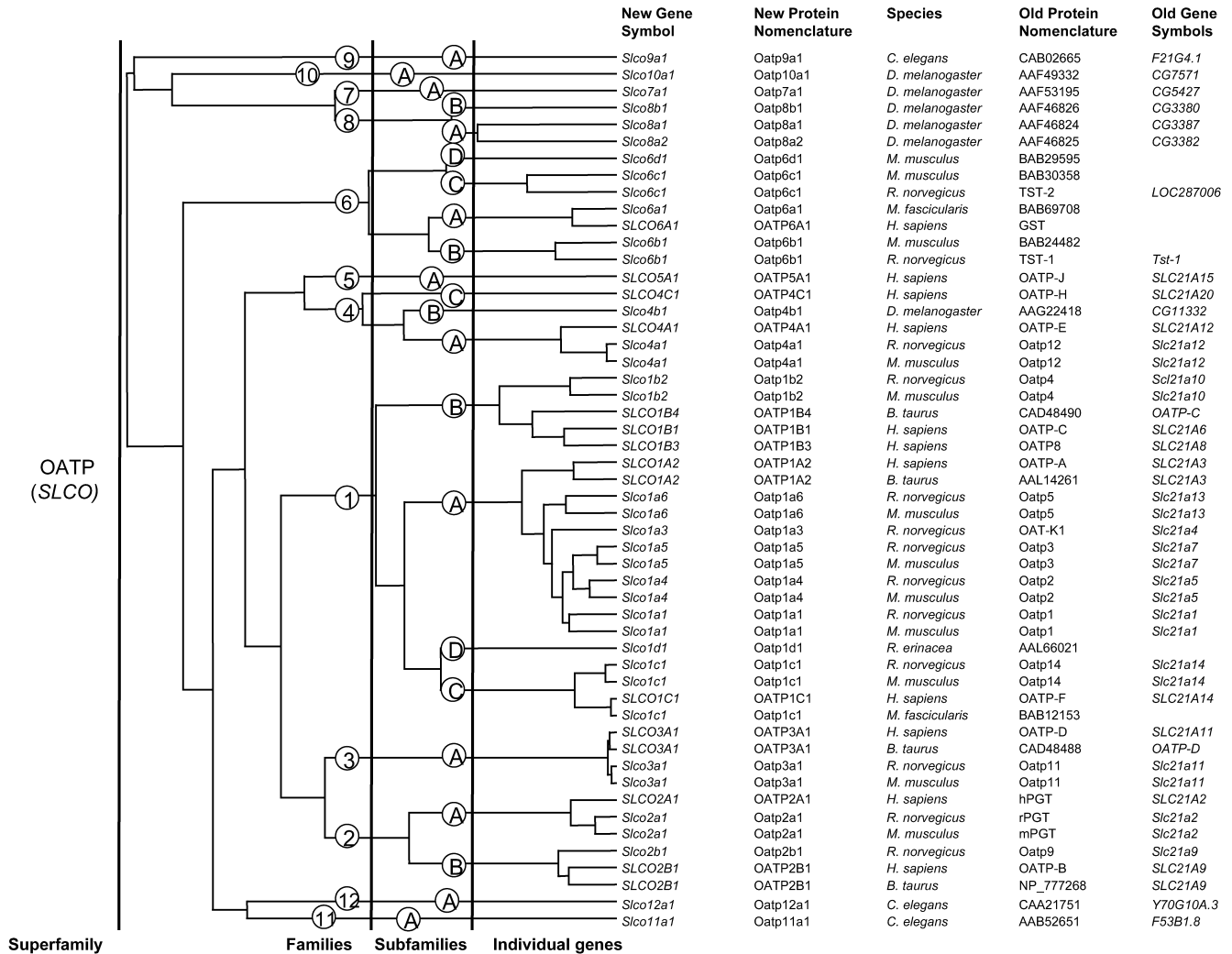


Fig. 3 Phylogenetic classification and new nomenclature of 52 members of the OATP/SLCO superfamily of membrane transporters. The superfamily is grouped into families ($\geq 40\%$ amino acid sequence identity) and subfamilies ($\geq 60\%$ amino acid sequence identity) as described in the text. The new gene symbol of the superfamily is “*Slco*” (rodents)/“*SLCO*” (human). For protein nomenclature the “Oatp” (rodents)/“OATP” (human) symbol is used. The new nomenclature consists of (1) the superfamily designation OATP (*SLCO*) (human members) or Oatp (*Slco*) (rodent members), (2) the family number, (3) the subfamily letter (capital letters for human members, small letters for rodents), and (4) continuous Arabic numbering of individual proteins (*genes*) according to the chronology of identification. For comparison, the old (current) protein and gene nomenclature is also given.

signature D-X-RW-(I,V)-GAWW-X-G-(F,L)-L at the border between extracellular loop 3 and TM 6 [1]. Based on sequence similarities with EST and genomic database entries, Oatp/OATP-related proteins were identified in many different species other than in humans, rat and mouse, including fruitflies (*Drosophila melanogaster*), bees (*Apis mellifera*), nematodes (*Caenorhabditis elegans*), sea urchins (*Strongylocentrotus purpuratus*), catfish (*Ictalurus punctatus*), zebrafish (*Danio rerio*), pufferfish (*Fugu rubripes*), frogs (*Xenopus laevis*), chick-

Superfamily members of human, rat, mouse, cow, *Drosophila* and *C. elegans* are given illustrating the species-independence of the new classification system. The phylogenetic tree was calculated using GCG programs PILEUP, DISTANCES and GROWTREE and visualized using the program TREEVIEW [54]. **Important remark:** In comparison to our previously suggested classification [1] the families OATP6 and OATP10 have been exchanged (i.e. OATP6 = previous OATP10; OATP10 = previous OATP6). By this change all families containing human OATPs are clustered within the families OATP1 to OATP6. Families OATP7 to OATP12 do not contain any human OATPs. It is suggested that in future this classification should be used rather than the previous one [1], since we feel that it is advantageous to group all human OATP-containing families together

en (*Gallus gallus*), cow (*Bos taurus*) and pig (*Sus scrofa*). However, no similarities were found with the sequenced genomes of bacteria and yeast. With respect to the evolution of the animal kingdom, Oatps/OATPs were so far only found in animals that belong to the bilaterians, i.e. to species that belong to the clade of protostomia (e.g. arthropods, nematodes) or to the clade of deuterostomia (e.g. vertebrates, echinoderms).

Table 2 Human and rodent members of the OATP/SLCO superfamily. Summary of new and old classification/nomenclature, predominant transport substrates, tissue distribution, chromosomal localization, accession number and known splice variants

New gene symbol ^a	New protein name ^a	Old gene symbol	Old protein names	Predominant substrate	Tissue distribution and cellular/subcellular expression	Gene locus ^b	Sequence accession id	Splice variant
<i>SLCO1A1</i>	Oatp1a1	<i>Slc21a1</i>	Oatp1, Oatp	Bile salts, organic anions, organic cations	Liver (basolateral membrane of hepatocytes), kidney (apical membrane of proximal tubule), choroid plexus (apical ciliary body)	4q44 (r) 6A3-A5 (m)	NM_017111 NM_013797	
<i>SLCO1A2</i>	OATP1A2	<i>SLC21A3</i>	OATP-A, OATP	Bile salts, organic anions, organic cations	Brain (endothelial cells), kidney, liver, ciliary body	12p12 (h)	NM_021094	
<i>SLCO1A3</i>	Oatp1a3_v1 Oatp1a3_v2	<i>Slc21a4</i>	OAT-K1 OAT-K2	Bile salts, organic anions	Kidney	4q44 (r)	NM_030837	AB012662
<i>SLCO1A4</i>	Oatp1a4	<i>Slc21a5</i>	Oatp2	Digoxin, bile salts, organic anions, organic cations	Liver, blood-brain barrier, choroid plexus, ciliary body, retina	4 (r) 6G2 (m)	NM_131906 NM_030687	
<i>SLCO1A5</i>	Oatp1a5	<i>Slc21a7</i>	Oatp3	Bile salts, organic anions	Jejunum, choroid plexus	4q44 (r) 6G2 (m) 6G2 (m)	NM_030838 NM_130861	
<i>SLCO1A6</i>	Oatp1a6	<i>Slc21a13</i>	Oatp5	Bile salts, organic anions	Liver	4q44 (r) 6G2 (m)	NM_130736 NM_023718	
<i>SLCO1B1</i>	OATP1B1	<i>SLC21A6</i>	OATP-C, LST-1, OATP2	Bile salts, organic anions	Liver	12p12 (h)	NM_006446	
<i>SLCO1B2</i>	Oatp1b2	<i>Slc21a10</i>	Oatp4, Lst-1	Bile salts, organic anions	Liver, ciliary body	4q44 (r) 6G2 (m)	NM_031650 NM_020495	
<i>SLCO1B3</i>	OATP1B3	<i>SLC21A8</i>	OATP8	Bile salts, organic anions, digoxin	Liver, cancer cell lines	12p12(h)	NM_019844	
<i>SLCO1C1</i>	OATP1C1	<i>SLC21A14</i>	OATP-F, OATP-RP5	T4, rT3, BSP	Brain, testis (Leydig cells)	12p12 (h)	NM_017435	
<i>SLCO1C1</i>	Oatp1c1	<i>Slc21a14</i>	Oatp14, BSAT1, Oatp2			4q44 (r)6G1 (m)	NM_053441 NM_021471	
<i>SLCO2A1</i>	OATP2A1	<i>SLC21A2</i>	hPGT	Eicosanoids	Ubiquitous	3q21 (h) 8q32	NM_005621 NM_022667	
<i>SLCO2A1</i>	Oatp2a1	<i>Slc21a2</i>	rPGT mPGT			(r)9F1 (m)	NM_033314	
<i>SLCO2B1</i>	OATP2B1	<i>SLC21A9</i>	OATP-B, OATP-RP2	E-3-S, DHEAS, BSP	Liver, placenta, ciliary body	11q13 (h)	NM_007256	
<i>SLCO2B1</i>	Oatp2b1	<i>Slc21a9</i>	Oatp9, moat1			15q26 (h) 7D1 (m)	NM_080786 NM_013272	BC000585
<i>SLCO3A1</i>	OATP3A1	<i>SLC21A11</i>	OATP-D, OATP-RP3	E-3-S, prostaglandin	Ubiquitous	20q13.1 (h) 2H4(m)	AF239219 NM_023908	
<i>SLCO3A1</i>	Oatp3a1	<i>Slc21a11</i>	Oatp11 MJAM				NM_016354 NM_133608	
<i>SLCO4A1</i>	OATP4A1	<i>SLC21A12</i>	OATP-E, OATP-RP1	Taurocholate, T3, prostaglandin	Ubiquitous		NM_148933	
<i>SLCO4A1</i>	Oatp4a1	<i>Slc21a12</i>	Oatp12, oatpE					
<i>SLCO4C1</i>	OATP4C1	<i>SLC21A20</i>	OATP-H		Kidney	5q21 (h)	AY273896	
<i>SLCO5A1</i>	OATP5A1	<i>SLC21A15</i>	OATP-J, OATP-RP4			8q13.1 (h)	NM_030958	
<i>SLCO6A1</i>	OATP6A1	<i>SLC21A19</i>	OATP-I, GST		Testis	5q21 (h)	NM_173488	
<i>SLCO6B1</i>	Oatp6b1 Oatp6b1	<i>Slc21a16</i>	Oatp16, TST-1, GST-1	Taurocholate, T3, T4, DHEAS	Testis, epididymis, ovary, adrenal gland	9 (r)1 (m)	NM_133412 AK006249	
<i>SLCO6C1</i>	Oatp6c1	<i>Slc21a18</i>	Oatp18, TST-2, GST-2	Taurocholate, T3, T4, DHEAS	Testis	9 (r)1 (m)	NM_173338 AK016647	
<i>SLCO6D1</i>	Oatp6d1	<i>Slc21a17</i>	Oatp17			1 (m)	AK014872	

^a All *capital symbols* denote human genes and gene products while *lower case symbols* stand for rodent genes and gene products (exception: OAT-K1 is a rat protein). To better discriminate between human, rat and mouse gene products sometimes a *lower case h, r or m* precedes the abbreviation. However, this is not part of the gene or protein symbol

^b (h) human, (r) rat, (m) mouse

Functional characteristics, physiological importance and pharmacological implications

Oatps/OATPs are sodium-independent transport systems [6, 8, 9, 10]. Their transport mechanism appears to be anion exchange, coupling the cellular uptake of organic compounds with the efflux of, for example, bicarbonate, glutathione and/or glutathione-S-conjugates [11, 12, 13, 14]. Although the latter has been demonstrated so far only for rat Oatp1a1 and Oatp1a4 [previously called Oatp2 (*Slc21a5*)], it is highly likely that all members of the OATP superfamily can mediate bidirectional organic substrate transport, making the overall directionality of transport dependent on the prevailing local substrate gradients. Oatp/OATP-mediated organic anion exchange seems to be pH-dependent and electroneutral [12]. In addition, it has been demonstrated that the phosphorylation state of rat Oatp1a1 is important for transport since extracellular ATP reduces Oatp1a1-mediated BSP transport in rat hepatocytes via phosphorylation at intracellular serine residues [15].

Most Oatps/OATPs transport a wide spectrum of amphipathic organic compounds. This broad substrate specificity was demonstrated first for rat Oatp1a1 [16]. Originally, Oatp1a1 was isolated as a sodium-independent bromosulphophthalein (BSP) and taurocholate uptake system of rat liver [6]. Subsequently, extensive functional characterization in different experimental systems established that it can mediate the transport of a wide range of amphipathic organic compounds including bile salts, steroid hormones and their conjugates, thyroid hormones, organic cations such as *N*-(4,4-azo-*n*-pentyl)-21-deoxy-ajmalinium and numerous drugs including the endothelin receptor antagonist BQ-123, the thrombin inhibitor CRC-220, the opioid receptor agonists [*D*-penicillamine 2,5] enkephalin (DPDPE) and deltorphin II, the angiotensin-converting enzyme inhibitors enalapril and temocaprilat, the HMG-CoA reductase inhibitor pravastatin and the antihistamine fexofenadine [1]. Such a broad and partially overlapping substrate specificity has also been documented for most other members of the OATP1A- and OATP1B-subfamilies (Table 2) indicating that they play an important role, together with the P-glycoproteins (Mdr/MDRs) and the multidrug resistance associated proteins (Mrps/MRPs), in overall drug absorption and drug disposition.

The broad substrate specificity of many Oatps/OATPs raises the question as to the common chemical and/or structural denominators of Oatp/OATP substrates. No systematic studies have been performed in this direction so far. However, from the available data it can be concluded that in general Oatp/OATP substrates are anionic amphipathic molecules with a rather high molecular weight (>450) and a high degree of albumin binding under physiological conditions. Based on recent 3D-QSAR studies a pharmacophore model containing two hydrogen bond acceptors, one hydrogen bond donor and two hydrophobic regions was obtained. These character-

istics are met by most Oatp/OATP substrates including bile salts, steroids and cyclic and linear peptides.

Rifamycin SV and rifampicin are two structurally related antibiotics that have been shown to interact with Oatp/OATP-mediated transport. It turns out that rifamycin is a potent inhibitor of all human liver OATPs as well as of rat Oatp1a1 and Oatp1a4, while rifampicin mainly inhibits human OATP1B3 [previously called OATP8 (*SLC21A8*)] and rat Oatp1a4 [17, 18]. These data indicate that co-administration of a specific OATP-inhibitor could be used to increase the oral bioavailability of drugs that otherwise have a high OATP-mediated hepatic first-pass elimination. Hence, preferential or even selective inhibition of hepatic Oatps/OATPs has important implications for drug development and drug therapy.

Although some Oatps/OATPs are preferentially, or even selectively, expressed in the liver (e.g. Oatp1b2, OATP1B1, OATP1B3) (Fig. 4), many Oatps/OATPs exhibit multiple tissue expression (e.g. Oatp1a1, Oatp1a4, Oatp1a5, OATP1A2, OATP2B1) (Fig. 4, Table 2) [1]. As indicated in Fig. 4, all liver Oatps/OATPs are localized at the basolateral (sinusoidal) plasma membrane domain of hepatocytes. In contrast, in choroid plexus Oatp1a4 is localized basolaterally whereas Oatp1a1 and/or Oatp1a5 [previously called Oatp3 (*Slc21a7*)] is (are) localized at the apical plasma membrane (Fig. 4) [1]. In addition, Oatp1a1 and Oatp1a5 are also localized at the apical plasma membrane domains in renal proximal tubular and intestinal epithelial cells, respectively (Fig. 4). Hence, while Oatp1a1 appears to be differentially targeted in different epithelial cells, Oatp1a4 exhibits consistent basolateral, and Oatp1a3 [previously called OAT-K1 (*Slc21a4*)] and Oatp1a5 consistent apical, expression in polar epithelial cells (Fig. 4). The molecular targeting mechanisms for various Oatps/OATPs in distinct epithelial cells remain to be elucidated.

Properties of individual human (and rodent) OATPs

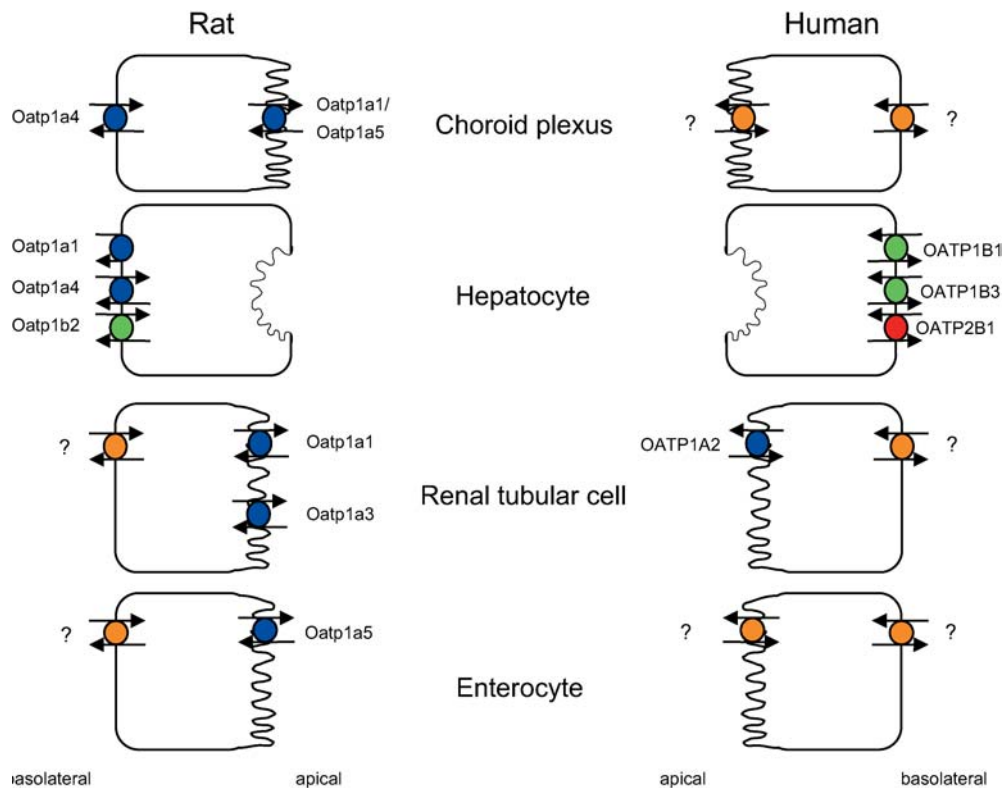
Family OATP1

Family OATP1 consists of four subfamilies, of which the three subfamilies OATP1A, OATP1B and OATP1C contain 17 individual genes in humans, rat and mouse (Figs. 2, 3).

Subfamily OATP1A

This subfamily contains a single human member, OATP1A2 (Figs. 2, 3, Table 2), which is a glycoprotein of 670 amino acids [8] and shares between 66 and 77% amino acid sequence identity with its rodent orthologs [1]. Although three different transcript variants encoding two different proteins are deposited in the database, only OATP1A2 with 670 amino acids has been functionally analyzed. The existence of the other two variants has been predicted only in silico. OATP1A2 was originally cloned

Fig. 4 Distribution and polar expression of Oatps/OATPs in selected rat and human epithelial tissues. The Oatps/OATPs from the same subfamily are labelled with the same *color*, unknown potential members are given in *orange*



from a human liver cDNA library, but its strongest expression is in brain [8].

In addition, OATP1A2 is expressed in liver and colon cancer cells as well as in the human hepatoma cell line HepG2 [3, 19, 20]. In human liver, OATP1A2 exhibits an apparent molecular mass of approximately 85 kDa [20], while in brain capillary endothelial cells (blood-brain barrier) its apparent molecular mass is ~ 60 kDa because of incomplete glycosylation [21].

Transport substrates of OATP1A2 include bile salts and BSP, steroid conjugates, the thyroid hormones T4, T3 and rT3, prostaglandin E2, the endothelin receptor antagonist BQ-123, the thrombin inhibitor CRC-220, the opioid receptor agonists DPDPE and deltorphin II, fexofenadine, certain magnetic resonance imaging contrast agents, ouabain, the lipophilic organic cations *N*-(4,4-azo-*n*-pentyl)-21-ajmalinium, rocuronium and *N*-methyl-quinine and -quinidine and the cyanobacterial toxin microcystin [1]. Thus, human OATP1A2 transports the largest number of amphipathic substrates of all human OATPs [22]. Its expression at the blood-brain barrier suggests an important role for OATP1A2 in (1) the delivery of drugs and neuroactive peptides to the brain, and (2) the removal of organic metabolites from the brain.

Down-regulation of rodent Oatps has been demonstrated in several models of cholestatic liver diseases [23] and some of the transcriptional and post-transcriptional regulatory mechanisms have been investigated [1]. Interestingly, the expression of human OATP1A2 is maintained or even moderately increased in patients with primary sclerosing cholangitis [20] suggesting that its expression

might be differently regulated at the transcriptional and post-transcriptional level as compared to other Oatps/OATPs.

OATP1A2 has five rat (Oatp1a1 [6], Oatp1a3 [24], Oatp1a4 [9], Oatp1a5 [25], and Oatp1a6 [previously called Oatp5 (*Slc21a13*) (AF053317)]) and four mouse (Oatp1a1 [26], Oatp1a4 [27], Oatp1a5 [10], Oatp1a6 [28]) homologs within the subfamily OATP1A (Figs. 2, 3, Table 2). As evidenced from their clustering on chromosomes 4 and 6 in rat and mouse, respectively, they arose through several gene duplications after divergence of the rodent species from man. Except for Oatp1a6, which so far seems to be an orphan transporter, all members of the OATP1A-subfamily have been characterized in great details at the functional level [1].

Subfamily OATP1B

This subfamily has two human members, OATP1B1 [previously called OATP-C (*SLC21A6*)], and OATP1B3 (Figs. 2, 3, Table 2). OATP1B1 was cloned from human liver [3, 29, 30, 31] and encodes a 691-amino-acid glycoprotein. It shares 80% amino acid identity with OATP1B3, but only 64%/65% identity with its rat/mouse ortholog Oatp1b2 [previously called Oatp4 (*Slc21a10*)] [1]. Expression of OATP1B1 appears to be restricted to the basolateral (sinusoidal) plasma membrane of hepatocytes [3, 29, 30, 31] (Fig. 4, Table 2). Its apparent molecular mass is 84 kDa, which is reduced after deglycosylation to 54 kDa [31]. Its apparent exclusive

expression in human liver suggests that OATP1B1 plays a crucial role in the hepatic clearance of albumin-bound amphipathic organic compounds.

The transport functions of OATP1B1 have been characterized in *X. laevis* oocytes [22, 30] and in stably transfected HEK-293 cells [3, 29, 31]. Its spectrum of transport substrates includes bile salts, conjugated and unconjugated bilirubin, BSP, steroid conjugates, the thyroid hormones T4 and T3, eicosanoids, cyclic peptides, drugs such as benzylpenicillin, methotrexate, pravastatin and rifampicin as well as the natural toxins microcystin and phalloidin [1]. Thus, OATP1B1 exhibits a similar wide substrate spectrum as the OATP1A-subfamily members.

Several polymorphisms in the *SLCO1B1* (= gene symbol of OATP1B1; Figs. 2, 3, Table 2) gene have been described recently [32, 33]. A number of the identified *SLCO1B1* alleles were associated with a dramatic reduction of V_{\max}/K_m values indicating a significant decrease of OATP1B1-mediated transport function. The OATP1B1 variant OATP1B1-L193R has been shown to be associated with defects in protein maturation as well as in transport function [34]. Whether other polymorphisms of *SLCO1B1* also result in decreased OATP1B1 function in vivo and/or in additional phenotypic alterations remain to be investigated.

Transcriptional expression of OATP1B1 appears to be decreased in primary sclerosing cholangitis since these patients experience a decrease of mRNA levels to about 50% as compared to healthy control livers [35]. In addition, similar to Oatp1a1 and Oatp1a4, basal expression of human OATP1B1 is dependent on the liver-enriched transcription factor HNF-1 α [36].

OATP1B3 (Figs. 2, 3, Table 2) was cloned from human liver and encodes a glycoprotein of 702 amino acids [37, 38]. It has an apparent molecular mass of 120 kDa, which is reduced after deglycosylation to 65 kDa [38]. Under normal physiological conditions, OATP1B3 is predominantly, if not exclusively, expressed at the basolateral plasma membrane of hepatocytes [37, 38] (Fig. 4, Table 2). However, OATP1B3 has been shown to also be expressed in various human cancer tissues as well as in different tumor cell lines derived from gastric, colon, pancreas, gallbladder, lung and brain cancers [37]. The pathobiological significance of OATP1B3 expression in human cancer tissues remains to be investigated.

The spectrum of transport substrates of OATP1B3 was investigated in *X. laevis* oocytes and in stably transfected HEK-293 cells. It includes bile salts, monoglucuronosyl bilirubin, BSP, steroid conjugates, the thyroid hormones T3 and T4, leukotriene C₄, linear and cyclic peptides, the cardiac glycosides digoxin and ouabain, the antineoplastic organic anion methotrexate, the antibiotic rifampicin and the natural toxins microcystin and phalloidin [1]. Thus, OATP1B3 has a similar broad substrate specificity as OATP1B1. However, OATP1B3 also exhibits unique transport properties such as, for example, for the intestinal peptide cholecystokinin 8 (CCK-8) [39], the opioid

peptide deltorphin II [22] and the cardiac glycosides digoxin and ouabain [22].

Hepatic expression of OATP1B3 depends on HNF-1 α [36] as well as on the bile acid nuclear receptor FXR/BAR [40]. The latter findings indicate that induction of *SLCO1B3* gene expression by bile acids could serve to maintain hepatic extraction of xenobiotics and peptides under cholestatic conditions.

In rat and mouse the single ortholog Oatp1b2 [41, 42] has been identified for the two human OATP1B-subfamily members (Figs. 2, 3, Table 2). Thus, in contrast to the OATP1A-subfamily, gene duplication in the OATP1B-subfamily occurred in man after divergence of the rodent species. Although Oatp1b2 is also mainly expressed in the liver and is functionally similar to human OATP1B1 and OATP1B3 [1], our recent preliminary studies indicate that Oatp1b2 is expressed additionally in the ciliary body epithelium of the eye.

Subfamily OATP1C

This subfamily contains human OATP1C1 [previously called OATP-F (*SLC21A14*)] (Figs. 2, 3, Table 2), which was isolated from a human brain library [43] and represents a 712-amino-acid protein that exhibits 85%/84% amino acid sequence identities with its rat/mouse ortholog Oatp1c1 [previously called Oatp14 (*Slc21a14*)]. These three genes form the OATP1C-subfamily (Figs. 2, 3, Table 2). On the mRNA level OATP1C1 is expressed in brain and testis (Leydig cells) [43] (Table 2).

Although OATP1C1 belongs to the OATP1 family (Figs. 2, 3), the members of which are paradigmatic for their high degree of multispecificity, the substrate spectrum of OATP1C1 is rather limited [43]. While some substrates such as BSP, estradiol-17 β -glucuronide, estrone-3-sulfate and the thyroid hormone T3 are transported to some extent, OATP1C1 exerts an especially high transport affinity for T4 (thyroxine) (K_m value ~90 nM) and rT3 (reverse tri-iodothyronine) (K_m value ~130 nM). Hence, it might play an important role in the delivery and disposition of thyroid hormones in brain and testis, and thus during brain development.

Rat Oatp1c1 has been isolated from a cDNA library enriched in mRNAs specific to the blood-brain barrier [44]. Nothing is known so far about the function and regulation of this putative organic anion transporter. Interestingly, however, mouse Oatp1c1 has been isolated from a cochlea cDNA library (accession number NM_021471) indicating that it might play a physiological role in the inner ear.

Family OATP2

Family OATP2 consists of the two subfamilies OATP2A and OATP2B with a total of five individual genes in man, rat and mouse (Figs. 2, 3).

Subfamily OATP2A

This subfamily contains human OATP2A1 [previously called PGT (*SLC21A2*)] (Figs. 2, 3, Table 2), which is a protein of 643 amino acids that shares 82%/83% amino acid sequence identities with its rat/mouse orthologs [1]. Although OATP2A1 has been cloned from a kidney library [45], its mRNA is ubiquitously expressed with highest levels in heart, skeletal muscle and pancreas. Neither the protein expression nor its transcriptional and/or post-transcriptional regulations have been studied in any detail. On the functional level, OATP2A1 has been characterized in transiently transfected HeLa cells, where it transported different prostaglandins and thromboxane B₂. Human OATP2A1 has the single ortholog Oatp2a1 in rat [7] and mouse [46] (Figs. 2, 3, Table 2).

Subfamily OATP2B

This subfamily contains human OATP2B1 [previously called OATP-B (*SLC21A9*)] (Figs. 2, 3, Table 2), which was originally isolated from human brain as a 709-amino-acid protein [47]. It shows a 77% amino acid sequence identity with its rat ortholog Oatp2b1 [previously called Oatp9 (*Slc21a9*)] [1]. Although human OATP2B1 was originally cloned from a brain library, its strongest expression is in the liver, followed by the spleen, placenta, lung, kidney, heart, ovary, small intestine, and brain [3, 22, 48]. In addition, OATP2B1 is expressed in several fetal tissues and in colon adenocarcinoma (CX-1) cells [3]. In human liver, OATP2B1 is exclusively expressed at the basolateral (sinusoidal) plasma membrane of hepatocytes and exhibits an apparent molecular mass of 85 kDa [22]. Thus, besides OATP1B1 and OATP1B3, OATP2B1 is the third OATP localized at the sinusoidal membrane of human hepatocytes (Fig. 4).

Functionally, OATP2B1 has been studied in *X. laevis* oocytes and in transiently transfected HEK293 cells [3, 22]. Compared to other OATPs it has a narrow substrate specificity and transports only BSP, estrone-3-sulfate and dehydroepiandrosterone-sulfate (DHEAS). For other compounds such as PGE₂ and estradiol-17 β -glucuronide controversial results have been presented [1].

Oatp2b1 [49] is the single ortholog of human OATP2B1 and has been isolated as a multispecific organic anion transporter from rat brain with similar function as but broader substrate specificity than OATP2B1 [1].

Family OATP3

Family OATP3 consists of a single subfamily (OATP3A) with a total number of three highly homologous individual genes in man, rat and mouse (Figs. 2, 3).

Subfamily OATP3A

This subfamily contains human OATP3A1 [previously called OATP-D (*SLC21A11*)] (Figs. 2, 3, Table 2), which has been isolated from a human kidney library as a 710-amino-acid protein [3]. At the amino acid level, OATP3A1 shows a 97% sequence identity with its rat and mouse ortholog Oatp3a1 [previously called Oatp11 (*Slc21a11*)] [1]. Thus, the OATP3A subfamily has been highly conserved during evolution, which is also documented by the highly homologous ortholog found in *B. taurus* (Fig. 3) and by several highly conserved sequences obtained when searching the genome databases of various species. Based on RT-PCR experiments, OATP3A1 is ubiquitously expressed and has also been detected in several cancer cell lines [3]. Thus, on the basis of mRNA expression OATP3A1 exhibits the widest tissue distribution of all OATPs so far investigated.

The functional transport properties of OATP3A1 have not been studied extensively. In HEK293 cells transiently expressing OATP3A1, only estrone-3-sulfate, PGE₂ and benzylpenicillin have been identified as substrates [3]. Despite this limited characterization of its transport properties, the high degree of amino acid identities within this subfamily as well as the wide tissue distribution of OATP3A1 indicate that these gene products might serve an important physiologic function. A splice variant with a different C-terminal end (OATP3A1_v2) has been deposited in the database (BC000585, Table 2), however, no functional data are available so far.

Rat and mouse Oatp3a1 have so far only been identified and deposited in the database as cDNAs encoding 710-amino-acid proteins (accession numbers: rat: AF239219; mouse: AF226324).

Family OATP4

Family OATP4 consists of three subfamilies, of which the two subfamilies OATP4A and OATP4C contain four individual genes in man, rat and mouse (Figs. 2, 3).

OATP4A

This subfamily contains human OATP4A1 [previously called OATP-E (*SLC21A12*)] (Figs. 2, 3, Table 2), which was isolated from human kidney and brain as a 722-amino-acid protein [3, 50]. It shows 76% amino acid sequence identity with its rodent ortholog Oatp4a1 [previously called Oatp12 (*Slc21a12*)] (Figs. 2, 3, Table 2). OATP4A1 mRNA is expressed ubiquitously with strongest expression in liver, heart, placenta and pancreas [50]. At the protein level it has been localized to the apical surface of the syncytiotrophoblast [51].

In crRNA-injected *X. laevis* oocytes OATP4A1 transported taurocholate and the thyroid hormones T3, T4 and rT3 [50], while in transiently transfected HEK293 cells

additional uptake of steroid conjugates, PGE₂ and benzylpenicillin was found [3].

Oatp4a1 [50] was isolated from a rat retina cDNA library as a 722-amino-acid protein and has so far only been characterized minimally. It seems to mediate transport of taurocholate, T3 and PGE₂ [50].

Subfamily OATP4C

This subfamily contains human OATP4C1 [previously called OATP-H (*SLC21A20*)] (Figs. 2, 3, Table 2), which is so far the only *SLCO* gene in this subfamily. Its cDNA sequence has been deposited in the database. Its functional properties are currently under investigation in our laboratory.

Family OATP5

Family OATP5 consists of the single subfamily OATP5A with a single human gene (Figs. 2, 3).

Subfamily OATP5A

This subfamily contains human OATP5A1 [previously called OATP-J (*SLC21A15*)] (Figs. 2, 3, Table 2), which has been isolated and deposited in the database (NM_030958) as a cDNA encoding a protein of 848 amino acids with unknown transport properties.

Family OATP6

Family OATP6 consists of the four subfamilies OATP6A, OATP6B, OATP6C and OATP6D, which contain six individual genes in man, rat and mouse (Figs. 2, 3). Please note that this family has previously been classified as OATP10 [1].

Subfamily OATP6A

This subfamily contains human OATP6A1 [previously called OATP-I (*SLC21A19*)] (Figs. 2, 3, Table 2), which has been isolated from human testis but so far no functional characterization has been published [52].

Subfamily OATP6B

This subfamily contains rat and mouse Oatp6b1 [previously called GST-1 (*Slc21a16*)] (Figs. 2, 3, Table 2). Rat Oatp6b1 has recently been published to be a gonad-specific transport system for taurocholate, DHEAS and thyroxine [52]. Mouse Oatp6b1 has been identified as an OATP-related protein with no functional characterization so far [53].

Subfamily OATP6C

This subfamily contains the rat gonad-specific organic anion transporter Oatp6c1 [previously called GST-2 (*Slc21a18*)] (Figs. 2, 3, Table 2) [52]. Mouse Oatp6c1 has been identified as an OATP-related protein with no functional characterization so far [53].

Subfamily OATP6D

This subfamily contains a single mouse Oatp6d1 [previously called Oatp17 (*Slc21a17*)] (Figs. 2, 3, Table 2) that was identified as an OATP-related protein with no functional characterization so far [53].

Conclusions and perspectives

The OATP/*SLCO* superfamily consists of multi- and oligospecific membrane transport systems, that mediate sodium-independent transmembrane solute transport. The multispecific transporters accept a broad range of amphipathic endo- and xenobiotics. Their multiple expression in the liver, kidney, small intestine, choroid plexus, blood-brain barrier and many other tissue barriers puts them into a strategic position for absorption, distribution and excretion of xenobiotic substances. Thus, multispecific Oatps/OATPs are important transporters of the overall body detoxification system. Alternatively, Oatps/OATPs with a rather restricted substrate specificity appear to be more highly conserved during evolution, exhibit a narrower tissue distribution, and might have important physiological functions in specific organs.

Although several individual members of the OATP/*SLCO* superfamily have been characterized in detail, numerous questions remain unanswered and require more thorough investigations in the near future. They include: (1) the determination of the exact tissue expression of all individual Oatps/OATPs, (2) the definitive characterization of the driving force(s) involved in Oatp/OATP-mediated substrate transport, (3) a detailed understanding of the molecular basis of the broad substrate specificity, (4) the development of specific inhibitors for individual Oatps/OATPs, (5) investigation of the transcriptional and post-transcriptional regulation of individual Oatp/OATP expression, (6) elucidation of interactions of Oatps/OATPs with other proteins, (7) identification and characterization of gene polymorphisms, and (8) determination of the overall significance of individual Oatps/OATPs for physiology, pathophysiology, pharmacology and toxicology.

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