Tissue distribution and ontogeny of mouse organic anion transporting polypeptides (Oatps)

Xingguo Cheng, Jonathan Maher, Chuan Chen, and Curtis D. Klaassen

Department of Pharmacology, Toxicology and Therapeutics
University of Kansas Medical Center, Kansas City, KS 66160 (X.G.C, J.M.M, C.C., C.D.K.)
Running title: tissue distribution and ontogeny of mouse Oatps

Address correspondence to:
Curtis D. Klaassen, Ph.D.
Department of Pharmacology, Toxicology and Therapeutics
University of Kansas Medical Center
3901 Rainbow Boulevard
Kansas City, KS 66160
Phone: 913-588-7714 Fax: 913-588-7501
E-mail: cklaasse@kumc.edu

Number of text pages: 34
Number of tables: 2
Number of figures: 8
Number of references: 49
Number of words in Abstract: 250
Number of words in Introduction: 500
Number of words in Discussion: 1297

List of nonstandard abbreviations: Oatps, organic anion transporting polypeptides; Pgt, prostaglandin transporter; Gst, gonad-specific transporter; PCN, pregnenalone-16α-carbonitrile; bDNA assay, branched DNA signal amplification assay.
Abstract

Organic anion transporting polypeptides (Oatps) are Na\(^+\)-independent solute carriers for cellular uptake of organic compounds. The purpose of this study is to determine: 1) the constitutive mRNA expression of the 15 mouse Oatp genes in 12 tissues, 2) whether there are gender differences in Oatp expression, and 3) the ontogenic expression of Oatps in liver and kidney. The mRNA expression of the 15 mouse Oatps was quantified using the branched DNA technique. Oatp1a1, 1a4, 1b2, and 2b1 are expressed in liver at relatively high levels, with Oatp1b2 being exclusively expressed in liver. Oatp1a1, 1a6, 3a1, and 4c1 are highly expressed in kidney. Oatp1a4 and 1c1 are highly expressed in brain. Oatp1a5, 6b1, 6c1, and 6d1 are predominant in testes. Oatp2a1, 4a1, and 5a1 are predominantly expressed in placenta. In liver, expression of Oatp1a1 was male-predominant, whereas expression of Oatp1a4 and 1a6 was female-predominant. In kidney, expression of Oatp1a1, 3a1, and 4c1 was higher in males than females. Hepatic expression of Oatp1a1, 1a4, 1a6, 1b2, and 2b1 gradually increased after birth and reached adult levels by 6 weeks of age. Only Oatp2a1 was expressed at adult levels at birth. In kidney, expression of mouse Oatp1a1, 1a6, and 3a1 was lower at birth than at 6 weeks of age, whereas, expression of mouse Oatp1a4, 2a1, and 2b1 was similar at birth and at 6 weeks of age. These data on the tissue distribution and ontogenic expression of mouse Oatps, will aid in understanding the pharmacokinetics and toxicokinetics of drugs and other chemicals.
Introduction

Organic anion transporting polypeptides (rodents: Oatps; human: OATPs) mediate sodium-independent transport of various amphipathic organic solutes, such as bile acids, dyes (e.g. sulfobromophthalein), drugs (e.g. rifampicin, digoxin), toxins (e.g. microcystin), steroid conjugates, eicosanoids, and thyroid hormones into cells. Currently, 9 human OATPs, 13 rat, and 15 mouse Oatps have been identified. Hydropathy analysis predicts that all OATPs/Oatps contain 12-transmembrane domains. Additionally, all OATPs/Oatps contain the consensus sequence D-X-RW-(I,V)-GAWW-X-G-(F,L)-L at the border of extracellular loop 3 and transmembrane domain 6, termed the “OATP superfamily signature” (Hagenbuch and Meier, 2003).

Only a few of the OATPs/Oatps have been characterized at the functional, structural, and regulatory levels. Rat Oatp1a1, the first cloned member of the OATP/Oatp gene family, is expressed in liver and kidney, with broad substrate specificity (Jacquemin et al, 1994). Rodent Oatp1b2 and human OATP1B1 and 1B3 are selectively expressed in liver, where they are involved in hepatic uptake of albumin-bound compounds (Abe et al, 1999; König et al, 2000; Li et al, 2002). Oatp1a6, 1c1, and 4a1 are expressed mainly in kidney, brain, and placenta, respectively, and their physiological roles remain unclear. The recently cloned human and rat OATP4C1/Oatp4c1 transports digoxin across the basolateral membrane of renal proximal tubules (Mikkaichi et al, 2004). Recently, rat Oatp6b1, 6d1, and human OATP6A1 were cloned (Suzuki et al., 2003). These three transporters are predominantly expressed in testes and transport dehydroepiandrosterone (DHEA) and DHEA sulfate into testes (Suzuki et al., 2003).

Neonates are more sensitive to the toxicity of some chemicals than adults. This is an important factor to consider in drug therapy, and in chemical exposure. The increased
susceptibility of immature rodents to some chemical exposures was first investigated in the late 1950s, and reduced hepatic biotransformation of some chemicals was shown to be responsible for the increased susceptibility (Jondorf et al., 1958; Fouts and Adamson, 1959). However, for a number of chemicals, it has been shown that newborns have a decreased ability to clear chemicals from blood. For example, ouabain is transported into hepatocytes by active transport and is excreted into bile largely without being biotransformed (Eaton and Klaassen, 1978). Newborn rodents are more sensitive to cardiac glycoside toxicity because of their low capacity to remove ouabain from the blood (Klaassen, 1972). In addition, Stacey and Klaassen (1979) showed that ouabain uptake into hepatocytes in newborns is low, and increases with age. Liver and kidney are two major detoxication organs that eliminate chemicals from the body. Developmental changes of transporters in both organs can significantly influence the disposition of endo- and exogenous compounds.

Mice are becoming a more commonly used experimental animal model because of the availability of knockout mice. However, information on transporter systems, including Oatps, in mice is poorly characterized. Therefore, the purpose of this study is to determine: 1) the constitutive expression of the 15 mouse Oatp genes by measuring their mRNA levels in 12 tissues, 2) whether there are gender differences in mouse Oatp expression, and 3) the ontogeny of mouse Oatps in mouse liver and kidney.
Materials and Methods

Tissue Distribution. Eight-week-old adult male and female C57BL/6 mice (n = 10/gender) were purchased from Jackson Laboratories (Bar Harbor, Maine), and housed according to the American Animal Association Laboratory Animal Care guidance. Eleven tissues (liver, kidney, lung, stomach, duodenum, jejunum, ileum, large intestine, brain, testis, and ovary) were collected. Placenta was removed from pregnant mice on gestation day 17. The tissues were snap-frozen in liquid nitrogen. The intestine was longitudinally dissected, rinsed in saline, and divided into three equal-length sections (referred to as duodenum, jejunum, and ileum), before being snap-frozen in liquid nitrogen. All tissues were stored at -80°C.

Ontogeny. Mice were bred in the animal facilities at the University of Kansas Medical Center. Liver and kidney from male and female C57BL/6 mice were collected at -2, 0, 5, 10, 15, 22, 30, 35, 40, and 45 days of age (n = 5/gender/age).

RNA Isolation. Total RNA was isolated using RNAzol Bee reagent (TelTest Inc., Friendswood, TX) as per the manufacturer's protocol. The concentration of total RNA in each sample was quantified spectrophotometrically at 260 nm. The integrity of each RNA sample was evaluated by formaldehyde-agarose gel electrophoresis before analysis.

Branched DNA (bDNA) Signal Amplification Assay. The bDNA technique is a robust, high-throughput method used for characterizing mRNA expression. The mRNA for Oatp1a1, 1a4, 1a5, 1a6, 1b2, 1c1, 2a1, 2b1, 3a1, 4a1, 4c1, 5a1, 6b1, 6c1, and 6d1 was measured using the bDNA assay (Quantigene® bDNA signal amplification kit; Bayer Diagnostics, East Walpole, MA), with modifications according to Hartley and Klaassen (2000). The gene sequences of mouse Oatps were accessed from GenBank (Table 1). Multiple oligonucleotide probe sets (containing capture probes, label probes, and blocker probes) specific to a single mRNA
transcript were designed using ProbeDesigner® software, version 1.0 (Bayer Corp., Emeryville, CA). Probe sets for each Oatp are shown in Table 2. Each probe developed in ProbeDesigner was submitted to the National Center for Biotechnology Information for nucleotide comparison by the basic local alignment search tool (BLASTn; NCBI, Bethesda, MD) to ensure minimal cross-reactivity with other known mouse sequences and expressed sequence tags. Oligonucleotides with a high degree of similarity (>80%) to other mouse gene transcripts were eliminated from the design. Probes were designed with a melting temperature of approximately 63°C, enabling hybridization conditions to be held constant (i.e., 53°C) during each hybridization step, and for each probe set. All probes were synthesized (i.e., 50 nmol synthesis scale) by Operon Technologies (Palo Alto, CA), and obtained desalted and lyophilized. Total RNA (1 µg/µl) was added to each well (10 µl/well) of a 96-well plate containing 50 µl of capture hybridization buffer and 50 µl of diluted probe set. For each gene, total RNA was allowed to hybridize to the probe set overnight at 53°C. Subsequent hybridization steps were carried out per the manufacturer's protocol, and luminescence was measured with a Quantiplex® 320 bDNA luminometer interfaced with Quantiplex® data management software (version 5.02), for analysis of luminescence from 96-well plates. The luminescence for each well is reported as relative light units per 10 µg of total RNA.

Statistics. Differences between genders were determined by student’s T test. Statistical significance was considered at $p < 0.05$. 

DMD #3640
Results

*Tissue Distribution of mouse Oatps.* mRNA expression of 15 mouse Oatps was quantified in 12 major tissues. Data are shown in Fig. 1 to 4. Expression of Oatp1a1 mRNA (Fig. 1) was highest in liver and kidney of male mice, but its expression in other tissues was much lower. A gender difference in Oatp1a1 mRNA expression was observed in both liver and kidney, with higher levels in males. Expression of Oatp1a4 mRNA (Fig. 1) was highest in liver and brain, followed by testes and ovaries. A gender difference in Oatp1a4 expression in liver was observed, with higher levels being expressed in females. Expression of Oatp1a5 mRNA (Fig. 1) was highest in testes, moderate in ovary, and low in the other tissues. Oatp1a6 mRNA (Fig. 1) was almost exclusively expressed in kidney among the collected tissues. Oatp1a6 mRNA was expressed much less in liver than kidney. However, a gender difference of Oatp1a6 was noted in liver, with higher levels in females.

Expression of Oatp1b2 mRNA (Fig. 2) was predominant in liver, with negligible expression in the other 11 tissues. Oatp1c1 (Fig. 2) was the only Oatp primarily expressed in brain. Oatp2a1, a prostaglandin transporter, was highest in placenta, moderate in lung and stomach, and lower in other tissues (Fig. 2). Oatp2b1 (Fig. 2) appeared to be ubiquitously expressed, with highest levels in liver and small intestine.

Oatp3a1 (Fig. 3) expression was highest in kidney and lung, with moderate expression in testes and ovaries. In kidney, Oatp3a1 mRNA was 3.3-fold higher in males than that in females, as previously noted (Melia et al, 1998). Also shown in Fig. 3, mouse Oatp4a1, like rat Oatp4a1, was abundantly expressed only in placenta (Leazer and Klaassen, 2003). Oatp4c1 (Fig. 3) was mainly found in lung and kidney. A gender difference in renal expression of Oatp4c1 was observed, with higher levels in males than females. Oatp5a1 (Fig. 3) expression was
predominant in placenta, with lower levels in testes and lung. Oatp6b1, 6c1, and 6d1 (Fig. 4), three mouse homologues of the human gonad-specific transporter (GST), were exclusively expressed in testes.

**Ontogeny of Oatps in male and female mouse liver.** The neonatal patterns of Oatp mRNA expression in male and female mouse liver are shown in Figs. 5 and 6. In adult mice, Oatp1a1 expression was mainly detected in liver and kidney, with higher levels in males than females. As shown in Fig. 5, there was minimal expression of Oatp1a1 in mouse liver before 15 days of age. Thereafter, hepatic Oatp1a1 levels reached detectable levels at day 23, and reached adult levels by 30 days of age. Male-predominant expression was observed at all ages when Oatp1a1 was detectable (day 23 and thereafter). Fig. 5 illustrates that the expression of Oatp1a4 was also low at birth, but gradually increased to adult levels by approximately 23 days of age. The levels of Oatp1a4 mRNA in males decreased by 30 days of age, resulting in females expressing more Oatp1a4 than males. The ontogeny of Oatp1a6 expression is also shown in Fig. 5. Expression of Oatp1a6 mRNA was detected in liver of mice of all ages. Between day 5 and 10 there was an increase of Oatp1a6 mRNA. Similar to that observed for Oatp1a4, Oatp1a6 decreased in males between 15 and 45 days of age, resulting in higher Oatp1a6 expression in liver of adult females than males.

Oatp1b2 is a relatively liver-specific transporter, as indicated in Fig. 2. The expression of Oatp1b2 was minimal 2 days before birth, but its expression between birth and 10 days of age was about half that seen in adult mice (Fig. 6). Adult levels of Oatp1b2 were attained by 23 days of age. No gender difference in expression of Oatp1b2 was observed at any age. Oatp2a1 (Pgt) expression in liver was similar at all ages. Oatp2b1 expression at different ages is also shown in
Fig. 6. Before 15 days of age, Oatp2b1 expression was minimal, increased moderately at day 15, and reached adult levels by 23 days of age.

**Ontogeny of Oatps in male and female mouse kidney.** The postnatal developmental patterns of Oatp mRNA expression in male and female mouse kidney are shown in Figs. 7 and 8. As shown in Fig. 7, there was minimal expression of Oatp1a1 in mouse kidney at 22 days of age, followed by detectable levels at day 30, and reaching adult levels by 45 days of age. The male-predominant expression was observed at day 30 and 45. Fig. 7 illustrates that the expression of Oatp1a4 was similar at all ages. In contrast to Oatp1a4 expression in liver, Oatp1a4 shows no gender difference in kidney. The expression of Oatp1a6 was low at birth (Fig. 7), and gradually increased until 15 days of age, when Oatp1a6 reached adult levels.

Oatp2a1 mRNA expression in both male and female mouse kidney was similar at all ages after birth, but was lower before birth (Fig. 8). Ontogenic expression of Oatp2b1 in kidney was similar to that of Oatp2a1 expression, being expressed at a low level 2 days before birth, but increasing to adult levels at birth. Oatp3a1 expression in mouse kidney was low before 30 days of age, but at 30 days of age, the expression of Oatp3a1 in males increased, whereas it remained low in the females.
Discussion

The expression of mouse Oatps vary among tissues. The Oatps that have relatively high expression in liver are Oatp1a1, 1a4, 1b2, and 2b1, among which Oatp1b2 is almost exclusively expressed in liver. The Oatps that have relatively high mRNA expression in kidney are Oatp1a1, 1a6, 3a1, and 4c1. Furthermore, Oatp1a4 and 1c1 are highly expressed in brain. Oatp1a5, 6b1, 6c1, and 6d1 are predominantly expressed in testes, and Oatp2a1, 4a1, and 5a1 are predominantly expressed in placenta.

The tissue distribution of Oatp homologues in rats and mice is similar, but not identical. In both rats and mice, Oatp1a1 is highly expressed in liver and kidney (Li et al., 2002); Oatp1a4 in liver and brain (Noé et al., 1997; Guo et al., 2002a); Oatp1a6 in kidney (Ogura et al., 2000; Choudhuri et al., 2001); Oatp1b2 in liver (Li et al., 2002); Oatp1c1 in brain (Sugiyama et al., 2003); Oatp4a1 in placenta (Leazer and Klaassen, 2003); and Oatp6b1 and 6c1 in testes (Suzuki et al., 2003). The high expression of Oatp1a5 in mouse testes has not been reported previously, whereas in rats, it has been shown that Oatp1a5 is highly expressed in choroid plexus (Choudhuri et al., 1998), moderate in the retina (Abe et al., 1998), and slight in liver, kidney, ileum, and testes (Choudhuri et al., 2003; Augustine et al., 2005). Also, there is no mouse or human homologue of rat Oatp1a3 (Oat-K1), which is highly expressed in rat kidney (Saito et al., 1996). It should also be noted that humans do not have any rodent Oatp1a subfamily members (Oatp1a1, 1a4, 1a5, and 1a6), however, OATP1A2, a specific human OATP1A subfamily member, does not have rodent homologues. Also, other Oatp subfamily members have comparable tissue distribution in humans and mice. For example, OATP1B/Oatp1b members (mouse Oatp1b2, human OATP1B1, 1B3) are predominantly expressed in liver of both humans and mice (Abe et al., 1999; Li et al., 2002). OATP1C1/Oatp1c1 is detected in brain (Sugiyama et al., 2003).
OATP2A1/Oatp2a1 and 2B1/2b1 is expressed ubiquitously (Lu et al., 1996a; Nishio et al., 2000). OATP6/Oatp6 subfamily members (mouse 6b1, 6c1, and 6d1, human OATP6A1) are exclusively expressed in testes of humans and mice (Suzuki et al., 2003).

Organ-specific expression of Oatps contribute to tissue-specific distribution of drugs and to tissue-specific toxicity. For example, pravastatin must enter the liver in order to exert its anti-lipidemic effect. Human OATP1B1 has been shown to transport pravastatin with high affinity (Hsiang et al., 1999). Phalloidin and microcystin both selectively accumulate in liver leading to hepatotoxicity. Rat Oatp1b2, human OATP1B1, and OATP1B3 are known to transport phalloidin and microcystin (reviewed by Hagenbuch and Meier, 2003). Conversely, poor extraction of a drug by liver (due to a deficiency in uptake transporters) can cause elevated plasma levels of the drug, leading to toxicities in organs other than liver. A well-defined example is the uptake of cardiac glycosides into neonatal rat liver, which is immature with respect to adult liver, resulting in a LD50 for ouabain in newborns about 1/100th of that in adult rats (Klaassen, 1972). This observation corresponds well with the low expression of Oatp1a4 in liver of young rats (Guo et al., 2002a), and the finding that Oatp1a4 transports cardiac glycosides with high affinity (Noé et al., 1997). Therefore, understanding tissue distribution and substrate specificity of various Oatps will help predict tissue distribution of Oatp substrates, and provide information concerning which Oatp should be targeted or avoided when developing a new drug.

The present study indicates that there is relatively poor expression of mouse Oatps in the gastrointestinal tract, namely the stomach, duodenum, jejunum, ileum, and large intestine. Of the Oatps, only Oatp2b1 has relatively high expression in intestine. The relatively poor expression of Oatps in the intestine suggests that Oatps probably play a relatively minor role in intestinal absorption of chemicals. Actually, it is generally believed that most xenobiotics are
mainly absorbed from the intestine by simple diffusion (Schwenk, 1987). Instead, Oatps appear to play an important role in distribution and elimination of chemicals, as suggested by high expression of Oatps in liver, kidney, lung, brain, testes, and placenta. As previously stated, Oatp1b2 is responsible for transport of microcystin and phalloidin into liver to produce hepatotoxicity, as well as uptake of sulfobromothelein (BSP) into liver for subsequent excretion into bile.

Gender differences in Oatp1a1 expression were observed in mouse liver and kidney, with higher expression in males than females. It has been shown that in rat and mouse kidney, male-predominant expression of Oatp1a1 is androgen-dependent (Isern et al., 2001; Lu et al., 1996). This gender specific pattern may explain some physiological/toxicological phenomena. For instance, Oatp1a1 is localized to the apical membrane domain of proximal tubules in kidney, where it reabsorbs organic anions from the lumen. The male-predominant expression of Oatp1a1 may be responsible for the 250-fold higher rate of urinary excretion of exogenously administered radioactive estradiol-17β-D-glucuronide in females as compared with male rats (Gotoh et al., 2002).

In contrast to the lack of gender differences in the expression of Oatp1a4 and 1a6 in rats, gender differences in the expression of these two transporters were observed in mouse liver, with higher expression in females than males, the opposite of Oatp1a1 (Li et al., 2002). Oatp3a1 and 4c1 were expressed at higher levels in female kidney than in males. These gender differences might be due to sex hormones, or due to gender-related secretion patterns of growth hormone (Waxman et al., 1991; Noshiro and Negishi, 1986; Aida and Negishi, 1993; Buist et al., 2003). Further, investigation is needed to elucidate the regulatory mechanisms of these gender-related differences in Oatp expression.
The ontogenic expression of the various Oatps in mouse liver exhibited different developmental patterns of expression. The low expression of Oatp1a4 in development may result in a higher toxicity of ouabain in newborn mice. In newborn rats, low expression of Oatp1a4 results in less uptake of ouabain into liver, and thus high amounts of ouabain remain in blood and other tissues, causing toxicity (Klaassen, 1972; Guo et al, 2002a). The importance of Oatp1a4 has been further illustrated by the finding that pregnenalone-16α-carbonitrile (PCN), a prototypical rodent pregnane-X-receptor (PXR) ligand, stimulates hepatic clearance of cardiac glycosides in newborn rats, resulting in decreased toxicity of cardiac glycosides (Klaassen, 1974a,b). Oatp1a4 is a sinusoidal hepatic uptake transporter, with high affinity for cardiac glycosides (Noé et al., 1997). PCN treatment dramatically accelerates the maturation of hepatic Oatp1a4 mRNA and protein levels in neonatal rats (Guo et al., 2002a). Thus, newborn rats are more sensitive to cardiac glycoside toxicity because of their low capacity to remove ouabain from the blood, and PCN protects newborns from cardiac glycoside toxicity because it induces Oatp1a4 and the uptake of ouabain into liver.

Kidney is another important organ for chemical disposition. The kidney in newborns is immature and renal functions are limited. The present data indicate that renal expression of Oatps is minimal at or before birth, and then gradually increases to adult levels. Low renal expression of Oatps in newborns may protect the kidney from toxicity of Oatp substrates.

Oatp6b1, 6c1, and 6d1 are mouse homologues of human and rat gonad-specific transporters, and are thought to be responsible for testicular uptake of dehydroepiandrostone (DHEA) and DHEA sulfate, precursors of in vivo androgen and thus estrogen biosynthesis (Suzuki et al, 2003). In this study, Oatp6b1, 6c1, and 6d1 were found to be exclusively expressed in testes.
In conclusion, the present study shows that mouse Oatp expression is highly variable among tissues. There are also gender- and age-related differences in the expression of these uptake transporters. These variances most likely result in tissue-, gender-, and age-related differences in the pharmaco- and toxicokinetic profiles of xenobiotics. Furthermore, the similarities and differences in Oatp expression between rat, mouse, and human will aid in extrapolation of rodent pharmacokinetic data to humans.
References


Footnotes:

This work was supported by NIH Grant ES-09649 to Curtis D. Klaassen.

Send reprint requests to

Curtis D. Klaassen, Ph.D.
Department of Pharmacology, Toxicology and Therapeutics
University of Kansas Medical Center
3901 Rainbow Boulevard
Kansas City, KS 66160
Figure Legends

**Fig. 1.** Tissue distribution of Oatp1a1, 1a4, 1a5, and 1a6 mRNA.

Total RNA from both male and female C57BL/6 mouse tissues \((n = 10/\text{gender})\) was analyzed by the bDNA assay for expression of each Oatp mRNA. Data are presented as mean ± S.E.M. Asterisks indicate statistically significant differences between male and female mice \((p<0.05)\).

**Fig. 2.** Tissue distribution of Oatp1b2, 1c1, 2a1, and 2b1 mRNA.

Total RNA from both male and female C57BL/6 mouse tissues \((n = 10/\text{gender})\) was analyzed by the bDNA assay for expression of each Oatp mRNA. Data are presented as mean ± S.E.M. Asterisks indicate statistically significant differences between male and female mice \((p<0.05)\).

**Fig. 3.** Tissue distribution of Oatp3a1, 4a1, 4c1, and 5a1 mRNA.

Total RNA from both male and female C57BL/6 mouse tissues \((n = 10/\text{gender})\) was analyzed by the bDNA assay for expression of each Oatp mRNA. Data are presented as mean ± S.E.M. Asterisks indicate statistically significant differences between male and female mice \((p<0.05)\).

**Fig. 4.** Tissue distribution of Oatp6b1, 6c1, and 6d1 mRNA.

Total RNA from both male and female C57BL/6 mouse tissues \((n = 10/\text{gender})\) was analyzed by the bDNA assay for expression of each Oatp mRNA. Data are presented as mean ± S.E.M. Asterisks indicate statistically significant differences between male and female mice \((p<0.05)\).

**Fig. 5.** Ontogenic expression of mouse Oatp1a1, 1a4, and 1a6 mRNA in mouse liver.

Total RNA from C57BL/6 mice at each age \((n = 5/\text{gender})\) was analyzed by the bDNA assay. Data are presented as mean ± S.E.M. Asterisks indicate statistically significant differences between male and female mice \((p<0.05)\).

**Fig. 6.** Ontogenic expression of mouse Oatp1b2, 2a1, and 2b1 mRNA in mouse liver.
Total RNA from C57BL/6 mice at each age (n = 5/gender) was analyzed by the bDNA assay. Data are presented as mean ± S.E.M. Asterisks indicate statistically significant differences between male and female mice (p<0.05).

**Fig. 7.** Ontogenic expression of mouse Oatp1a1, 1a4, and 1a6 mRNA in mouse kidney.

Total RNA from C57BL/6 mice at each age (n = 5/gender) was analyzed by the bDNA assay. Data are presented as mean ± S.E.M. Asterisks indicate statistically significant differences between male and female mice (p<0.05).

**Fig. 8.** Ontogenic expression of mouse Oatp2a1, 2b1, and 3a1 mRNA in mouse kidney.

Total RNA from C57BL/6 mice at each age (n = 5/gender) was analyzed by the bDNA assay. Data are presented as mean ± S.E.M. Asterisks indicate statistically significant differences between male and female mice (p<0.05).
Table 1. Nomenclatures and Genebank Accession Numbers for Mouse Oatps.

<table>
<thead>
<tr>
<th>Current nomenclature</th>
<th>Slc nomenclature</th>
<th>Accession #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oatp1a1</td>
<td>Slc21a1</td>
<td>AB031813</td>
</tr>
<tr>
<td>Oatp1a4</td>
<td>Slc21a5</td>
<td>AB031814</td>
</tr>
<tr>
<td>Oatp1a5</td>
<td>Slc21a7</td>
<td>NM_130861</td>
</tr>
<tr>
<td>Oatp1a6</td>
<td>Slc21a13</td>
<td>AF213260</td>
</tr>
<tr>
<td>Oatp1b2</td>
<td>Slc21a10</td>
<td>AB031959</td>
</tr>
<tr>
<td>Oatp1c1</td>
<td>Slc21a14</td>
<td>NM_021471</td>
</tr>
<tr>
<td>Oatp2a1</td>
<td>Slc21a2</td>
<td>NM_033314</td>
</tr>
<tr>
<td>Oatp2b1</td>
<td>Slc21a9</td>
<td>BC019209</td>
</tr>
<tr>
<td>Oatp3a1</td>
<td>Slc21a11</td>
<td>NM_023908</td>
</tr>
<tr>
<td>Oatp4a1</td>
<td>Slc21a12</td>
<td>BC030720</td>
</tr>
<tr>
<td>Oatp4c1</td>
<td>-</td>
<td>NM_172658</td>
</tr>
<tr>
<td>Oatp5a1</td>
<td>Slc21a15</td>
<td>XM_129381</td>
</tr>
<tr>
<td>Oatp6b1</td>
<td>Slc21a16</td>
<td>AK006249</td>
</tr>
<tr>
<td>Oatp6c1</td>
<td>Slc21a18</td>
<td>AK016647</td>
</tr>
<tr>
<td>Oatp6d1</td>
<td>Slc21a17</td>
<td>AK014872</td>
</tr>
</tbody>
</table>
Table 2. Oligonucleotide probes generated for analysis of mouse Oatp mRNAs expression by Quantigene branched DNA signal amplification assay

<table>
<thead>
<tr>
<th>Name</th>
<th>Target region</th>
<th>Function Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oatp1a1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1279-1307 CE</td>
<td>agtgatcttaactcttcataataaaagcTTTTTctcttggaaagaaggt</td>
</tr>
<tr>
<td></td>
<td>1308-1313 CE</td>
<td>tgctatgtatcagtcctctcttgacTTTTTctcttggaaagaaggt</td>
</tr>
<tr>
<td></td>
<td>1431-1452 CE</td>
<td>ccccatatagagggtctgacTTTTTctcttggaaagaaggt</td>
</tr>
<tr>
<td></td>
<td>1476-1497 CE</td>
<td>ttaagcagctgcaccttgtgtTTTTTctcttggaaagaaggt</td>
</tr>
<tr>
<td></td>
<td>1603-1622 CE</td>
<td>ccaatgcagctgaatttTTTTTctcttggaaagaaggt</td>
</tr>
<tr>
<td></td>
<td>1623-1646 CE</td>
<td>gactgcagatggtctctgtgaTTTTTctcttggaaagaaggt</td>
</tr>
<tr>
<td></td>
<td>1228-1252 LE</td>
<td>ggaggcaagctataaacacctatgaTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1253-1278 LE</td>
<td>cactgattaaatatccaaggcatactTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1332-1354 LE</td>
<td>tattcagataagggcagccaaTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1406-1430 LE</td>
<td>tctttataaggtgtgtaatcacaTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1453-1475 LE</td>
<td>gcagctcagcaaggacattttTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1498-1517 LE</td>
<td>cactggatccatgtgtgctTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1518-1533 LE</td>
<td>gctagccatgctccccacTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1538-1557 LE</td>
<td>cgaggccagctgtcagttaaTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1558-1579 LE</td>
<td>ccaacagcttcacagctcgTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1647-1667 LE</td>
<td>gctttctcacaacagccccagTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1668-1689 LE</td>
<td>gcagcttggtgtcatacactcaggTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>1355-1383 BL</td>
<td>tcaacaatatgtagtacagaaatgaaaaaaa</td>
</tr>
<tr>
<td></td>
<td>1384-1405 BL</td>
<td>gcacgtgggaatattacacagg</td>
</tr>
<tr>
<td></td>
<td>1580-1602 BL</td>
<td>gaaacacatgtggtgtccagtt</td>
</tr>
<tr>
<td><strong>Oatp1a4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>526-545 CE</td>
<td>gccttgccagttttgtcgtTTTTTctcttggaaagaaggt</td>
</tr>
<tr>
<td></td>
<td>591-616 CE</td>
<td>gaggaatagtgagtgtatgatattaaaaagTTTTTcctttggaagaaggt</td>
</tr>
<tr>
<td></td>
<td>715-735 CE</td>
<td>caactctttggtggctgctTTTTTctctttggaagaaggt</td>
</tr>
<tr>
<td></td>
<td>452-474 LE</td>
<td>ttgataacccaactacagctTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>546-570 LE</td>
<td>gcaacatctacaacaaatcatgataagTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>667-690 LE</td>
<td>tecgtaacacaaagaacttggtTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>793-812 LE</td>
<td>ttggtatttcaccattccgaTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>833-858 LE</td>
<td>tcagattttgcaaaaatctttcatgatTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>886-907 LE</td>
<td>gcgttagttgctcctgtttctTTTTTtaggcataggacccgtgtct</td>
</tr>
<tr>
<td></td>
<td>859-885 BL</td>
<td>aaaaatctcttataataaaggaaggtt</td>
</tr>
<tr>
<td></td>
<td>475-497 BL</td>
<td>gatcccttcatactcaaggtcctca</td>
</tr>
<tr>
<td></td>
<td>498-525 BL</td>
<td>aagtaactcagaaatataatcaacagaa</td>
</tr>
<tr>
<td></td>
<td>571-590 BL</td>
<td>aacacccagggcccataact</td>
</tr>
<tr>
<td></td>
<td>617-640 BL</td>
<td>tgtttctatattcatatctgccc</td>
</tr>
<tr>
<td></td>
<td>641-666 BL</td>
<td>gacaagttgctgtaggtaaaattgt</td>
</tr>
<tr>
<td></td>
<td>691-714 BL</td>
<td>ggctttaagttcttgttgtttt</td>
</tr>
</tbody>
</table>
736-762  BL  cacattaagttttcattttcata
763-792  BL  cgtataatgtttctacagtaataatcata
813-832  BL  ggaatatcaccagggcatga

Oatp1a5  95-118  CE  aatcctttctctgttttccatTTTTTctcttggaagaatagt
119-137  CE  atctgacccatggtttgcTTTTTctcttggaagaatagt
188-213  CE  atataaattcctgagagtgatttggaTTTTTctcttggaagaatagt
214-239  CE  tcttatgttgaagcatggaattcTTTTTctcttggaagaatagt
412-430  CE  teggcccaatgaggaatgtTTTTTctcttggaagaatagt
506-526  CE  ttgcttgtgcttaaggtctgTTTTTctcttggaagaatagt
41-69    LE  gactattctttaaacaagcttcacctacgaTTTTTaggcataggacccgtgtct
70-94    LE  ggttatcttggtatgttctcaaatTTTTTaggcataggacccgtgtct
164-187  LE  tacatatgcaatgtaattgcTTTTTaggcataggacccgtgtct
263-286  LE  gctcacataattgtaattgcaatTTTTTaggcataggacccgtgtct
338-362  LE  ccaatgttttaaatTTTTTaggcataggacccgtgtct
363-385  LE  gcctataacacatcaaatTTTTTaggcataggacccgtgtct
527-548  LE  ctttgcacactcttcaggttcTTTTTaggcataggacccgtgtct
549-576  LE  acatatatcacttaattgtcttttattttTTTTTaggcataggacccgtgtct
577-600  LE  ccaagttttaggttttctctacagTTTTTaggcataggacccgtgtct
601-622  LE  catgtgtgggttctcctacctattTTTTTaggcataggacccgtgtct
138-163  BL  cagaaacactctgtcttagaagaagc
240-262  BL  agatgtggggagtatcatctttctgtc
287-310  BL  caacaaagagtttactaatctcaaa
311-337  BL  tgtcacaacagtaactcagagtataat
386-411  BL  ggtatggtattttgttctattttttctttTTTTTaggcataggacccgtgtct
431-456  BL  ggttgaatgctgttttctatttccata
457-480  BL  ctttgtgaggcaaaagtctgtgta
481-505  BL  ttgctgtttttctacacaccaagag

Oatp1a6  471-497  CE  gaggttagtgatattatgaacacccacaaaaTTTTTcctcttggaagaatagt
498-518  CE  cgtatctgcccagtaggaatTTTTTcctcttggaagaatagt
742-768  CE  ccaatgtataaggaggaattttctgtattTTTTTcctcttggaagaatagt
973-994  CE  ctttggaggttttttgaagTTTTTcctcttggaagaatagt
995-1017 CE  tccctcattatctgaattctcTTTTTcctcttggaagaatagt
425-449  LE  cacaatatcatgattttttctgtattttTTTTTaggcataggacccgtgtct
450-470  LE  ggccctacaattgcaacccaaTTTTTaggcataggacccgtgtct
546-567  LE  aagctgttttggagacagtttgcTTTTTTaggcataggacccgtgtct
568-590  LE  ggatctgttttctacacacaaaTTTTTaggcataggacccgtgtct
640-668  LE  ctacagctacatataatcatcataatTTTTTaggcataggacccgtgtct
669-692  LE  cacaatatccacagtaattttTTTTTTaggcataggacccgtgtct
693-714  LE  cctaaagggcatatggaggtttTTTTTTaggcataggacccgtgtct
769-794  LE  caatctcttccacttcttaaaatTTTTTTaggcataggacccgtgtct
841-865  LE  tgtatcagacccctgtctacaTTTTTTaggcataggacccgtgtct
DMD #3640

866-888 LE gttggaggtttaggtcagttcagcTTTTTgagcataggaccttgtct
889-908 LE caccgacccacagtctgatTTTTTgagcataggaccttgtct
930-951 LE aggcatctacctgacacagaTTTTTgagcataggaccttgtct
519-545 BL tgttaggttaagttgtggtttcatatt
591-614 BL tgtcatctgttggcttcatagtttgtcttggcataggaccttgtct
615-639 BL ttagtttgctgacaaagggtcttggcataggaccttgtct
715-741 BL ttagtttgctgacaaagggtcttggcataggaccttgtct
795-817 BL catcaaatatcaggttagtggtgttggcataggaccttgtct
818-840 BL ttagtttgctgacaaagggtcttggcataggaccttgtct
909-929 BL ctagttttggatggttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtttgtt
DMD #3640

2014-2035 BL tgggattctctgcaagaacctt
2036-2056 BL aacaccaaagtacacaggggc
2057-2079 BL ttgaggcatgaagtgtcaatca
2121-2142 BL ctgaaagcgtgggagtcataca
2187-2210 BL aaagtacagccatgcttaggaaga
2262-2286 BL cttgaagacatccctatttttc
2327-2346 BL cctggccagtacttggtcgt
2347-2370 BL ttgaggcatgaagtgtcaatca
2448-2469 BL aacaccaaagtacacaggggc
665-685 BL gagtggacccctttccaa
2121-2144 LE ttctctggtcctgatgcttatagcTTTTTaggcataggacccgtgtcct
2184-2202 LE tgccactcctgtcaggtgTTTTTaggcataggacccgtgtcct
2203-2221 LE ttggcaaacgctcagaggaTTTTTaggcataggacccgtgtcct
2242-2261 LE ggttggctctccgataccgtTTTTTaggcataggacccgtgtcct
2262-2281 LE aggacccctcaggcactggacTTTTTaggcataggacccgtgtcct
2057-2078 BL tctctgctctgttgcctcaaga
2167-2183 BL ggggctgggaccgtcaa
481-502 CE tgctggtctcctctggtctatcTTTTTctcttggaaagaaagt
557-576 CE gatcccaaatggctgaatggTTTTTctcttggaaagaaagt
679-700 CE cggaggctctcgcagctgctTTTTTaggcataggacccgtgtcct
779-798 CE gcctgaagaggtgacgcTTTTTctcttggaaagaaagt
464-480 LE ggccacgggtgtctgtgctTTTTTaggcataggacccgtgtcct
503-522 LE cacatacagctctccatgcTTTTTaggcataggacccgtgtcct
523-540 LE ggcrgacagctgagcggacTTTTTctcttggaaagaaagt
541-556 LE gcaccgtcccaacgcTTTTTaggcataggacccgtgtcct
599-618 LE cagagggctggtagtggagctTTTTTaggcataggacccgtgtcct
661-678 LE gcccagccaggtgcctTTTTTaggcataggacccgtgtcct
701-721 LE tgcctactctgccgtctTTTTTaggcataggacccgtgtcct
722-742 LE ggctcaggttcactgtagccgTTTTTaggcataggacccgtgtcct
743-761 LE atccccgggctacccgTTTTTaggcataggacccgtgtcct
762-778 LE ccagccacaggctcctgTTTTTaggcataggacccgtgtcct
577-598 BL ctgcagagtctgtccatagga
619-644 BL gcgtagcagaataaagatggagata
645-660 BL augcccccaacacgcg
1991-2013 CE gaagaactggaggtgctatagTTTTTaggcataggacccgtgtcct
2097-2120 CE ttgggctctctccaTTTTTaggcataggacccgtgtcct
2145-2166 CE cctctggtagaacctgtgctTTTTTaggcataggacccgtgtcct
2222-2241 CE ggttttgctctgtgctTTTTTaggcataggacccgtgtcct
1932-1949 LE ctcgccccacaggtcgagTTTTTaggcataggacccgtgtcct
1950-1970 LE tcgctagagcttcgacagcTTTTTaggcataggacccgtgtcct
1971-1990 LE ggttttggacagtctttggTTTTTaggcataggacccgtgtcct
2014-2034 LE caccaggatcacttttgaaTTTTTaggcataggacccgtgtct
2035-2056 LE tggccaaactaagtaaagcaTTTTTaggcataggacccgtgtct
2079-2096 LE gttgctctgttgcctggcTTTTTaggcataggacccgtgtct
2121-2144 LE ttctctgtctctgatagcTTTTTaggcataggacccgtgtct
2184-2202 LE tggcactcttggtcaggtgTTTTTaggcataggacccgtgtct
2203-2221 LE tggccaaaggtcaggaagaaTTTTTaggcataggacccgtgtct
2242-2261 LE gttgctctctgatagcTTTTTaggcataggacccgtgtct
2262-2281 LE tggcactcctggtcaggtgTTTTTaggcataggacccgtgtct
2057-2078 BL tctctgctctgttgcctcaaga
2167-2183 BL gggggctgggaccgtcaa

Oatp3a1 511-529 CE ggtgccttctgctctccatTTTTTctcttggaaagaaagt
571-589 CE gcagattgtagtccggtgtgcTTTTTctcttggaaagaaagt
726-750 CE atcgtagaaggttccaggtgaTTTTTctcttggaaagaaagt
772-794 CE agaaagccgccaggaatatccTTTTTctcttggaaagaaagt
491-510 LE cggatctcgacagccgctgtTTTTTaggcataggacccgtgtct
530-550 LE cccattggtggcacagacatcTTTTTaggcataggacccgtgtct
551-570 LE ggcctgtcatcactgctggaTTTTTaggcataggacccgtgtct
590-607 LE cggctgtcctcaagttgaaTTTTTaggcataggacccgtgtct
608-632 LE caataacgacagcatcagctgtTTTTTaggcataggacccgtgtct
684-706 LE cacgtgctgctaatcatgggaTTTTTaggcataggacccgtgtct
707-725 LE cggagggttcctctctccgTTTTTaggcataggacccgtgtct
751-771 LE cccagctgcctcactacccaaTTTTTaggcataggacccgtgtct
633-650 BL ccaggagccactgagccc
651-668 BL cgggggttagacaggtacgac
669-683 BL cccccaggggtctca
795-817 BL cgcatccacataatcttgggtac

Oatp4a1 1750-1770 CE ggtgccttttagtgcagcgtgTTTTTctcttggaaagaaagt
1792-1811 CE ggtgttagtctctggttcgtggTTTTTctcttggaaagaaagt
1894-1914 CE cagctccgctatccttcttgTTTTTctcttggaaagaaagt
1939-1956 CE gcattgccagaagagactctgtTTTTTctcttggaaagaaagt
1691-1709 LE ctgcagctgtaggctggTTTTTaggcataggacccgtgtct
1710-1729 LE cacgtgctgctaatcatgggaTTTTTaggcataggacccgtgtct
1730-1749 LE ctttagcagacacggctccTTTTTaggcataggacccgtgtct
1771-1791 LE caacagtatgagcgcggacaaTTTTTaggcataggacccgtgtct
1812-1831 LE gcctcagtacgccagcagccTTTTTaggcataggacccgtgtct
1832-1856 LE cgtaccagggaggttagatgctctTTTTTaggcataggacccgtgtct
1857-1874 LE cactcagcggcagctgtTTTTTaggcataggacccgtgtct
1875-1893 LE cccagggtcctgtcctggTTTTTaggcataggacccgtgtct
1915-1938 LE gagaacctctcaaggtgtagatgctTTTTTaggcataggacccgtgtct
1957-1974 LE cggcactctctgctgtTTTTTaggcataggacccgtgtct
Oatp4c1 2110-2135 CE ttctgactttgaaatgatacctctgtTTTTTctcttggaaagaagt
2162-2186 CE ttttctgctttgtctagatcctcttTTTTTctcttggaaagaagt
2292-2310 CE tccctctcttttacccctcaTTTTTAggcataaggacccgctgtct
2412-2434 CE gcttttggtgaactttagaggcaTTTTTaggcataaggacccgctgtct
2136-2161 LE cgaccgaaatagtagacacaatgacaTTTTTaggcataggacccgctgtct
2187-2207 LE cctcetctttttacccctcaTTTTTAggcataaggacccgctgtct
2208-2227 LE gcctgtcctaaagcaatctTTTTTAggcataaggacccgctgtct
2228-2248 LE aggtgttcttcacagggacaggaTTTTTaggcataaggacccgctgtct
2269-2291 LE ttcacacgttggctacacactTTTTTaggcataaggacccgctgtct
2311-2334 LE atctgttcatggaatgatcaccTTTTTaggcataaggacccgctgtct
2361-2386 LE ggggtttttttttttttttttttttttttttttTTTTTaggcataaggacccgctgtct
2387-2411 LE ggcaacttcatgtttgtgagttgtgTTTTTaggcataaggacccgctgtct
2462-2484 LE ggtttttcataggttgacaoaagTTTTTaggcataaggacccgctgtct
2094-2109 BL tcctgggggcggtggt
2249-2268 BL agacaatgtgtgctttggac
2335-2360 BL tgtgtttttttttttttttttttttttttttTTTTTaggcataaggacccgctgtct
2435-2461 BL ttgtttgtttttttaaaatagga

Oatp5a1 329-349 CE agtgcctcagttgggaatccctcTTTTTctcttggaaagaagt
370-389 CE acctctcagtttgctgggcTTTTTctcttggaaagaagt
453-472 CE gcatgggaatcccttgcgaTTTTTctcttggaaagaagt
494-517 CE ggaacttacggttctggaaaagTTTTTctcttggaaagaagt
310-328 LE gcaaccttctctctgaatTTTTTaggcataaggacccgctgtct
350-369 LE ttgcccacattctacaatTTTTTaggcataaggacccgctgtct
390-410 LE ggcataaatgtgacgaggattTTTTTaggcataaggacccgctgtct
473-493 LE tccccgactatgcttggfTTTTTaggcataaggacccgctgtct
518-536 LE cctgccagggatgtcgaagTTTTTaggcataaggacccgctgtct
555-577 LE gcctttagatgcttggfTTTTTaggcataaggacccgctgtct
598-622 LE cgtattcaactcaaccacaatTTTTTaggcataaggacccgctgtct
578-597 BL cattcattctcctctcccg
411-429 BL cccggggtgctgagggctg
430-452 BL gagcagttttttctctggacttcc
537-554 BL cagcactccggggctctgtctg

Oatp6b1 1004-1023 CE ttgcaaccttctacaatTTTTTctcttggaaagaagt
1171-1195 CE gcctgggaatcccttgcgaTTTTTctcttggaaagaagt
1223-1243 CE ccttctgggaatccctttgcgaTTTTTctcttggaaagaagt
1444-1466 CE tgcctttttttttttttttttttttttttttTTTTTaggcataaggacccgctgtct
1024-1046 LE cattccatggatccttcagaaTTTTTaggcataaggacccgctgtct
1071-1093 LE aaacagggcattgatctcaattTTTTTaggcataaggacccgctgtct
1148-1170 LE cacattggggaataaaataggtTTTTTaggcataaggacccgctgtct
1267-1291 LE gcctggagttcaattttattttatatTTTTTaggcataaggacccgctgtct
1292-1317 LE cgtttctgtcctcacaattattttatatTTTTTaggcataaggacccgctgtct
1318-1346 LE tcattttttatcatagatcacaTTTTTaggcataaggacccgctgtct
DMD #3640

1347-1372 LE aatacagaatcccatcagtatgaacaTTTTTaggcataggacccgtgtct
1373-1392 LE gtttggtccaatttgcaaaaTTTTTaggcataggacccgtgtct
977-1003 BL ttaaatgcaagaacaatttgaagtt
1047-1070 BL tggtagtaaatttccagaagttg
1094-1118 BL caattggaagaagaagaaaaagc aaa
1119-1147 BL gattggtaatactagtaaactgagaaagag
1196-1222 BL tctaaaagttgtaataatttgcactctat
1244-1266 BL gctgtaattggaagaagacagtgg
1393-1417 BL aaaaatgccaagagagataaagaag
1418-1443 BL cttccaactcgtggaacacattatatt
1467-1492 BL tttgctcttttttatttttttt

Oatp6c1

757-777 CE tccctgctatgccatggatacTTTTTctcttggaaagaaagt
846-871 CE agatatgcgaaagtctcctagctaaTTTTTctcttggaaagaaagt
919-941 CE gactgtttttttccttggagTTTTTctcttggaaagaaagt
1086-1106 CE gggaggttcctttcttcgcTTTTTctcttggaaagaaagt
690-712 LE actatgtgtttcctcccggtattTTTTTaggcataggacccgtgtct
713-738 LE aatagataaattttgatctgttggagTTTTTctcttggaaagaaagt
739-756 LE actgccacgatgtggaaTTTTTAggcataggacccgtgtct
778-799 LE atgcaagagataaatttttcctgcTTTTTctcttggaaagaaagt
942-962 LE caccttgcggttgtaatttctTTTTTAggcataggacccgtgtct
1134-1156 LE cccttcaataggtgtaatTTTTTAggcataggacccgtgtct
800-823 BL ggaatgtggtcctaaatgaaggtt
824-845 BL atagaagcgcgcatgaacttggt
872-896 BL tacatccacaggaagttctctac
897-918 BL gctgaaatcctgcttgccctcc
963-984 BL accccactctgcaacagttgtga
985-1009 BL gcaatattaaacaaagtttttccac
1010-1034 BL gaaagatacacaatgagattgtca
1035-1060 BL aaactagtggaaaacataccatcat
1061-1085 BL aagttttataccttagtgacaccagg
1107-1133 BL catatccttaagttccctctgcaaggtt

Oatp6d1

154-176 CE ttctctgggtctcttagtggttTTTTTctcttggaaagaaagt
226-253 CE cgatctgacttttcataatctgtgtatatTTTTTctcttggaaagaaagt
545-565 CE cctgttaagaagcgcgagctTTTTTctcttggaaagaaagt
130-153 LE ggtggtctcagcatgtctacacacrrTTTTTAggcataggacccgtgtct
203-225 LE ctggaaaactctctctctctctgagatTTTTTAggcataggacccgtgtct
254-276 LE cctccggaggcattttagttttTTTTTAggcataggacccgtgtct
277-297 LE gagagcccaacactatgtgctTTTTTAggcataggacccgtgtct
345-366 LE cgaggctaaaaaagcagagagtTTTTTAggcataggacccgtgtct
367-392 LE aagacgacataaatcatactagctgaccaTTTTTAggcataggacccgtgtct
446-475 LE aaattctactagatcctcaatagctttacccTTTTTAggcataggacccgtgtct

This article has not been copyedited and formatted. The final version may differ from this version.

DMD Fast Forward. Published on April 20, 2005 as DOI: 10.1124/dmd.105.003640
Downloaded from dmd.aspetjournals.org on January 1, 2021
Fig. 1

- **Oatp1a1 (Oatp1)**
  - MALE
  - FEMALE

- **Oatp1a4 (Oatp2)**

- **Oatp1a5 (Oatp3)**

- **Oatp1a6 (Oatp5)**

**RNA**

- Liver
- Kidney
- Lung
- Stomach
- Duodenum
- Jejunum
- Ileum
- Large intestine
- Brain
- Gonad
- Placenta
Fig. 2

Oatp1b2 (Oatp4)
Oatp1c1 (Oatp14)
Oatp2a1 (Pgt)
Oatp2b1 (Oatp9)

MALE
FEMALE

LIVER     KIDNEY     LUNG    STOMACH    DUODENUM   JEJUNUM   ILEUM   L. INTESTINE   BRAIN   GONAD   PLACENTA
Fig. 3

- **Oatp3a1 (Oatp11)**
  - MALE
  - FEMALE

- **Oatp4a1 (Oatp12)**
- **Oatp4c1**

- **Oatp5a1 (Oatp15)**

**RNA**: RLU/10µg total RNA

**Tissues**: LIVER, KIDNEY, LUNG, STOMACH, DUODENUM, JEJUNUM, ILEUM, L. INTESTINE, BRAIN, GONAD, PLACENTA

* denotes statistical significance.
Fig. 4

Graph showing the expression levels of Oatp6b1 (Gst), Oatp6c1 (Gst2), and Oatp6d1 (Gst1) in various organs for male and female mice. The organs include liver, kidney, lung, stomach, duodenum, jejunum, ileum, intestine, brain, gonad, and placenta. The y-axis represents Oatp mRNA (RLU/10µg total RNA) with different thresholds for male and female expression levels. The x-axis lists the organs. Asterisks (*) indicate significant differences between genders.
Fig. 5

Liver Oatp mRNA (RLU/10µg total RNA)

- **Oatp1a1 (Oatp1)**
  - MALE
  - FEMALE

- **Oatp1a4 (Oatp2)**

- **Oatp1a6 (Oatp5)**

**Age (days after birth)**

-2  0  5  10  15  23  30  35  40  45
Fig. 6

Liver Oatp mRNA (RLU/10µg total RNA)

- Oatp1b2 (Oatp4)
- Oatp2a1 (Pgt)
- Oatp2b1 (Oatp9)

Age (days after birth): -2, 0, 5, 10, 15, 23, 30, 35, 40, 45

MALE and FEMALE
Fig. 7

Kidney Oatp mRNA (RLU/10μg total RNA)

Oatp1a1 (Oatp1)

Oatp1a4 (Oatp2)

Oatp1a6 (Oatp5)

Age (days after birth)

MALE
FEMALE

RNA
Fig. 8

![Bar chart showing the expression of Oatp2a1 (Pgt), Oatp2b1 (Oatp9), and Oatp3a1 (Oatp11) mRNA in male and female rats at different ages. The x-axis represents age (days after birth), and the y-axis represents kidney Oatp mRNA (RLU/10µg total RNA). Asterisks indicate statistically significant differences (*) compared to the control group.](chart-image-url)