Regional distribution of solute carrier (SLC) mRNA expression along the human intestinal tract


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Running title: Intestinal solute carrier expression in humans

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Abbreviations: SLC, solute carrier; CNT, concentrative nucleoside transporter; ASBT, apical sodium-dependent bile acid transporter; SERT, serotonin transporter; PEPT, peptide transporter; OCTN, organic zwitterion/cation transporter; OATP, organic anion transporting polypeptide; ENT, equilibrative nucleoside transporter; IBD, inflammatory bowel disease; 5-HT, 5-hydroxytryptamine; IBS, irritable bowel syndrome; OCT, organic cation transporter; MCT1, monocarboxylate transporter; OAT, organic anion transporter; ca, colon ascendens; ct, colon transversum; cd, colon descendens.
Abstract

Intestinal absorption of drugs, nutrients, and other compounds is mediated by uptake transporters expressed at the apical enterocyte membrane. These compounds are returned to the intestinal lumen or released into portal circulation by intestinal efflux transporters expressed at apical or basolateral membranes, respectively. One important transporter superfamily, multiple members of which are intestinally expressed, are the solute carriers (SLCs). SLC expression levels may determine the pharmacokinetics of drugs that are substrates of these transporters. In this study we characterize the distribution of fifteen human SLC transporter mRNAs in histologically normal biopsies from five regions of the intestine of ten patients. The mRNA expression levels of CNT1, CNT2, ASBT, SERT, PEPT1 and OCTN2 exhibit marked differences between different regions of the intestine: the first five are predominantly expressed in the small intestine, while OCTN2 exhibits strongest expression in the colon. Two transporter mRNAs studied (OCTN1, OATP2B1) are expressed at similar levels in all gut sections. Additionally, ENT2 mRNA is present at low levels across the colon, but not in the small intestine. The other six SLC mRNAs studied are not expressed in the intestine. Quantitative knowledge of transporter expression levels in different regions of the human gastrointestinal tract could be useful for designing intestinal delivery strategies for orally administered drugs. Furthermore, changes in transporter expression that occur in pathological states, such as inflammatory bowel disease, can now be defined more precisely by comparison with the expression levels measured in healthy individuals.
Introduction

The members of the solute carrier (SLC) superfamily are membrane-associated transporters that facilitate the passage of solutes, including peptides, bile acids and drugs, across cell membranes in epithelial tissues, such as intestine and liver (Hediger et al., 2004). In the intestine, SLCs are critically involved in drug absorption, thus determining distribution and pharmacokinetic characteristics of many drugs.

The human SLCs belong to 46 families (http://www.bioparadigms.org/slc/menu.asp), and are expressed in a polarized manner, either at the apical or basolateral cell membranes. The SLC28 and SLC29 families encode the high-affinity concentrative (CNT) and the low-affinity equilibrative (ENT) nucleoside transporters, respectively (Gray et al., 2004; Baldwin et al., 2004). Nucleoside transporters are essential for de novo nucleic acid synthesis, and for anticancer and antiviral therapy with nucleoside analogues. CNTs are mainly localized at the apical membranes of absorptive epithelia and mediate nucleoside uptake, whereas ENTs are responsible for nucleoside efflux at basolateral membranes. Most transporters of the SLC22 family are polyspecific, transporting multiple different substrates, and are subdivided into three groups: organic cation transporters (OCTs), organic anion transporters (OATs), and organic zwitterion/cation transporters (OCTNs) (Koepsell and Endou, 2004). Two members of the last group, OCTN1 and OCTN2, have attracted much attention, as polymorphisms in the genes encoding them have been linked to inflammatory bowel disease (IBD) (Peltekova et al., 2004). The SLCO family consists of organic anion transporting polypeptides (OATPs), most of which have a broad substrate specificity (Hagenbuch and Meier, 2004). While many OATPs play vital roles in the liver, some of them also have important functions in the intestine. A member of the SLC10 family, ASBT (apical sodium-dependent bile acid transporter; SLC10A2), is critical for enterohepatic circulation of bile acids by mediating their absorption at the apical membranes of enterocytes (Hagenbuch and Dawson, 2004). Reduced ASBT expression may cause decreased
bile acid absorption and diarrhea in Crohn’s disease patients (Jung et al., 2004). Loss-of-function mutations in ASBT cause primary bile acid malabsorption, a rare intestinal disorder characterized by congenital diarrhea and reduced plasma cholesterol levels (Oelkers et al., 1997). The oligopeptide transporter PEPT1 (SLC15A1) at the apical membrane of intestinal epithelium mediates the uptake of nutrient-derived peptides, as well as of peptidomimetic drugs (Adibi, 2003). Colonic expression of PEPT1 is induced in patients suffering from IBD (Merlin et al., 2001), although it is unclear whether the aberrant PEPT1 expression is a cause or a consequence of inflammation. Serotonin transporter (SERT; SLC6A4) is a terminator of 5-hydroxytryptamine (5-HT) signalling, by mediating 5-HT reuptake at basolateral enterocyte membranes (Mawe et al., 2006). Reduced SERT expression is associated with ulcerative colitis and irritable bowel syndrome (IBS) (Coates et al., 2004). Furthermore, SERT polymorphisms are linked to IBS (Camilleri et al., 2002; Yeo et al., 2004).

Expression levels of SLCs may determine the degree of intestinal absorption of their transport substrates. Thus, knowledge about the distribution of SLCs along the intestine may assist in designing novel enterally delivered drugs. Relative SLC mRNA abundance along the human gut has been examined in two recent studies. Hruz et al. (2006) investigated ASBT expression in five intestinal regions, while Englund et al. (2006) studied the distribution of five SLCs (PEPT1, MCT1, OATP2B1, OCT1, OCTN2) in three gut segments. Here, we extend these analyses to 15 SLCs (CNT1/2/3, ENT1/2, OCTN1/2, OCT1, OAT2, OATP1A2/2B1/4A1, ASBT, SERT1, PEPT1), using histologically normal biopsies from five intestinal segments obtained from ten individuals.

**Materials and Methods**

**Patients.** The study was approved by the ethical committee of the University Hospital Zurich (EK-837) and informed consent was obtained from all patients. Histologically normal biopsies
from five intestinal sections, namely duodenum, ileum, colon ascendens (ca), colon transversum (ct), and colon descendens (cd), were obtained from ten Caucasian subjects undergoing upper and lower intestinal endoscopy. Information of each patient (age, gender, reason for endoscopy, drug intake, additional diagnoses) is shown in Table 1.

**RNA isolation, reverse transcription, and real-time PCR.** Biopsies were rinsed in phosphate-buffered saline, transferred to 1 ml TRIzol (Invitrogen, Basel, Switzerland), and disintegrated by repeated syringing through 21 gauge needles. After isolation of RNAs, their concentrations were determined using NanoDrop ND-1000 (Witec AG, Littau, Switzerland). The A260/280 ratios of all RNAs were 1.9-2.1. 3 µg of each RNA were reverse transcribed by random priming in 40 µl reactions (Reverse Transcription System, Promega Catalys, Wallisellen, Switzerland), and diluted to a volume of 150 µl with nuclease-free water. Real-time PCR was performed on ABI PRISM 7700 sequence detection system (Applied Biosystems, Rotkreuz, Switzerland), using 5 µl of cDNA, 1.25 µl of TaqMan Gene Expression Assays (Applied Biosystems; Supplementary Table 1), and 12.5 µl of 2 × Universal PCR MasterMix (Applied Biosystems) in a final reaction volume of 25 µl. The cycling conditions were: stage 1 (50°C, 2 min), stage 2 (95°C, 10 min), 40 x stage 3 (95°C, 15 sec, followed by 60°C, 1 min). Each PCR was performed in triplicate, and the standard deviations of all triplicates were less than 7%. For each TaqMan Assay, a dilution series (30, 300, 3000, 30000, 300000, and 3000000 copies) of the corresponding cloned PCR product (see below) was included on each PCR plate, to generate standard curves for absolute quantification of cDNA copy numbers. Data are expressed as SLC cDNA copy numbers in relation to villin cDNA copy numbers. This method assumes that the reverse transcription efficiency of all mRNAs is comparable.

**Cloning of PCR products.** Before real-time PCR, preparative PCRs using TaqMan Gene Expression Assays and Human Universal QUICK-Clone cDNA (Takara Bio Europe, Saint-Germain-en-Laye, France) as a template were performed. PCR products were cloned into the
pCRII vector (Invitrogen) or, in the case of OCTN2, into the pGEM-T vector (Promega Catalys). The sizes of the PCR products are listed in Supplementary Table 1. The insert-containing plasmids were purified using QIAfilter Midi Kit (Qiagen, Hombrechtikon, Switzerland), quantitated with NanoDrop ND-1000, and diluted as described above.

**Statistical analysis.** The mRNA expression levels of SLC genes between different gut sections were analyzed by one-way ANOVA, followed by post hoc analysis with Tukey's test (GraphPad Prism, San Diego, CA). p values less than 0.05 were considered as significant.

**Results**

**Relative abundance of different SLC mRNAs within intestinal sections.** The mRNA levels of 15 SLCs in five different intestinal regions were measured by real-time PCR and expressed as copy numbers of SLC cDNA in relation to copy numbers of villin cDNA. Villin is commonly used as the reference gene for epithelial content in intestinal samples (Zimmermann et al, 2005; Hruz et al, 2006). We note that, in agreement with the study by Englund et al (2006), in our patient group villin mRNA expression was slightly higher in duodenum than in colon segments (colon ascendens p<0.01; colon transversum p<0.05; colon descendens p<0.01), possibly causing a slight bias towards low duodenal SLC expression. In contrast to the study by Englund et al, we found no significant difference in villin mRNA expression between ileum and colon.

The mean SLC mRNA expression level ranged from 4x10^-5 for CNT1 in colon descendens to 3.9x10^1 for PEPT1 in duodenum (Table 2). We defined those SLC mRNAs, which exhibited a mean expression level greater than 0.01 [copies of SLC cDNA/copies of villin cDNA ratio] as "detectable". The SLCs with a mean mRNA expression level less than 0.01 in a specific intestinal section were defined as "not detectable". Four SLCs (PEPT1, OCTN1, OCTN2, OATP2B1) were detectable in all five gut sections, five SLCs (CNT1, CNT2, ASBT, SERT, ENT2) were detectable in at least one intestinal section, and six SLCs (CNT3, OCT1, OAT2, ENT1, OATP1A2, OATP4A1) were not detectable in any gut section. Eight SLCs (CNT1,
CNT2, ASBT, SERT, PEPT1, OCTN1, OCTN2, OATP2B1) were expressed in both duodenum and ileum (Table 2). In these sections, the PEPT1 mRNA was expressed the highest amongst the 15 SLCs, the mean expression level being ~3.8 in both duodenum and ileum (Table 2). The only other SLC mRNA expressed at a higher level than the villin mRNA (with a ratio [mean SLC expression/ mean villin expression] greater than one) in any intestinal section was the OCTN1 mRNA in the ileum (expression level 1.27). In all three colon regions the OCTN1 mRNA was the most abundant SLC mRNA (Table 2). Four other SLC mRNAs were also detectable in all three segments of the colon, namely PEPT1, OCTN2, OATP2B1, and ENT2, although the last two were expressed at considerably lower levels than the PEPT1, OCTN1, and OCTN2 mRNAs.

**Regional distribution of SLC mRNAs between different intestinal segments.** For all SLC mRNAs that were detectable in the gut, there was high interindividual variability of expression, as demonstrated by high standard deviations in Table 2 and Fig. 1A-I. Four SLC mRNAs were only detectable in duodenum and ileum: CNT1, CNT2, ASBT, and SERT. CNT1 mRNA expression in these two intestinal segments was comparable (Fig.1A). Expression of the CNT2 mRNA was higher (p<0.05) in duodenum than ileum, whereas ASBT (p<0.001) and SERT (p<0.05) mRNA expression was higher in ileum, when compared to duodenum. Four SLC mRNAs (PEPT1, OCTN1, OCTN2, OATP2B1) were detectable in all intestinal sections examined (Fig. 1E, F, G, H). PEPT1 was equally highly expressed in duodenum and ileum (Fig. 1E), but at significantly lower levels in all colon segments (p<0.001). PEPT1 mRNA expression ranged from 0.9 to 8.7 in duodenum and from 1.8 to 8.8 in ileum, demonstrating a high degree of interindividual variability. There was no significant difference in OCTN1 (Fig. 1F) and OATP2B1 (Fig. 1H) mRNA expression between any gut sections. Expression of the OCTN2 mRNA was significantly higher in all three colon sections (colon ascendens p<0.001; colon transversum p<0.05; colon descendens p<0.05) than in duodenum (Fig. 1G). The level of OCTN2 mRNA expression was also higher in colon than in ileum, although the only colon section where this difference reached statistical significance was colon ascendens (p<0.001). The
ENT2 mRNA was expressed at a similar level in all colon segments, but was not detectable in either duodenum or ileum (Fig. 1I; Table 2). While in other regions of the colon the ENT2 mRNA expression exhibited relatively little interindividual variation, in colon descendens of patient 2 the ENT2 expression considerably deviated from the mean value derived from the ten patients.

Discussion

We have quantified the regional mRNA expression of 15 SLC genes along the human intestinal tract, using histologically normal tissue derived from duodenum, ileum, colon ascendens, colon transversum, and colon descendens. We found marked differences in SLC mRNA levels between intestinal sections. Nine SLC mRNAs were detectable in at least one section of the intestine. Amongst these, we observed three different expression patterns: 1) SLCs predominantly or exclusively expressed in the duodenum and ileum (CNT1, CNT2, ASBT, SERT, PEPT1), 2) SLCs expressed in all five intestinal sections at similar levels (OCTN1, OATP2B1), 3) SLCs expressed at a higher level in colon than in the small intestine (OCTN2, ENT2). None of the SLC mRNAs exhibited significantly different expression levels between the three colon segments. Six SLC mRNAs were not detectable in any intestinal section: CNT3, ENT1, OCT1, OAT2, OATP1A2 and OATP4A1. Our results are in agreement with recent studies showing that the OCT1 and OAT2 mRNAs are either absent or expressed at very low levels in the human colon (Englund et al., 2006; Seithel et al., 2006).

It is important to note that the mRNA levels may not reflect the exact amount of the SLC protein or functional activity of a transporter, which may be subject to post-transcriptional regulation. However, obtaining sufficient amounts of intestinal tissue from healthy individuals to allow protein extraction or functional studies, in addition to RNA isolation, for all 15 SLCs
studied here is not feasible. However, we believe that quantitation of mRNA levels provides a relevant indication of the abundance of SLC transporters in specific gut sections.

For those SLC mRNAs that were detectable, our analysis of CNT1, CNT2, SERT, OCTN1, and ENT2 expression is the first systematic study of their regional distribution in the human intestine. Our data pertaining to ASBT, PEPT1, and OATP2B1 mRNA distribution are in agreement with two recent studies that also investigated the relative mRNA levels of subsets of SLC genes along the human intestine (Hruz et al., 2006; Englund et al., 2006). There is one difference between our results and those obtained by Englund et al.: in our study OCTN2 mRNA expression was similar between duodenum and ileum, while Englund et al. reported that OCTN2 expression level is higher in the ileum, compared to duodenum. The reason for this discrepancy is unclear at present.

We observed a high degree of interindividual variability in the expression of SLC mRNAs in the intestine. This may result from differences in intestinal metabolic microenvironment between patients, caused by genetic, hormonal, and dietary variations, or from differential exposure to drugs and environmental toxins. All these factors may affect transcriptional rates of specific SLC genes, thus causing transient or long-term changes in mRNA levels. Transcriptional regulatory mechanisms have been studied for a few of the SLC genes investigated in this study. Our current approach may provide physiological support for such molecular studies, or suggest novel pathways, by which the SLC genes are regulated. For example, consistent with the proposal that the human ASBT promoter is activated by the glucocorticoid receptor (Jung et al., 2004), ileal ASBT mRNA expression is particularly high in patient 4 (Fig. 1C) receiving glucocorticoid therapy (Table 1). Interestingly, OATP2B1 expression is similarly elevated in the ileum and colon of patient 4 (Fig. 1H), suggesting that the OATP2B1 gene may also be activated by glucocorticoids. Duodenal expression of six SLCs (CNT1, CNT2, SERT, PEPT1, OCTN2, OATP2B1) in patient 7 was clearly above the mean level derived from all ten patients (Fig. 1A, 1B, 1D, 1E, 1G, 1H). This patient had been treated
with carbamazepine (Table 1), a known agonist of the transcriptional regulator of drug transport and detoxification pathways, pregnane X receptor (PXR) (Luo et al., 2002). It will be interesting to study whether the SLCs highly expressed in patient 7 might thus be coordinately regulated by PXR.

We did not observe statistically significant gender differences in SLC expression. However, to exclude sex-dependent effects on SLC expression, the patient cohort should be large enough to allow division of female subjects into pre- or postmenopausal ones, and into women that are, or are not, taking hormone-containing contraceptives.

The patients in this study showed no apparent signs of intestinal diseases. Results obtained in healthy subjects form a basis for understanding changes in SLC gene expression in intestinal diseases, and may help in adapting therapeutic interventions in such pathologies. Changes in SLC expression occur in IBD, although it remains unclear, whether these are consequences of the inflammatory pathways or causative factors in the pathogenic process, or both. For example, PEPT1 is normally expressed at the apical membrane of the enterocytes of the small intestine, but has been reported to be abnormally expressed in the colon in states of chronic inflammation (Merlin et al., 2001). SERT mRNA expression is reduced in patients suffering from IBS and ulcerative colitis (Coates et al., 2004), implying that mucosal 5-HT uptake is impaired in these diseases. Variants of the OCTN1 and OCTN2 genes are linked to Crohn's disease (Peltekova et al., 2004), and OCTN1 and OCTN2 expression levels may also be associated with intestinal inflammation.

Intestinal drug absorption determines drug efficacy and pharmacokinetics. Several SLCs in this study mediate enteral uptake of specific drugs. For example, nucleoside analogues used in anticancer and antiviral therapy are absorbed via CNT1 and CNT2. ASBT is an efficient uptake system for bile acids, but has not been shown to transport drugs. However, it is an attractive target for delivery of prodrugs designed as bile acid derivatives (Balakrishnan and Polli, 2006). Determining regional expression levels of drug and prodrug transporters provides indications
about the site of intestinal absorption of a drug. This may help in designing enterally delivered drugs with more accurate absorption properties and more predictable pharmacokinetic characteristics.

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References


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Figure legend:

**Fig. 1: Individual mRNA expression patterns of SLCs along the human intestinal tract.**

The columns represent relative mRNA expression levels (SLC cDNA copy numbers normalized to villin cDNA copy numbers). Data points (○) indicate the mRNA expression levels in individual patients. Individuals with SLC mRNA expression level greater than mean+1SD are identified by their ID-Nrs. (A) CNT1; (B) CNT2; (C) ASBT; (D) SERT; (E) PEPT1; (F) OCTN1; (G) OCTN2; (H) OATP2B1; (I) ENT2. duo, duodenum; ile, ileum; ca, colon ascendens; ct, colon transversum; cd, colon descendens.
<table>
<thead>
<tr>
<th>ID-Nr:</th>
<th>sex:</th>
<th>age:</th>
<th>reason for endoscopy:</th>
<th>additional diagnoses:</th>
<th>drugs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>male</td>
<td>60</td>
<td>Barrett's esophagus, colonic diverticulosis</td>
<td>high cholesterol, arterial hypertension</td>
<td>ACE-inhibitor, NSAID, statin</td>
</tr>
<tr>
<td>2</td>
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<td>59</td>
<td>colonic polyps, reflux esophagitis</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>male</td>
<td>49</td>
<td>unclear abdominal pain, diarrhoea</td>
<td>polymyalgia rheumatica, arterial hypertension, diabetes type II</td>
<td>beta-blocker, Ca2+-channel blocker, diuretics, glucocorticoids, NSAID, PPI, vitamin B complex, alendronate</td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>61</td>
<td>reflux esophagitis, elevated ESR of unknown cause</td>
<td>chronic renal failure, fibromyalgia, polyarthritis</td>
<td>angiotensin II receptor antagonist, beta-blocker, Ca-channel, NSAID, opiate, PPI, misoprostol</td>
</tr>
<tr>
<td>5</td>
<td>female</td>
<td>66</td>
<td>iron deficiency anemia</td>
<td>systemic sclerosis, high cholesterol, arterial hypertension</td>
<td>ACE-inhibitor, estrogen, NSAID, PPI</td>
</tr>
<tr>
<td>6</td>
<td>female</td>
<td>62</td>
<td>iron deficiency anemia</td>
<td>epilepsy</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>7</td>
<td>male</td>
<td>44</td>
<td>unclear anemia</td>
<td>arterial hypertension, chronic renal failure, diabetes type I, high serum lipids</td>
<td>beta-blocker, NSAID, statin, insulin, cholecalciferol, ezetimibe</td>
</tr>
<tr>
<td>8</td>
<td>female</td>
<td>38</td>
<td>iron deficiency anemia</td>
<td>beta thalassemia, myeloproliferative syndrome</td>
<td>NSAID, PPI, hydroxycarbamide</td>
</tr>
<tr>
<td>9</td>
<td>female</td>
<td>63</td>
<td>unclear abdominal pain, retrosternal burning</td>
<td>bronchial asthma</td>
<td>NSAID, fenoterol</td>
</tr>
</tbody>
</table>

Angiotensin-converting enzyme inhibitor (ACE-inhibitor), non-steroidal anti-inflammatory drug (NSAID), proton pump inhibitor (PPI), erythrocyte sedimentation rate (ESR)
Table 2: Relative mRNA expression levels of SLCs in intestinal sections (n=10):

<table>
<thead>
<tr>
<th>SLC</th>
<th>Duodenum: mean±SD (median)</th>
<th>Ileum: mean±SD (median)</th>
<th>Colon ascendens: mean±SD (median)</th>
<th>Colon transversum: mean±SD (median)</th>
<th>Colon descendens: mean±SD (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPT1</td>
<td>3.87±2.52 (3.52)</td>
<td>3.79±2.19 (3.02)</td>
<td>OCTN1 0.43±0.40 (0.24)</td>
<td>OCTN1 0.70±0.61 (0.59)</td>
<td>OCTN1 0.86±0.94 (0.67)</td>
</tr>
<tr>
<td>OCTN1</td>
<td>0.53±0.54 (0.37)</td>
<td>1.27±1.33 (0.83)</td>
<td>OCTN2 0.34±0.20 (0.30)</td>
<td>OCTN2 0.24±0.08 (0.26)</td>
<td>PEPT1 0.25±0.16 (0.20)</td>
</tr>
<tr>
<td>CNT2</td>
<td>0.32±0.26 (0.27)</td>
<td>0.42±0.25 (0.39)</td>
<td>PEPT1 0.14±0.12 (0.11)</td>
<td>PEPT1 0.15±0.10 (0.14)</td>
<td>OCTN2 0.24±0.09 (0.24)</td>
</tr>
<tr>
<td>OCTN2</td>
<td>0.09±0.07 (0.09)</td>
<td>0.15±0.11 (0.14)</td>
<td>OATP2B1 0.02±0.02 (0.02)</td>
<td>OATP2B1 0.03±0.04 (0.02)</td>
<td>ENT2 0.05±0.09 (0.02)</td>
</tr>
<tr>
<td>ASBT</td>
<td>0.09±0.05 (0.08)</td>
<td>0.10±0.05 (0.10)</td>
<td>ENT2 0.02±0.01 (0.02)</td>
<td>ENT2 0.02±0.01 (0.01)</td>
<td>OATP2B1 0.03±0.03 (0.02)</td>
</tr>
<tr>
<td>CNT1</td>
<td>0.06±0.06 (0.05)</td>
<td>0.09±0.06 (0.08)</td>
<td>SERT 0.007±0.003</td>
<td>ASBT 0.006±0.006</td>
<td>ASBT 0.005±0.004</td>
</tr>
<tr>
<td>SERT</td>
<td>0.04±0.02 (0.02)</td>
<td>0.06±0.04 (0.05)</td>
<td>ASBT 0.007±0.008</td>
<td>SERT 0.004±0.003</td>
<td>OATP4A1 0.004±0.002</td>
</tr>
<tr>
<td>OATP2B1</td>
<td>0.02±0.02 (0.02)</td>
<td>0.06±0.10 (0.01)</td>
<td>OATP4A1 0.006±0.004</td>
<td>OATP4A1 0.004±0.003</td>
<td>CNT2 0.004±0.004</td>
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<tr>
<td>ENT2</td>
<td>0.009±0.006</td>
<td>0.006±0.005</td>
<td>CNT2 0.003±0.003</td>
<td>CNT2 0.003±0.003</td>
<td>SERT 0.003±0.003</td>
</tr>
<tr>
<td>OAT2</td>
<td>0.006±0.006</td>
<td>0.005±0.006</td>
<td>CNT3 0.002±0.003</td>
<td>OCT1 0.002±0.002</td>
<td>CNT3 0.003±0.004</td>
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<tr>
<td>CNT3</td>
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<td>0.003±0.004</td>
<td>OCT1 0.002±0.001</td>
<td>ENT1 0.001±0.001</td>
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<tr>
<td>OATP4A1</td>
<td>0.002±0.001</td>
<td>0.002±0.001</td>
<td>ENT1 0.001±0.0008</td>
<td>CNT3 0.001±0.001</td>
<td>ENT1 0.001±0.001</td>
</tr>
<tr>
<td>ENT1</td>
<td>0.001±0.0008</td>
<td>0.001±0.001</td>
<td>OAT2 0.0006±0.001</td>
<td>OATP1A2 0.0005±0.0006</td>
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<tr>
<td>OCT1</td>
<td>0.0004±0.0004</td>
<td>0.001±0.0009</td>
<td>OATP1A2 0.0004±0.0004</td>
<td>OAT2 0.0005±0.0006</td>
<td>OAT2 0.0007±0.001</td>
</tr>
<tr>
<td>OATP1A2</td>
<td>0.0002±0.0001</td>
<td>0.0004±0.0004</td>
<td>CNT1 0.0002±0.0001</td>
<td>CNT1 0.0001±0.0003</td>
<td>CNT1 0.00004±0.00004</td>
</tr>
</tbody>
</table>

SLCs are shown in a descending order according to their relative mRNA expression levels in different intestinal sections. SLCs with relative mean mRNA expression levels >0.01, and thus considered detectable, are highlighted in bold. The corresponding median values obtained from the ten patients are given in parentheses for the detectable SLC mRNAs.
Fig. 1

A) CNT1

B) CNT2

C) ASBT

D) SERT

E) PEPT1

F) OCTN1

G) OCTN2

H) OATP2B1

I) ENT2