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Organic Solute Transporter Alpha Deficiency: A Disorder With Cholestasis, Liver Fibrosis, and Congenital Diarrhea

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Solute carrier family 51 alpha subunit (*SLC51A*) encodes the alpha subunit of the heteromeric organic solute transporter alpha-beta (OST α -OST β), an important contributor to intestinal bile acid (BA) reabsorption in the enterohepatic circulation.^(1,2) Here, we identified the first case of OST α deficiency in a child with unexplained elevated liver transaminases, cholestasis, and congenital diarrhea.

Case Report

A 2.5-year-old Pakistani boy, born from a first-cousin union, was evaluated in a liver clinic. His past medical history is significant for chronic malabsorptive diarrhea of 10-15 oily daily stools, easy bruising, two episodes of prolonged bleeding that required blood

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Supporting Information

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transfusions, and failure to thrive. Stool studies included normal pH, and negative occult blood, reducing substance, and ova cysts. The patient was exclusively breastfed until 1 year of age, when he was started on soy-based formula milk, nutritional rehabilitation, and fat-soluble vitamin supplementation, with improvement in his weight and height. At age 2.5, he was found to have elevated transaminases and alkaline phosphatase (Table 1). Liver biopsy revealed a lobular architecture suggestive of early cirrhosis with portal and periportal fibrosis and many thin fibrous septa (Fig. 1A,B). Portal areas showed minimal lymphocytic inflammation, no interface activity, and patchy mild bile ductular proliferation (Fig. 1C,D). Bile ducts were missing in three of the portal tracts (Fig. 1E), not meeting criteria for bile duct paucity. The hepatocytes showed rare foci of subtle hepatocytic cholestasis (Fig. 1F). Duodenal and colonic biopsies showed no significant abnormality (Fig. 1G,H). Since a comprehensive workup was unrevealing (Supporting Table S1), his exome was sequenced. Consistent with consanguinity, the proband harbors 23 rare homozygous protein-altering variants, including 22 missense variants predicted to be tolerated by a meta-analytic support vector machine (MetaSVM) and therefore unlikely to be pathogenic in this child. Notably, the other homozygous mutation led to a premature termination at codon 186 in *SLC51A* (NM_152672,c.556C>T,p.Gln186*), which encodes OST α . This variant allele is extremely rare, with only one instance among more than 251,400 alleles sequenced from diverse populations, including South Asians (gnomAD: <https://gnomad.broadinstitute.org>, last accessed September 25, 2019). Sanger sequencing confirmed the homozygous variant in the proband and showed the heterozygous carrier state of both his parents and an unaffected sister (Fig. 1I,J). Furthermore, the proband's colon tissue showed undetectable *SLC51A* transcripts (Fig. 1K). Analysis of the BA concentrations in the proband's blood spot by liquid chromatography–tandem mass spectrometry (LC-MS/MS) showed that BA concentrations were within the normal range despite underlying cholestasis. He was started on ursodiol at 5 years and 1 month and 9 months later on cholestyramine. While the coagulopathy resolved, his growth is adequate and he has two or three bulky daily bowel movements; his transaminases, direct bilirubin, and gamma-glutamyl-transferase (GGT) levels remain elevated (Table 1).

Discussion

Our findings provide the first demonstration of human OST α deficiency in a child with elevated liver transaminases, cholestasis, liver fibrosis, and congenital diarrhea. The evidence implicating *SLC51A* genotype as the cause of the proband's phenotype is strong. First, the proband represents the first homozygote for an extremely rare premature termination mutation in *SLC51A*. Second, there is an absence of *SLC51A* mRNA expression in the proband's colon tissue, consistent with his recessive premature termination mutation in *SLC51A* leading to mRNA decay. Third, the proband's clinical phenotype is consistent with a defect in BA metabolism. Fourth, human deficiency for OST β , which forms a heterodimer with OST α in the active transporter, has been described in two siblings who also presented with congenital diarrhea and features of cholestasis at pediatric age.⁽³⁾ Altogether, these 3 patients with either OST α or OST β deficiency have elevated transaminases (alanine aminotransferase [ALT] > aspartate aminotransferase [AST]) and GGT and low-normal circulating BAs. It is noteworthy that the liver biopsy from our

proband revealed a more advanced liver disease than the liver injury reported in the two OST β -deficient siblings.⁽³⁾ The full clinical spectrum attributable to the loss of *SLC51A* will need to be determined by the identification and study of additional patients with OST α deficiency.

Collectively, this case underscores how an unbiased genomic approach is highly valuable in clinical hepatology practice,⁽⁴⁾ while uncovering gene contributions in human health and disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.

Histological and molecular findings in a child with OST α deficiency. (A) Liver parenchyma (hematoxylin and eosin) shows distorted lobular architecture and expanded portal areas with mild ductular proliferation. (B) Trichrome stain reveals portal and periportal fibrosis along with many thin fibrous septa, with nodularity of the lobular architecture suggestive of early cirrhosis. (C) Cytokeratin 7 immunostain highlights the portal tracts and shows mild bile ductular proliferation in most of the portal areas. (D) Higher magnification of cytokeratin 19 immunostain of one of the portal tracts showing presence of two bile duct profiles (arrows). (E) Two portal areas are depicted: one with few bile ductular profiles (arrow) and one devoid of any bile ducts (circle). The portal areas show only minimal lymphocytic inflammation and no interface activity. The hepatocytes are otherwise unremarkable. (F) Periportal area showing rare foci of subtle hepatocytic cholestasis (arrows). (G) Duodenal and (H) colonic mucosa show no significant histologic abnormality. (I) Proband and his unaffected family members are shown in black and white symbols, respectively. Consanguineous union is depicted by a double line. *SLC51A* alleles are denoted as wild type or mutant (p.Gln186*). (J) Sanger sequencing chromatograms of

the proband and his unaffected parents and sibling are shown. The *SLC51A* p.Gln186* mutation is homozygous in the proband and heterozygous in the unaffected parents and sister. (K) Relative expression of *SLC51A* and *SLC51B* to *GAPDH* in proband's colon tissue compared to normal-appearing colon tissue from two unrelated individuals shows absent *SLC51A* and preserved *SLC51B* mRNA expression in proband's colon tissue. Scale bars, 100 μ m in (A-C) and 50 μ m in the remaining panels. Abbreviations: GAPDH, glyceraldehyde-3-phosphate dehydrogenase; Mut, mutant; N.D., not detected; WT, wild type.

TABLE 1.
Clinical and Laboratory Findings in Proband Who Harbors a Homozygous Premature Termination Mutation (P.Gln 186^{*}) in *SLC51A*

Laboratory Test	Reference	Proband's Age in Years			
		2.5	3.8	4	5
AST (U/L)	15-40	126 (H)	112(H)	98 (H)	66 (H)
ALT (U/L)	4-25	227(H)	126 (H)	117 (H)	90 (H)
Bilirubin total/direct (mg/dL)	0.1-1.2/<0.3	0.7/n.a.	1.6 (H)/n.a.	1.8/1.2 (H)	2.3/1.9 (H)
GGT (U/L)	5-32	n.a.	n.a.	n.a.	104 (H)
ALP (U/L)	100-320	708 (H)	1320 (H)	661 (H)	268
INR	0.9-1.1	3.1 (H)	1.6 (H)	1.6 (H)	1.1
Vitamin D, 25-OH (ng/mL)	16-65	8.7	n.a.	n.a.	28 [*]
Albumin (mg/dL)	3.5-5.5	n.a.	n.a.	3.7	n.a.
BAs measured in DBS samples [‡]					
Cholic acid	0.003-0.19	n.a.	n.a.	n.a.	0.02
Dihydroxycholanoates [‡] (μM)	0.09-2.21	n.a.	n.a.	n.a.	0.11
Glychocholic acid (μM)	0.005-2.52	n.a.	n.a.	n.a.	0.11
Glycodihydroxycholanoates [§] (μM)	0.22-4.16	n.a.	n.a.	n.a.	0.33
Taurocholic acid (μM)	0.001-0.612	n.a.	n.a.	n.a.	0.06
Taurodihydroxycholanoates (μM)	0.03-0.43	n.a.	n.a.	n.a.	0.07

^{*} On vitamin D supplement.
[‡] Prior to initiation of ursodeoxycholic acid supplement.
[‡] Chenodeoxycholic acid + deoxycholic acid.
[§] Glycochenodeoxycholic acid + glycodeoxycholic acid.
^{||} Taurochenodeoxycholic acid + taurodeoxycholic acid.
Abbreviations: ALP, alkaline phosphatase; DBS, dried blood spots; H, high; INR, international normalized ratio; n.a., not available.