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OSTα deficiency: A disorder with cholestasis, liver fibrosis and congenital diarrhea

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INTRODUCTION

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

CASE REPORT

A 2.5 year-old Pakistani male, born from a first-cousin union, was evaluated in 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 transfusions and failure to thrive. Stool studies included normal pH, and negative occult blood, reducing substance and ova cysts. Patient was exclusively breastfed until 1 year of age, when he was started on soy-based formula milk, nutritional rehabilitation and fat-soluble vitamins supplementation, with improvement in his weight and height. At age 2.5, he was found to have elevated transaminases and alkaline phosphatase (Table1). Liver biopsy revealed a lobular architecture suggestive of early cirrhosis with portal and peri-portal fibrosis and many thin fibrous septa (Figure1A,B). Portal areas showed minimal lymphocytic inflammation, no interface activity and patchy mild bile ductular proliferation (Figure1C,D). Bile ducts were missing in three of the portal tracts (Figure1E), not meeting criteria for bile duct paucity. The hepatocytes showed rare foci of subtle hepatocytic cholestasis (Figure1F). Duodenal and colonic biopsies showed no significant abnormality (Figure1G,H). Since a comprehensive work-up was unrevealing (TableS1), 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 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 OSTα. This variant allele is extremely rare, with only 1 instance of this variant among more than 251,400 alleles sequenced from diverse populations, including South Asians (last accessed gnomAD:https://gnomad.broadinstitute.org, 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 (Figure1I,J). Furthermore, the proband's colon tissue showed undetectable *SLC51A* transcripts (Figure1K). Analysis of the BA concentrations in the proband's blood spot by LC-MS/MS showed that BA concentrations were within the normal range in spite of 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 2-3 bulky daily bowel movements; his transaminases, direct bilirubin and GGT levels remain elevated (Table1).

DISCUSSION

Our findings provide the first demonstration of human OSTα-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 OSTβ, which forms a heterodimer with OSTα 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 three patients with either OSTα or OSTβ deficiency have elevated transaminases (ALT>AST) and GGT, and low-normal circulating BAs. It is noteworthy that liver biopsy from our proband revealed a more advanced liver disease than the liver injury reported in the two OSTβ-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 OSTα-deficiency.

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

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FIGURE LEGEND

Figure 1. Histological and molecular findings in a child with OSTα deficiency. (A) Liver parenchyma (H&E) 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 WT (wild-type) or Mut (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 as compared to normal-appearing colon tissue from two unrelated individuals show absent *SLC51A* and preserved *SLC51B* mRNA expression in proband's colon tissue. N.D., not detected. Scale Bars measure 100μm in panels A, B and C and 50μm in the remaining panels.

Table 1. Clinical and laboratory findings in proband who harbors a homozygous premature termination mutation (P.Gln186*) in *SLC51A*.

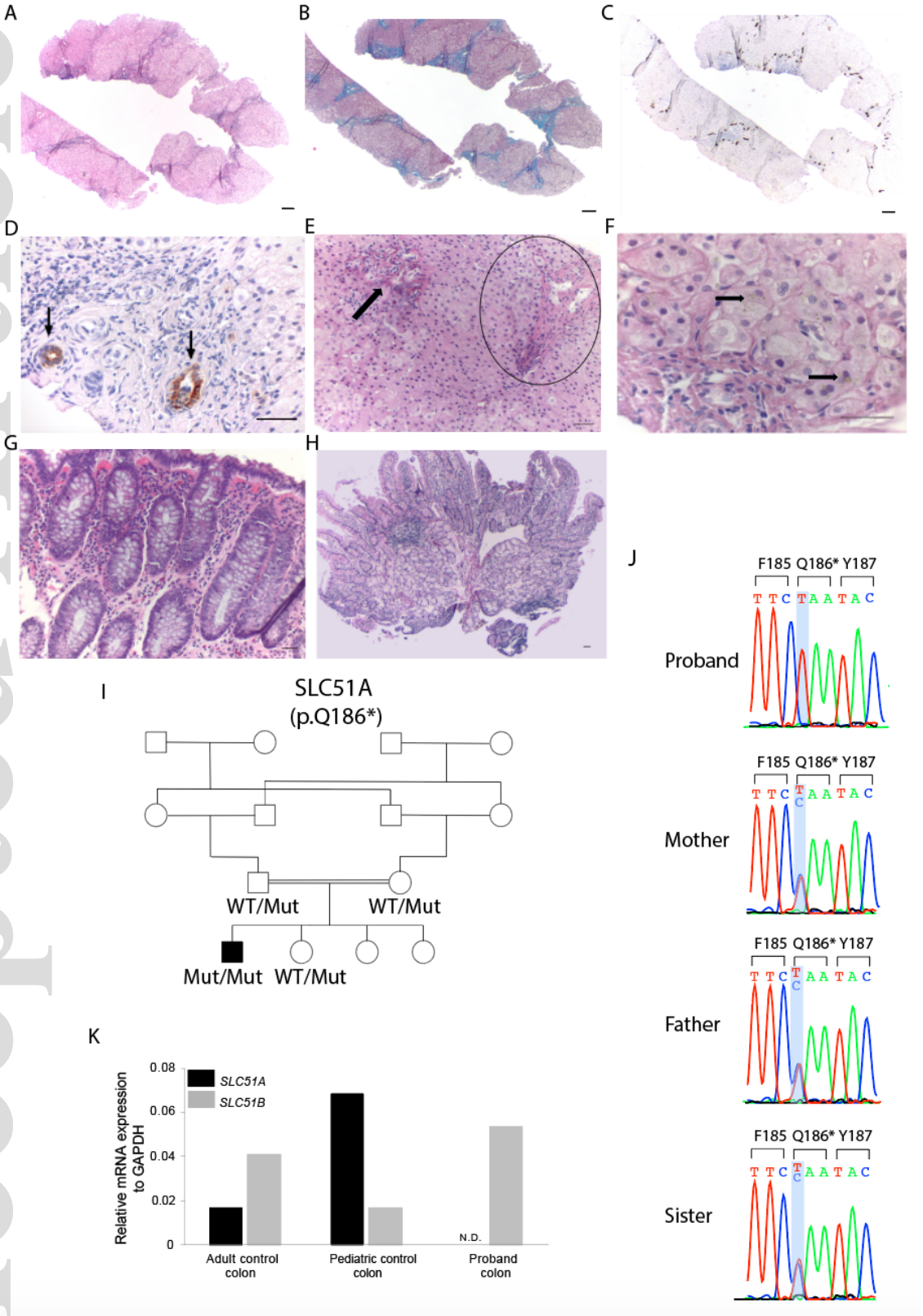
Laboratory Test	Reference	Proband's Age in Years			
		2.5	3.8	4	5
AST (U/L)	*15-40*	126 (H)	112(H)	98 (H)	66 (H)
ALT (U/L)	*4-25*	227(H)	126 (H)	117 (H)	90 (H)
Bilirubin total/direct (mg/dL)	*0.1-1.2/<0.3*	0.7/n.a.	1.6 (H)/n.a.	1.8/1.2 (H)	2.3/1.9 (H)
GGT (U/L)	*5–32*	n.a.	n.a.	n.a.	104 (H)
ALP (U/L)	*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.
Bile Acids 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

n.a., not available; H, high; DBS, dry blood spots

Figure 1



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