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Sodium taurocholate cotransporter polypeptide deficiency from two pairs of twins with homozygous and heterozygous of p.Ser267Phe variant, respectively: Case report

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To the Editor:

CASE 1: a pair of monozygotic twins who was test tube baby and delivered at the gestation age of 36 weeks and 1 day. As one day male newborns, who presented mild jaundice in the skin for half a day. Physical examination revealed the birth weight of 2700 and 2280 g, respectively. Muscular tension of limbs, and reflex of hug and grip decreased. The mental reaction of the twins was poor. Laboratory test revealed that the serum levels of total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), total bile acids (TBA), aspartate transaminase (AST) and alkaline phosphatase (ALP) were all increased; alanine transaminase (ALT), thyroid stimulating hormone (TSH), 25-hydroxy vitamin D (VD) and zinc sulfate (ZS) were normal. A diagnosis of low birth weight preterm infants with Sodium taurocholate cotransporting polypeptide deficiency (NTCPD) with heterozygous missense mutations in c.800C>T (p.Ser267Phe) was confirmed. The twins were started on symptomatic and supportive treatment. After 18 months of close clinic follow-up, the twins grew well and had no other special clinical signs (Fig. 1A and Supplementary Table 1). CASE 2: a pair of dizygotic female twins who was delivered at the gestation age of 35 weeks and 5 days, and presented obvious jaundice in the skin and sclera for 32 days. Physical examination revealed the birth weight of 3880 and 3.700 g, respectively. The mental reaction of the twins was poor. Laboratory test revealed that the serum levels of TBIL, DBIL, IBIL, TBA, ALT, TSH, and ALP were all increased; VD and ZS were decreased; AST was normal. Both urine and serum were positive for cytomegalovirus (CMV)-DNA ($\geq$ 500 cps/mL). The elder sister was diagnosed with NTCPD with homozygotes missense mutations in c.800C>T (p.Ser267-Phe), developmental delay (DD) and asymptomatic infection of CMV; the younger one was diagnosed with hypercholanemia, hyperbilirubinemia, DD and asymptomatic infection of CMV. After 9 months of close clinic follow-up, the twins demonstrated catch-up growth and their transaminase, TSH, ALP, VD and ZS gradually returned to normal, but the elder sister's TBIL, DBIL, IBIL and TBA levels remained high, and mild anemia, which could only be continuously observed (Fig. 1B and Supplementary Table 1).

NTCPD is caused by variants in the human solute carrier family 10 member 1 (SLC10A1) gene [1,2]. Of note, the c.800C>T (p. Ser267Phe) in SLC10A1 gene is the most predominant variant accounting for 94.50 % [3], and commonly presented as type of a homozygous or heterozygous. As an inborn error of metabolism, the c.800C>T (p.Ser267Phe) variant exhibited a near complete loss of function of bile acid uptake, and mainly caused the phenotype of neonatal or infant persistent hypercholanemia [4]. Currently, there are controversies about whether homozygous and heterozygous variants have different clinical manifestations and treatment prognosis [3,5]. In terms of our cases, the phenotype and prognosis of dizygotic twins were relatively poor than heterozygous variant monozygotic male twins, and presented persistent hypercholanemia, hyperbilirubinemia, and slowly improved DD, especially in the elder sister with homozygous variant. We consider that the child has two key and important etiologies simultaneously, homozygous c.800C>T and premature birth. On the basis of the loss function of multiple transporters on hepatocyte membrane, bilirubin and bile acids from various pathways were increased, while the compensatory capacity of liver clearance was reduced, and finally leading to severe clinical symptoms and long-term prognosis. This may also reasonably explain why some NTCPD patients present with intractable hypercholanemia. In conclusion, the genotypic and phenotypic features yet remain open for investigation, and the prognosis needs more clues and comprehensive insights.

Abbreviations: NTCPD, sodium taurocholate cotransporting polypeptide deficiency; SLC10A1, solute carrier family 10 member 1; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; TBA, total bile acids; AST, aspartate transaminase; ALT, alanine transaminase; TSH, thyroid stimulating hormone; ALP, alkaline phosphatase; VD, 25-hydroxy vitamin D; ZS, zinc sulfate; CMV, cytomegalovirus; DD, developmental delay.

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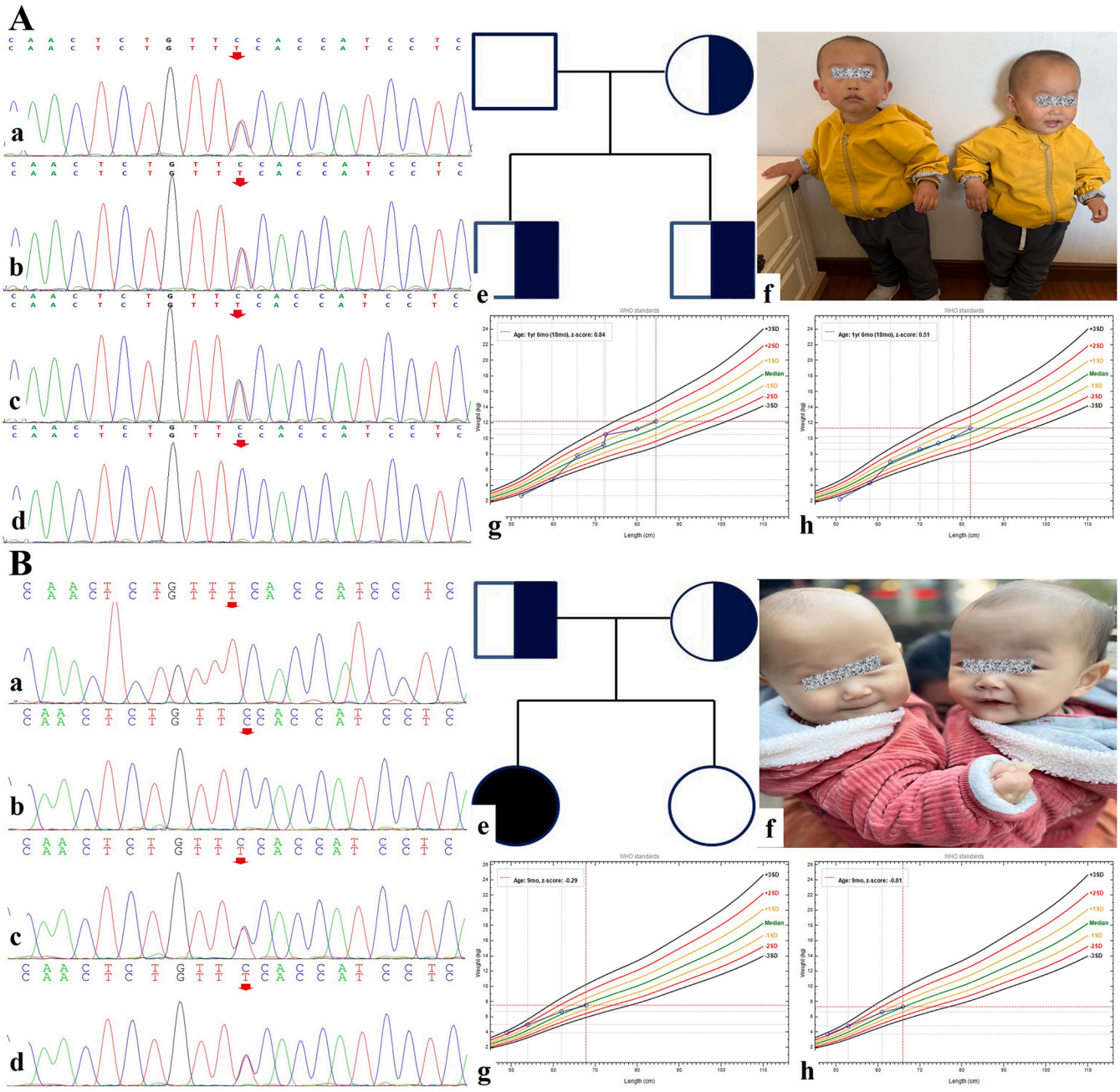

Fig. 1. Whole family genetic analysis for CASE 1 and 2. A a-c Sanger sequencing of exon 4 in SLC10A1 gene with the heterozygous c.800C>T (p.Ser267Phe) mutation in the twins and their mother (Red arrow). d SLC10A1 gene in their father was normal (Red arrow). e Diagrams for family trees with the causative gene SLC10A1. f The 18th month observation of growth and development of the twins (Left is elder brother, right is younger). g-h The 18 months records of body weight-height changes of the twins (g is elder brother, h is younger). B a Sanger sequencing of exon 4 in SLC10A1 gene with a homozygotes c.800C>T (p.Ser267Phe) mutation in the elder sister (Red arrow). b SLC10A1 gene in the younger one was normal (Red arrow). c-d SLC10A1 gene with the heterozygous c.800C>T (p. Ser267Phe) mutation in their parents (Red arrow). e Diagrams for family trees with the causative gene SLC10A1. f The 9th month observation of growth and development of the twins (Left is elder sister, right is younger). g-h The 9 months records of body weight-height changes of the twins (g is elder sister, h is younger).

Ethics approval and consent to participate

this study was approved by the Medical Ethics Committee of Kunming Children's Hospital. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards. Particularly, written informed consent was obtained from patient's parents.

Consent for publication

Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images, and the proof can be requested at any time.

Availability of data and materials

all data, models, and code generated or used during the study appear in the submitted article.

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CRediT authorship contribution statement

Meifen Wang: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Writing – original draft, Writing – review & editing. **Tao Chen:** Conceptualization, Investigation, Resources, Validation, Writing – original draft. **Meirui Li:** Data curation, Investigation, Software, Visualization. **Rui Chen:** Data curation, Formal analysis, Investigation. **Junchao Peng:** Formal analysis, Investigation, Methodology, Software. **Jiwei Li:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinre.2024.102303.

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