Case Report: Novel Compound-Heterozygous Variants of SKIV2L Gene that Cause Trichohepatoenteric Syndrome 2

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Background: Trichohepatoenteric syndrome (THES) is a rare disease that mainly causes intractable diarrhea. It is classified into THES1 and THES2, which are associated with the tetratricopeptide repeat domain 37 (TTC37) gene and Ski2-like RNA helicase (SKIV2L) gene, respectively. THES is not very prevalent in China or worldwide, but new cases have increasingly been reported.

Methods and Results: Here, we report the clinical and genetic information of a 1.5-month-old girl who was admitted to our hospital due to diarrhea and failure to thrive. Whole-exome sequencing (WES) revealed novel compound-heterozygous variants of the SKIV2L gene, c.3602_3609delAGCGCCTG (p.Q1201Rfs*2), and c.1990A>G (p.T664A) as the causative factors, which were confirmed via Sanger sequencing. Upon continuous feeding with an amino-acid formula through a gastric tube and parenteral nutrition, the patient resumed thriving and her stool frequency decreased.

Conclusion: We report a girl carrying novel variants of the SKIV2L gene that cause THES2, thereby providing valuable information on the diagnosis of THES2 and expanding the spectrum of disease-causing SKIV2L mutations.

Keywords: trichohepatoenteric syndrome (THES) 2, SKIV2L gene, intractable diarrhea, whole-exome sequencing (WES), pediatrics

INTRODUCTION

Trichohepatoenteric syndrome (THES), initially called syndromic diarrhea (SD), was first described by Stankler et al., in 1982 and coined by Verloes et al., in 1997 (Stankler et al., 1982; Verloes et al., 1997). The typical symptoms of THES are intrauterine growth retardation and neonatal intractable diarrhea, leading to poor weight gain and failure to thrive. Patients may also have hair abnormalities (trichorrhexis nodosa) or facial dysmorphisms (Verloes et al., 1997). Other clinical characteristics, including immunodeficiency, skin abnormalities, hepatic involvement, intellectual disability, and congenital heart disease, may also present. In Europe, the estimated prevalence of THES is 1:1,000,000, and the 10-years mortality rate is >50% (Fabre et al., 2013; Fabre et al., 2017). The mainstream management of THES is mainly based on parenteral nutrition and immunoglobulin supplementation.

THES is classified into THES1 (OMIM #222470) (69% of the cases) and THES2 (OMIM #614602) (31%). THES1 is caused by homozygous or compound-heterozygous mutations in the tetratricopeptide repeat domain 37 (TTC37) gene, whereas THES2 is associated with homozygous or compound-heterozygous mutations in the Ski2-like RNA helicase (SKIV2L) gene (Hartley et al., 2010; Fabre et al., 2017).
gene. SKIV2L patient with two novel compound-heterozygous variants of the (Zheng et al., 2016; Fung et al., 2020). Herein, we report a THES2 mutations, only three were detected in the Chinese population mutations associated with THES2. Of these THES2-causing Database (HGMD v2021.8) (Stenson et al., 2017), including 35 mutations have been reported to the Human Gene Mutation reported to be responsible for THES2. To date, 45 2014; van Schouwenburg et al., 2015; Stray-Pedersen et al., 2017; Riley et al., 2020). However, most mutations in SKIV2L have been reported to be responsible for THES2. To date, 45 SKIV2L mutations have been reported to the Human Gene Mutation Database (HGMD v2021.8) (Stenson et al., 2017), including 35 mutations associated with THES2. Of these THES2-causing mutations, only three were detected in the Chinese population (Zheng et al., 2016; Fung et al., 2020). Herein, we report a THES2 patient with two novel compound-heterozygous variants of the SKIV2L gene.

METHODS

Clinical Examination

The medical history of this patient was provided by her parents and included the birth history, clinical manifestations, and diagnostic and therapeutic actions. Physical examination and laboratory tests were performed, including blood and fecal routine tests, fecal culture, and hepatic, renal, and immunological function tests. Imagological examinations, including abdominal ultrasound, cardiac Doppler ultrasonography, and brain magnetic resonance imaging (MRI), were also applied.

Whole-Exome Sequencing

Whole-exome sequencing (WES) and Sanger sequencing were performed to identify the causative genes. Peripheral blood samples were collected from the patient and her parents and sent to Running Gene Inc. (Beijing, China). The whole sequencing process was described in a previous study (Chen et al., 2020). DNA samples were extracted from the blood samples, qualified, and fragmented into 200–300 bp fragments for library preparation. Probes were hybridized with the prepared libraries to capture exomes, according to the protocol of the Agilent Sure Select XT2 Target Enrichment System (Agilent, Santa Clara, CA). Captured DNA samples were sequenced on Novaseq 6,000 platform (Illumina, San Diego, CA). Raw data in FASTQ format were trimmed and filtered for quality control by using fastp (Chen et al., 2018). The qualified reads were aligned to human reference sequence GRCh37/hg19 by using BWA (Li and Durbin, 2009). Single-nucleotide variants (SNVs) and insertions/deletions (indels) were called out using GATK (Van der Auwera et al., 2013). All the called variants were annotated based on the genetic databases, including ExAC v1.0 (Lek et al., 2016), gnomAD v2.1.1 (Karczewski et al., 2020), ESP6500SI-V2 (Fu et al., 2013), 1kGenomes v3.7.6 (Autow et al., 2015), HGMD v2021.8 (Stenson et al., 2017), ClinVar (Landrum and Kattman, 2018), China National GeneBank (CNGB), and an in-house database (access date: August 31, 2021). Variants with high allele frequency (>1%) were filtered out. The pathogenicity of variants was assessed based on the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., 2015). The SKIV2L mutations were finally selected based on its clinical relevance and pathogenicity.

RESULTS

Case Presentation

A 1.5-month-old girl was admitted to our hospital due to persistent diarrhea and failure to thrive. She was the only child of her non-consanguineous parents without any familial history of diarrhea. She had experienced no recurrent infections before. She was born at 39 gestational weeks. Her birth height was 48 cm (10th percentile), and her birth weight was 2.5 kg (below the 3rd percentile) (intrauterine growth retardation). She received non-bloody watery stools seven to eight times a day and poor weight gain since birth. Deep hydrolysis formula and amino-acid formula were administered after diagnosis of allergy to cow-milk protein. However, her condition did not improve.

Physical examination showed that the infant was weak and displayed a severe loss of subcutaneous fat. Her hair was short and sparse (woolly and brittle) (Figure 1B). No abnormalities were observed on the skin. Normal results were shown in all laboratory and imagological examinations.

Genetic Analysis

WES and Sanger sequencing were performed to identify the causative genes. A pair of novel compound-heterozygous variants, c.3602_3609delAGCGCCTG (p.Q1201Rfs*2) with the maternal origin and c.1990A>G (p.T664A) with the paternal origin, in the SKIV2L gene (NM_006929) were identified (Figure 1C). Variant p. Q1201Rfs*2 can be interpreted as “likely pathogenic” according to the ACMG standard (PVSI1_strong + PM2+PP3). This variant is a null mutation which might truncate the protein, but the mutation is located at the last exon (PVSI1_strong). The variant is absent from the controls (ExAC v1.0, gnomAD v2.1.1, ESP6500SI-V2, 1kGenomes v3.7.6) (PM2). Multiple lines of in silico algorithms, including MutationTaster2 (Schwarz et al., 2014) (1, disease-causing), SIFT Indel (Sim et al., 2012) (0.783, damaging), CADD v1.6 (Rentzsch et al., 2019) (23 > cutoff = 15, deleterious), and CAPIC (Li et al., 2020) (0.941 > cutoff = 0.02,
pathogenic), predicted that it is deleterious, except for MutPred-LOF (Pagel et al., 2017) (0.317 < cutoff = 0.6, neutral) (PP3). The other variant c.1990A > G (p.T664A) can be classified as a "variant with uncertain clinical significance" (PM2 + PP3). This missense was not found in the controls (PM2) and also predicted to be deleterious by multiple lines of algorithms (MutationTaster2, 1.000, disease-causing; SIFT v6.2.1 (Sim et al., 2012), 0.00 < cutoff = 0.05; Provean (Choi and Chan, 2015), -4.91 < -2.5, deleterious; and Polyphen-2 (Adzhubei et al., 2013), HumDiv and HumVar, 0.991 and 0.913, probably damaging) (PP3). The missense variant is located in a highly conserved region (Figure 1D), suggesting the importance of the mutated residue. Thus, the changes in residue properties may damage the structure and function of the protein product. We considered both of these variants disease-causing.

**Treatment and Prognosis**

The patient was continuously fed with an amino-acid formula through a gastric tube, in addition to parenteral nutrition. Unfortunately, she developed a fever due to an infection from the central venous catheter of the parenteral nutrition. The infection was controlled by administering cefoperazone sodium and sulbactam sodium. Additionally, as the volume of the fed amino-acid formula was increased, the amount of the intravenous nutrient fluid was gradually decreased until the parenteral nutrition was finally discontinued. Finally, she was discharged at 3 months of age and thereafter fed with 20 ml of an amino-acid formula per hour through a gastric tube. The recent follow-up at the age of 7.5 months revealed that the child still grew slowly (height, 61 cm, below the 3rd percentile; weight, 4.25 kg, below the 3rd percentile) and had intermittent diarrhea.

**DISCUSSION AND CONCLUSION**

THES2 is a rare and severe genetic disorder known to be associated with pathogenic variants of SKIV2L. Based on previous reports (Fabre et al., 2012; Fabre et al., 2013; Morgan...
| References | Mutations in SKIV2L gene | Background | GENDER (M: F = 17:20) | Background | Onset age | Intrauterine growth restriction (25/28) | Intractable diarrhea (34/34) | Hair abnormalities (31/35) | Facial dysmorphisms (24/31) | Hepatic involvement (19/27) | Immunodeficiency (16/23) | Cardiac abnormalities (7/19) | Deceased (3/19) | Other features |
|------------|--------------------------|------------|------------------------|------------|-----------|------------------------------------|--------------------------|---------------------------|--------------------------|---------------------------|-----------------|------------------------|----------------|------------------|
| Present Case | c.1990A > G (p.T664A) and c.3602_3609delAGCGCCTG (p.G1201Rfs*2) | Asian | F | At birth | + | + | + | − | − | − | − | − | − | Physical developmental delay |
| Fabre et al. (2012) | c.1653_1656insA (p.G546Rfs*3) and c.2246C > T (p.R751*) and c.2442G > A (p.W814*) | European Middle-Eastern | F | 1–12 weeks (median 2.5 and mean 3.8 weeks) | + (4/6) | + (6/6) | − | − | − | − | − | − | + (2/4) | Villous atrophy (3/4), colitis (3/4), siderosis (1/4), cirrhosis (2/3) |
| Fabre et al. (2013) | c.3561_3581delGCTCTAAGCCCGCTGAGGG (p.S1189_L1195del) | European M | NA | + | + | + | − | − | − | − | − | − | − | − |
| Morgan et al. (2013) | c.3391delC (p.L1131Sfs*5) | Asian | F | 2 weeks | + | + | + | NA | + | + | NA | + | + | (9 months) | Villous atrophy, platelet abnormalities |
| Monies et al. (2015) | c.3561_3581delGCTCTAAGCCCGCTGAGGG (p.S1189_L1195del) | Middle-Eastern | M | 14 days | + | + | + | + | − | − | − | − | − | − | Failure to thrive, hyperpigmentation, mental retardation |
| Bourgeois et al. (2018) | c.3119del(T) (p.L1131del) | F | 14 days | + | + | + | NA | − | − | − | − | − | − | − |
| Lee et al. (2016) | c.1891G > A (p.G631S) and c.3187C > T (p.R1063*) | Asian | M | 17 days | + | + | − | − | − | − | − | − | − | − | Failure to thrive, jejunal villous atrophy, thrombocytosis, developmental delay, poor dentition |
| Zhang et al. (2016) | c.1120C > T (p.R374*) and c.1891G > A (p.G631S) | Asian | M | 4 weeks | + | + | + | + | − | − | − | − | − | − | Failure to thrive, mild mental retardation, hyperpigmentation |
| Hejna et al. (2017) | c.1420G > T (p.Q474*) and c.3262G > A (p.E1088*) | Asian | F | 14 days | + | + | + | + | − | − | − | − | − | − | Developmental delay, hearing abnormalities, hypothyroidism, protein losing enteropathy |
| Hick et al. (2017) | c.2203-1G > C and c.3187C > T (p.R1063*) | American | F | NA | + | + | + | − | − | − | − | − | − | − |

(Continued on following page)
TABLE 1 | (Continued) Genotypic and phenotypic features of THES2 and the corresponding SKIV2L mutations.

| References | Mutations in SKIV2L gene | Background | GENDER | Onset age | Intrauterine growth restriction | Irtractable diarrhea | Hair abnormalities | Facial dysmorphisms | Hepatic involvement | Immunodeficiency | Cardiac abnormalities | Deceased | Other features |
|------------|--------------------------|------------|--------|----------|-------------------------------|---------------------|-------------------|-------------------|------------------|-----------------|------------------------|-----------|---------------|
| Vardi et al. (2018) | c.1891G>A (p.G631S) | Middle-Eastern | F | 10 days | + | + | + | + | – | – | + | NA | – | Sepsis, electrolyte imbalance, convulsions, anemia, respiratory distress |
| | c.919−1G>A and c.2341−2A>G | European | F | 10 days | + | + | + | + | + | – | – | + | NA | – |
| | c.3113−3,141del (p.E1038Vfs*) | European | M | 10 days | + | + | + | + | + | – | – | + | NA | – |
| | c.3167G>A (p.R1063*) | European | F | 8 days | + | + | + | + | + | – | – | + | NA | – |
| | c.1647+1G>A | Asian | NA | – | – | – | – | – | – | – | – | – | – | – |
| | c.2203−1G>A and c.3187C>T (p.R1063*) | American | F | 0.8 years | + | + | – | – | + | – | – | – | – | Short stature, psychomotor delay |
| | c.1647T>G and c.1647+1G>A | Asian | NA | – | – | – | – | – | – | – | – | – | – | – |
| | c.1297C>T (p.R433C) | Middle-Eastern | F | 8 days | + | + | + | + | + | – | – | + | NA | – | Global developmental delay, bilateral inguinal hernia, failure to thrive |
| | c.256C>T (p.R79*) | American | F | NA | + | + | + | + | + | + | NA | – | Failure to thrive, psychomotor development delay, skin and hearing abnormalities, strabismus, sacral dimple, autism |
| | c.1211G>A (p.R404H) | American | F | NA | – | – | – | – | – | – | – | – | – | – |

Note: F, female; M, male; THES2, Trichohepatoenteric Syndrome 2; SKIV2L, superkiller viralidic activity 2-like; NA, Not available.

aPreviously described as c.3559_3579del (p.1187_1193del) in Monies et al., 2015 [39].
bPreviously described as c.3101_3,103 delAGA (p.Gln1034del) in Bourgeois et al., 2018 [7].
cPreviously described as c.1452delC (p.Pro484fs*46) in Bourgeois et al., 2018 [7].
dPreviously described as c.3112_3,140 del (p.Glu1038fs*) in Bourgeois et al., 2018 [7].
eWe considered “dysmorphism” in Bourgeois et al., 2018 [7] as facial dysmorphisms here.
fThe patient was diagnosed with Dubowitz syndrome in Dyment et al., 2021 [45].
et al., 2013; Monies et al., 2015; Lee et al., 2016; Zheng et al., 2016; Bick et al., 2017; Hiejima et al., 2017; Bourgeois et al., 2018; Vardi et al., 2018; Rudilla et al., 2019; Fung et al., 2020; Taher et al., 2020; Dyment et al., 2021; Klee et al., 2021), the incidence of this disease is not significantly different between genders (M:F = 17:20) (Table 1). Patients have their onset mostly in the neonatal period, ranging from birth to 0.8 years of age (mean, 29.5 days; median, 17 days). The symptoms of the current patient were noticed at birth. All THES2 patients have intractable diarrhea (34/34, 100%). Moreover, THES2 is also associated with intrauterine growth restriction (25/28, 89.3%), hair abnormalities (31/35, 88.6%), facial dysmorphism (24/31, 77.4%), hepatic involvement (19/27, 70.4%), immunodeficiency (16/30, 53.3%), and cardiac abnormalities (7/19, 36.8%). This disease has been described in Middle-Eastern (11/37, 29.7%), European (10/37, 27.0%), Asian (7/37, 18.9%), American (5/37, 13.5%), and African (4/37, 10.8%) populations, with the majority seen in the Middle-Eastern background.

According to the HGMD v2021.8, only 35 mutations in SKIV2L, including 32 disease-causing mutations (DM) and 3 possibly disease-causing mutations (DM?), have been reported to be associated with THES2. Nonsense mutations (10/35, 28.6%) are the most prevalent type of mutations, followed by missense (8/35, 22.9%), frameshift (7/35, 20.0%), canonical splice site (7/35, 20.0%), large-size (>20 bp) deletion (2/35, 5.7%), and in-frame deletion (1/35, 2.9%) mutations. Although THES2 is considered an autosomal recessive disorder, three patients have been reported to carry a heterozygous SKIV2L mutation (Bourgeois et al., 2018). In-depth genetic analyses focusing on deep-intronic mutations may explain this discrepancy.

THES2 is usually diagnosed based on both the common THES symptoms and biallelic pathogenic variants of the SKIV2L gene. However, no phenotype–genotype correlation has been established to date. How SKIV2L mutations or defects in the Ski complex lead to the observed symptoms is still unclear. It has been revealed that SKIV2L RNA exosome limits the activation of RIG-I-like receptors (RLR), thereby negatively regulating RLR-mediated antiviral response. Human patients with SKIV2L mutations also have a potent type I interferon signature in the blood cells (Eckard et al., 2014). Such uncontrolled regulations and overwhelming responses could probably drive immune disease, leading to chronic intestinal inflammation, i.e., intractable diarrhea. Given that SK12W is a helicase with ATPase activity, SK12W defects may affect the normal function of the Ski complex, and consequently, the mRNA targets of this mRNA surveillance are not degraded, whereby the observed phenotypes ensue. Additional research is required to determine the pathogenesis of THES2 and the relationships between mutations and the symptoms.

Most patients with THES may need lifelong total parenteral nutrition (TPN) to survive, but some of them develop complications associated with TPN. To date, only a few infants with THES have attained normal oral nutrition (Fabre et al., 2017). In the current study, the patient was fed with an amino-acid formula and parenteral nutrition but subsequently developed complications similar to those associated with TPN. It seems that a small supplement of amino acids can be therapeutic for THES2 patients, but extreme cases might require extraoral administration of an extensively hydrolyzed formula (Taher et al., 2020). THES2 is a severe and potentially fatal disorder; however, only a few patients have been reported to die from THES2 (Fabre et al., 2012; Taher et al., 2020). Nevertheless, most cases lacked long-term follow-up. Therefore, a long follow-up period is required for patients with THES2 to acquire information on the prognosis and effectiveness of the clinical interventions.

In summary, this study reported a pair of novel compound-heterozygous variants of the SKIV2L gene in a patient with THES2, thereby expanding the spectrum of the causative mutations. Early genetic diagnosis of this syndrome could enable early and proper treatment. An amino-acid formula continuously fed through a gastric tube, alongside parenteral nutrition, could also delay the complications and improve the outcome of such cases.

**DATA AVAILABILITY STATEMENT**

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by The study was approved by the Ethics Committee of Shenzhen Children’s Hospital. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)’ legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

**AUTHOR CONTRIBUTIONS**

Conceptualization: QZ and ZW. Data collection: XQ and JZ. Data analysis: LH and SZ. Funding acquisition: ZW. Investigation: QZ. Project administration: ZW. Writing original draft: QZ, LH, and SZ. Writing-review and editing: QZ, XQ, JZ, LH, ZW, and SZ. All authors have read and approved the manuscript.

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Conflict of Interest: LH is employed by Running Gene Inc. (Beijing, China).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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