Published in final edited form as:

Dig Dis Sci. 2018 May ; 63(5): 1192–1199. doi:10.1007/s10620-018-4983-x.

Genetic and Structural Analysis of a *SKIV2L* Mutation Causing Tricho-hepato-enteric Syndrome

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Abstract

Background—Advances in genomics have facilitated the discovery of monogenic disorders in patients with unique gastro-intestinal phenotypes. Syndromic diarrhea, also called tricho-hepato-enteric (THE) syndrome, results from deleterious mutations in *SKIV2L* or *TTC37* genes. The main features of this disorder are intractable diarrhea, abnormal hair, facial dysmorphism, immunodeficiency and liver disease.

Aim—To report on a patient with THE syndrome and present the genetic analysis that facilitated diagnosis.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interests to disclose.

Methods—Whole-exome sequencing (WES) was performed in a 4-month-old female with history of congenital diarrhea and severe failure to thrive but without hair anomalies or dysmorphism. Since the parents were first-degree cousins, the analysis focused on an autosomal recessive model. Sanger sequencing was used to validate suspected variants. Mutated protein structure was modeled to assess the effect of the mutation on protein function.

Results—We identified an autosomal recessive C.1891G > A missense mutation (NM_006929) in *SKIV2L* gene that was previously described only in a compound heterozygous state as causing THE syndrome. The mutation was determined to be deleterious in multiple prediction models. Protein modeling suggested that the mutation has the potential to cause structural destabilization of SKIV2L, either through conformational changes, interference with the protein's packing, or changes at the protein's interface.

Conclusions—THE syndrome can present with a broad range of clinical features in the neonatal period. WES is an important diagnostic tool in patients with congenital diarrhea and can facilitate diagnosis of various diseases presenting with atypical features.

Keywords

Congenital diarrhea; VEOIBD; SKIV2L; Primary immunodeficiency; Epithelial cells

Background

Significant progress has been made in recent years in understanding the causes of congenital diarrheal disorders (CDD) as well as of inflammatory bowel diseases (IBD) with extreme phenotypes, such as presentation at a very young age. Patients with CDD typically present in the first weeks of life with intractable diarrhea that can be life-threatening [1]. Various mechanisms can lead to CDD, including abnormalities in digestion and absorption of nutrients and electrolytes, defects in enterocyte structure and entero-endocrine cell differentiation abnormalities [2]. In most of these CDD, evaluation of the small bowel demonstrates villous atrophy or structural abnormalities, without signs of an enhanced inflammatory process. In contrast, rare monogenic disorders can cause intestinal inflammation associated with infiltration of immune cells to the lamina propria and subsequent mucosal injury. More than 50 different monogenic diseases causing intestinal inflammation have been identified, often presenting in the first years of life [3, 4]. These mutations are typically in genes implicated in immune or epithelial cell function and have a key role in maintaining mucosal homeostasis and preventing intestinal inflammation.

Tricho-hepato-enteric (THE) syndrome, initially called syndromic diarrhea, is a rare congenital disorder with an autosomal recessive inheritance pattern, caused by mutations in *SKIV2L* or *TTC37* genes [5, 6]. The main features of this disorder are intractable diarrhea with an onset in the first few months of life, abnormal hair, facial dysmorphism, intrauterine growth restriction, and immunodeficiency [7–9]. Additional manifestations are liver disease, including cirrhosis and siderosis, skin abnormalities, mental retardation, platelet dysfunction, and cardiac abnormalities.

Here, we report the clinical course and work-up of an infant with severe diarrhea developing in the second week of life that was found to have a homozygote mutation in *SKIV2L* gene.

Methods

Whole-Exome Sequencing (WES)

WES was performed using an Agilent v5 Sureselect capture kit and Illumina 2500 sequencing technology. For each sample, paired end reads (2×100 bp) were obtained, processed and mapped to the genome. We used the BWA mem algorithm (version 0.7.12) [10] for alignment of the sequence reads to the human reference genome (hg19). The HaplotypeCaller algorithm of GATK version 3.4 was applied for variant calling, as recommended in the best practice pipeline [11]. KGG-seq v.08 was used for annotation of identified variants [12], and in-house scripts were applied for filtering based on family pedigree and local dataset of variants detected in previous sequencing projects.

Sanger Sequencing

Validation of the candidate variant was performed by Sanger sequencing. Primer planning was performed using Primer 3 online tool. DNA amplification (PCR) was carried out in a 25 μ L reaction containing 50 ng of DNA, 10 μ M of each and Red load Taq Master*5 (LAEOVA). After an initial denaturation of 5 min at 95 °C, 30 cycles were performed (94 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s), followed by a final extension of 10 min at 72 °C. Sequencing was performed using an automated ABI Prism 3100 Genetic Analyzer (PerkinElmer). Sequencing results were analyzed using FinchTV tool.

Protein Modeling

Prediction of human SKIV2L protein structure was made using the Iterative Threading ASSEmbly Refinement (I-TASSER) server [13–15]. The PyMOL Molecular Graphics System, Version 1.7.6.0 Schrodinger, LLC, was used for visualization and graphics.

Ethical Consideration

The study was approved by Sheba Medical Center's Institutional Review Board, and informed consent was obtained accordingly.

Results

Clinical Presentation

A female infant was transferred to our institution from an outside hospital at the age of 4 months. She was born at 38 weeks of gestation after an uneventful pregnancy. Birth weight was 2.4 kg (small for gestational age). The patient was the first child of healthy Arab parents that were first-degree cousins. At the age of 10 days, while breastfeeding, she developed watery diarrhea with 5–7 stools per day. Change to a semi-elemental formula did not lead to clinical improvement. Given the severity of her symptoms and significant weight loss she was admitted at an outside hospital for further investigation and support.

Over a period of 3 months, the patient had a complicated medical course, including sepsis, electrolyte imbalance, convulsions, anemia requiring blood transfusions and respiratory distress that led to prolonged mechanical ventilation. Diarrhea persisted despite administration of an amino acid-based formula, Monogen (enriched with medium-chain triglycerides) and pancreatic enzyme supplementation.

Upon transfer to our institution at the age of 4 months, the patient was severely malnourished with generalized edema and cachexia. Her weight was 2.5 kg (Z score – 5.1). She had no signs of dysmorphism. The diarrhea was watery, high in volume (reaching at times 100 mL/kg/day) with no blood and stopped with cessation of feeding, suggesting an osmotic nature. THE syndrome was initially suspected, but there was no evidence of trichorrhexis nodosa on hair examination. Total parenteral nutrition was initiated at admission, and the patient was given intravenous immunoglobulins.

Immune Work-Up

Initial laboratory work-up showed lymphopenia, anemia, electrolyte imbalances, and profound hypoalbuminemia, but otherwise normal liver tests (Table 1). Immune work-up demonstrated hypogammaglobulinemia and slightly reduced T cell function as determined by low response to mitogenic stimulation. Normal T cell receptors repertoire and normal T cell receptor excision circles were found, and lymphocyte immune phenotyping was within normal limits (Table 1).

Imaging and Pathology

An abdominal ultrasonography was normal, and an esoph-agogastroduodenoscopy was macroscopically normal. However, histology of duodenal biopsies revealed severe villous blunting, areas of near flat epithelium and crypts that appeared regenerative in nature (Fig. 1a). No significant inflammation was present, and intraepithelial lymphocytes were not increased. A CD10 stain showed an intact brush border, and chromogranin stain showed a normal staining of endocrine cells (Fig. 1b, c). An electron microscopic examination did not demonstrate findings suggestive of microvillous inclusion disease (Fig. 1d). In addition, a sigmoidoscopy was macroscopically and histologically normal.

Genetic Work-Up

As part of the diagnostic work-up, WES was performed. Due to parental consanguinity, analysis focused on an autosomal recessive mode of inheritance, yielding 1,363 recessive variants that affect protein sequences. This list of variants was subsequently reduced to 38 rare variants, by filtering out variants present in 0.01 of our in-house exomes ($n \sim 1300$) and variants present with a minor allele frequency (MAF) 0.01 in either ExAC database, the 1000 Genomes Project (1 KG; <http://browser.1000genomes.org/index.html>), dbSNP 135 database or the NHLBI Exome Sequencing Project (ESP) (<http://evs.gs.washington.edu/EVS/>). A C.1891G > A missense mutation (NM_006929) in the *SKIV2L* gene was found. The point mutation, which was previously described only in heterozygous state with other mutations as causing THE syndrome [16, 17], is located in exon 17 of the *SKIV2L* gene and causes a substitution of a highly conserved glycine by serine in the amino acid chain at position 631 (p.Gly631Ser). The amino acid substitution is predicted to be damaging by in

silico tools (Sift, Polyphen2, LRT, Provean, MutationAssessor). The variant was not found in ExAC Database or in dbSNP, 1000G, ESP6500 and in-house database. This missense mutation was validated by Sanger sequencing (Fig. 2a).

In addition, a novel C.952 + 1G > A homozygous splicing mutation (NM_001197237) in *BTN2A2* gene was identified. The variant is rare, with only four heterozygous individuals in ExAC and was not found in our in-house database. The gene was reported to play a role as a co-inhibitory molecule that modulates T cell-mediated immunity by inhibiting T cell activation and inducing Foxp3(+) regulatory T cells [18–20]. However, no reports to date indicate an association between variants in *BTN2A2* with IBD, either in genome wide association studies or as part of monogenic disorders leading to intestinal inflammation or to CDD.

Computerized Modeling of the Mutation

To assess the impact of the glycine by serine substitution in position 631 of the SKIV2L protein, a structure prediction model was performed using I-TASSER. The top-scoring predicted structure is shown in Fig. 2b, c. I-TASSER also provided the root-mean-square deviation (RMSD) between predicted structure and previously characterized *S. cerevisiae* SKIV2L (PDB ID: 4BUJ), which allowed us to determine the accuracy of structural modeling. An overall 1.48 Å RMSD was measured between the protein structures, affirming the high prediction accuracy.

Glycine is an aliphatic amino acid and is also the smallest and most flexible of all amino acids, having no side chain. As such, it can function as a “glycine hinge” in the short loop connecting the alpha helix on the residue’s one side, to the beta strand on the residue’s other side, as shown in Fig. 2b, c. Serine, on the other hand, has a polar, medium-sized side chain. The mutation of the flexible glycine hinge into a larger serine may cause structural destabilization, affecting the entire area of the protein surrounding this residue, preventing the alpha helix and the beta strand from assuming their native conformations. In addition, the nearby threonine at amino acid position 592 is located in close structural proximity to residue 631 and is also part of a connecting loop (between two alpha helices). Threonine, like serine, is also a polar amino acid with a medium-sized side chain. As shown in Fig. 2b, c, the change from glycine 631 into serine causes S631 and T592’s side chains to be very close—a distance of 1.1 Å between the oxygen atoms in the two side chains.

The close proximity between the two oxygen atoms may cause repulsion and possibly push T592’s side chain outwards, toward the protein’s interface. Alternatively, the repulsion may push S631’s side chain inward, disrupting the tightly packed hinge area between an alpha helix and a beta strand. Nevertheless, this mutation may cause additional conformational changes that can lead to increased distance between the two atoms. Collectively, the G631S mutation has the potential to cause structural destabilization, either through conformational changes, interference with the protein’s packing, or changes at the protein’s interface.

Discussion

THE syndrome has a broad clinical spectrum and is a challenging diagnosis. Table 2 summarizes our patient's clinical phenotype in comparison with a previously published large series of patients with THE syndrome [9]. Our patient was born small for gestational age and suffered from intractable diarrhea that presented very early in life, but lacked other typical clinical signs of THE syndrome, including facial dysmorphism and hair abnormalities such as trichorrhexis nodosa, which is a hair defect characterized by nodes along the hair shaft that break easily and may be seen by microscopic examination. Fabre and colleagues reviewed 80 patients with THE syndrome, but only 14 of them were identified with mutations in *SKIV2L* gene [9]. In the entire cohort of THE patients, as well as in those with *SKIV2L* mutation, nearly all subjects had facial dysmorphism and hair abnormalities. It is plausible that dysmorphism in our patient would have been more evident over time, taking into account the young age of diagnosis in our patient. THE syndrome was suspected in our patient, though hair exam was normal. However, the patient had short and sparse hair at the time of examination, challenging the diagnosis even more. Our patient had severe hypogammaglobulinemia, similar to the immunodeficiency that is associated with THE syndrome due to *TTC37* mutation. Interestingly, reduced T cell immunity was observed as well, contributing to the immunodeficient state of the patient. Finally, our patient did not suffer from liver disease, though in the literature about 50% of patients with THE syndrome had normal liver function tests [7]. Thus, the clinical phenotype of these patients can be diverse, especially in early life.

Patients with THE syndrome typically present with severe diarrhea in the first weeks of life resulting from villous atrophy [2]. However, some of these patients can also develop colitis, ileitis [7, 8, 21, 22] and even perianal disease [23] later in life, suggesting an inflammatory component as well. Therefore, THE should be suspected not only in patients presenting with severe neonatal-onset chronic diarrhea, but also in those with very early-onset IBD.

The treatment of patients with THE syndrome is supportive, including chronic administration of parenteral nutrition and immunoglobulin supplementation [9]. Interestingly, in some patients the gastro-intestinal disease improves in childhood though the reason for this is unclear [9, 24]. Immunosuppressive medications have been used in patients with an IBD-like phenotype but were ineffective in nearly all cases [9]. Similarly, an allogeneic hematopoietic stem cell transplantation may correct the immunodeficiency but not the gastro-intestinal disease [9]. Therefore, the etiology of chronic diarrhea in these patients is likely derived from defects in both epithelial and immune cells.

Three cases were previously described with C.1891G > A mutation in a compound heterozygous state with different mutations [16, 17]. Interestingly, all three patients had facial dysmorphism, two had hair abnormalities and only one had trichorrhexis nodosa. All of these patients had milder diarrhea, which not necessarily required administration of total parenteral nutrition. Our patient developed severe diarrhea and despite providing an amino acid-based formula continuously at a low rate by naso-gastric tube and prolonged bowel rest, she was not able to tolerate enteral feeds. It is possible that the gastro-intestinal phenotype in our patient was more severe since she was homozygote for this genetic variant.

As part of the genetic analysis, a rare and novel splice-site mutation in *BTN2A2* gene was identified. This gene is not well known but few reports suggest that it has a role in modulation of T cell responses [18–20]. Recently, Lebrero-Fernandez and colleagues reported that *BTN2A2* expression is upregulated in biopsies from patients with active ulcerative colitis [25]. We cannot rule out the possibility that this variant may play a role in the pathogenesis of the disease in our patient, either as a causal or as a modifier gene. Nevertheless, the patient harbored a previously reported homozygous deleterious variant in *SKIV2L*. In addition, there were no signs of endoscopic or histologic gastro-intestinal inflammation, which would have been expected if clinical symptoms would have resulted from a gene implicated in T cell function. Therefore, we believe that this patient had THE resulting from the *SKIV2L* variant.

The mechanism leading to the multi-systemic disease in THE syndrome is not fully understood. *SKIV2L* and *TTC37* proteins are both part of the super-killer complex which participates as a cofactor in the exosome and is responsible for degradation of aberrant mRNA [26]. Thus, deleterious genetic variants in *SKIV2L* and *TTC37* may therefore lead to aberrant exosome function. Finally, Eckard and colleagues have shown that *SKIV2L* limits RIG-I-like receptor antiviral responses, and indeed, in a patient with a *SKIV2L* mutation a string type 1 interferon signature could be seen in the blood [27].

In conclusion, we present a patient with THE syndrome that was found to have a deleterious mutation in *SKIV2L* gene, despite the absence of classical dysmorphic features and hair anomalies. This case highlights the importance of advanced genetic testing for patients with congenital diarrhea or very early-onset IBD that can facilitate an accurate diagnosis, especially when the phenotype is uncharacteristic.

Acknowledgments

D.S.S. is supported by the Israel Science Foundation, the Israel-US Bi-national Science Foundation and Jeffery Modell Foundation grants. S.B.S. is supported by NIH Grants HL59561, DK034854, and AI50950, the Helmsley Charitable Trust, and the Wolpow Family Chair in IBD Treatment and Research.

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Fig. 1. Histopathological assessment and electron microscopy images of index patient. **a** Hematoxylin and eosin stain showing flattening of villi. **b** Intact CD10 and **c** chromogranin stains of duodenal tissue. **d** Electron microscopy image showing normal microvilli

Fig. 2. Genetic and predicted protein modeling of *SKIV2L* mutation. **a** Chromatograms of the different *SKIV2L* genotypes detected in the studied pedigree. Arrows indicate the position of the mutation (c.1891G > A). **b** Predicted structure of *SKIV2L* normal protein followed by **c** predicted structural change caused by identified *SKIV2L* mutation. The *SKIV2L* predicted structure is shown in green and represented in cartoon form. Lower images provide higher magnification. Residue T592 is shown in blue; Native residue, G631, shown in yellow, and mutated residue, S631, shown in magenta. All represented in sticks form

Table 1

Laboratory work-up of the patient at admission

Laboratory	Patient values	Normal range
<i>Chemistry panel</i>		
AST	30	0–100 IU/l
ALT	17	7–45 IU/l
Alkaline phosphatase	234	145–320 IU/l
GGT	54	7–39 IU/l
Total bilirubin	0.11	0.1–1.1 md/dl
Albumin	2.1	3.4–4.2 g/dl
<i>Coagulation</i>		
PT	34	%
INR	1.4	0.8–1.2
PTT	36	24–38 s
<i>Immune studies</i>		
IgG	150	260–690 mg/dL
IgA	34.8	8–57 mg/dL
IgM	18	26–100 mg/dL
IgE	5.5	5.5 mg/dL
TREC	300	400 copies/0.5 mg DNA
WBC (cells/mm ³)	7250	
Lymphocytes (cells/mm ³)	1443	
CD3 (cells/mm ³)	779	
CD4 (cells/mm ³)	577	436–1394 cells/mm ³
CD8 (cells/mm ³)	390	166–882 cells/mm ³
CD20 (cells/mm ³)	245	50–300 cells/mm ³
<i>Mitogen response</i>		
No mitogen	1304	Control 1707 CPM
PHA 6 mcg/mL	47,237	Control 106186 CPM
CD3 mitogen	12,090	Control 21760 CPM

TREC T cell receptor excision circle, *CPM* counts per minute, *PHA* phytohemagglutinin

Comparison of clinical features of the index patient to a large cohort of patients with THE syndrome [9]

Table 2

	Entire THE syndrome cohort (<i>n</i> = 80)	THE syndrome— <i>SKIV2L</i> mutation (<i>n</i> = 14)	Patient
Sex (female/male)	39/35	8/5	Female
Intractable diarrhea	76/77	14/14	+
Facial dysmorphism	66/67	10/10	–
Hair abnormalities	71/73	11/13	–
Trichorrhexis nodosa	46/59	5/13	–
Immunodeficiency	48/67	5/12	+
IUGR/SGA	48/63	9/9	+
Liver disease	41/61	8/10	–
Skin abnormalities	29/48	6/6	–
Cardiac abnormalities	15/43	4/4	Patent foramen ovale

IUGR intrauterine growth retardation, *SGA* small for gestational age