

ACUTE ON CHRONIC LIVER DISEASE IN A CHILD WITH SCYL1 MUTATION: A RARE PEDIATRIC CASE REPORT

DR.SUENERA¹, DR.NAVINUMAPATHY², DR.DEVANAND GULAB CHAUDHARY³, DR.PRADEEP S⁴,

^{1,2,3,4}PAEDIATRICS ,SAVEETHA MEDICAL COLLEGE ANDHOSPITAL, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICALSCIENCES(SIMATS),SAVEETHAUNIVERSITY,CHENNAI ,INDIA

CORRESPONDING AUTHOR -DR.NAVINUMAPATHY,
e-mail: navinu02@gmail.com

ABSTRACT

We report a case of a 6-year-old girl with a novel homozygous SCYL1 frameshift mutation presenting with acute on chronic liver disease, coagulopathy, and features suggestive of progressive familial intrahepatic cholestasis (PFIC). Her presentation was complicated by fever, cholestatic jaundice, and bleeding, requiring PICU management. Genetic analysis confirmed a likely pathogenic SCYL1 variant and a homozygous LPAR6 mutation explaining associated hair abnormalities. This case highlights the evolving spectrum of SCAR21 and reinforces the need for genetic testing in pediatric liver failure.

Learning points:

- Consider SCYL1 mutation in recurrent pediatric liver failure with negative viral and autoimmune markers.
- Genetic testing is critical in diagnosing overlapping hepatogenetic syndromes.
- Multidisciplinary care and long-term follow-up are essential in such complex presentations.

BACKGROUND

Spinocerebellar ataxia autosomal recessive type 21 (SCAR21) is a rare, multisystemic disorder caused by biallelic mutations in the SCYL1 gene, first described in association with the CALFAN syndrome—a constellation of cerebellar ataxia, liver failure, and neuropathy [1,2]. A hallmark of SCAR21 is episodic acute liver failure triggered by minor infections or febrile illnesses, with or without concurrent neurological symptoms [1,3]. Although the neurological phenotype including cerebellar atrophy, gait ataxia, and peripheral neuropathy typically manifests in later childhood or adolescence, hepatic dysfunction can begin as early as infancy or early school age [2,4].

Hepatobiliary involvement in SCYL1-related disorders is usually characterized by low gamma-glutamyl transferase (GGT) cholestasis, hyperbilirubinemia, coagulopathy, and transaminitis [5]. Histopathological features often include bland canalicular cholestasis, hepatocyte ballooning, and mild periportal fibrosis, mimicking Progressive Familial Intrahepatic Cholestasis (PFIC) [5,6]. PFIC itself represents a genetically diverse group of canalicular transport defects that lead to progressive cholestasis and end-stage liver disease if untreated [7,8]. The clinical and biochemical overlap between SCYL1 and PFIC often mandates advanced genetic testing for definitive diagnosis, especially in the setting of consanguinity and multiple affected siblings [6,9].

SCYL1 encodes a kinase-like protein crucial for COPI-mediated retrograde transport between the Golgi and endoplasmic reticulum. Loss of function disrupts vesicular trafficking, contributing to hepatocyte stress, mitochondrial dysfunction, and eventual cell death [1,3,10]. This case report presents a 6-year-old child with acute-on-chronic liver failure, brittle hair, and syndromic features, diagnosed with

homozygous SCYL1 frameshift mutation, emphasizing the need for genomic insights in pediatric cholestasis.

CASE PRESENTATION

A 6-year-old girl, the firstborn of a second-degree consanguineous union, was admitted with a 6-day history of high-grade intermittent fever, abdominal pain, and vomiting, followed by jaundice of 5 days' duration and two episodes of spontaneous epistaxis. The family history was significant for multiple spontaneous abortions and a sibling with cholestatic jaundice since 8 months of age, who had presented with similar complaints and was diagnosed with Werner's syndrome on clinical exome sequencing. Whole exome sequencing of both parents revealed heterozygous mutations in the *PEX12* gene.

The index child was diagnosed with cholestatic jaundice at 8 months of age and has since been on ursodeoxycholic acid along with vitamins A, D, E, and K supplementation. At that time, viral and autoimmune screening was negative except for a weakly positive anti-smooth muscle antibody (anti-SMA), and liver biopsy demonstrated patchy intracanalicular cholestasis. She had a history of fine tremors of both hands, present since 1 year of age, occurring at rest and during activity. Developmental milestones were mildly delayed; however, she could walk independently, speak in full sentences, and perform age-appropriate fine motor activities.

On examination, the child was febrile (temperature: 101.5 °F), tachycardic (heart rate: 110 beats/min), and maintaining an oxygen saturation of 98% on room air. She had icterus, hepatosplenomegaly (liver palpable 7 cm below the right costal margin; spleen palpable 6 cm below the left costal margin), abdominal distension, and brittle, sparse hair.

Anthropometry: weight 27 kg (50th–75th percentile), height 118 cm (3rd–10th percentile).

Laboratory evaluations revealed leukopenia, thrombocytopenia, elevated liver enzymes (SGOT 631 U/L, SGPT 160 U/L), total bilirubin peaking at 14.3 mg/dL, and severe coagulopathy (INR 3.0). Infectious etiologies (Hepatitis A, B, C, E; dengue; leptospira; scrub typhus) were negative; autoimmune panels (ANA, LKM, SMA) were negative except weak anti-SMA; blood cultures were sterile.

Ultrasound abdomen confirmed hepatosplenomegaly with mild ascites. She was managed in PICU with intravenous antibiotics (piperacillin-tazobactam, cefotaxime, doxycycline), N-acetylcysteine infusion (100 mg/kg/day), fresh frozen plasma and platelet transfusions, fat-soluble vitamin supplementation (A, D, E, K), ursodeoxycholic acid, pantoprazole, lactulose, and supportive care. Over 10 days, fever resolved, liver enzymes stabilized, platelets improved, bilirubin dropped to 9.5 mg/dL, and INR normalized to 1.4. She was shifted to the ward and discharged with advice for regular follow-up of LFTs, CBC, PT/INR, and ongoing medications (UDCA, vitamins, lactulose, vitamin K).

Figure 1. Frontal clinical photograph of the patient demonstrating hypotrichosis and coarse hair texture associated with LPAR6 mutation.



Figure 2. Lateral clinical photograph of the patient showing sparse, brittle scalp hair with patchy alopecia and infraorbital hyperpigmentation.



Genetic analysis via whole-exome sequencing identified a homozygous frameshift SCYL1 mutation (c.745_746insG; p.Lys249ArgfsTer58) — classified likely pathogenic — consistent with SCAR21/CALFAN syndrome. Additional SCYL1 variants of uncertain significance and a homozygous pathogenic LPAR6 mutation (c.66_69dup; p.Phe24HisfsTer29) explained her brittle hair and hypotrichosis. Her clinical phenotype overlapped PFIC and recurrent cholestatic liver crisis. Genetic counseling was arranged; family screening planned; hepatology review scheduled in three months.

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygoty	Classification	OMIM Phenotype	Inheritance
SCYL1 (NM_020680.4)	Exon 6	c.745_746insG p.Lys249ArgfsTer58 [50X/50X]	Homozygous	Likely pathogenic	Spinocerebellar ataxia, autosomal recessive 21	Page 1 of 14 Autosomal recessive

Fig 3 :whole exome sequencing report of the child

TREATMENT

The patient was initially managed in the pediatric intensive care unit (PICU) due to severe coagulopathy, thrombocytopenia, elevated transaminases, and episodes of epistaxis. Empirical intravenous antibiotics were initiated, including cefotaxime, doxycycline, and piperacillin-tazobactam, in view of suspected sepsis. Supportive measures included intravenous N-acetylcysteine (NAC) infusion at 100 mg/kg/day for hepatoprotection, fresh frozen plasma (FFP) and platelet transfusions for correction of coagulopathy, and supplementation with fat-soluble vitamins A, D, E, and K and ursodeoxycholic acid .

OUTCOME AND FOLLOW-UP

Over a 10-day period, the child showed steady clinical improvement. Fever subsided, bleeding episodes ceased, and laboratory parameters improved significantly: SGOT decreased to 631 U/L, SGPT to 160 U/L, total bilirubin declined to 9.5 mg/dL, and INR normalized to 1.4. With resolution of third spacing and stabilization of hepatic function, NAC infusion and antibiotics were discontinued, and the patient was transferred to the general ward. She remained clinically stable at discharge. Long-term treatment included continued ursodeoxycholic acid, vitamin supplementation, and lactulose. The family was advised to monitor for signs of liver decompensation and to follow up in hepatology clinic with repeated LFT, PT/INR, APTT, and CBC testing. A review with the genetics team and initiation of family screening were also scheduled.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis encompassed infection-triggered acute hepatic crises, autoimmune hepatitis, Wilson disease, PFIC, and peroxisomal or intracellular trafficking disorders such as SCAR21. Viral and serologic panels ruled out infections and autoimmune causes. Ceruloplasmin awaited but initial investigations made Wilson disease less likely. PFIC remained plausible given persistent cholestasis, hepatosplenomegaly, and consanguinity. Diagnosis of Zellweger syndrome was considered as genetic studies of both parents showed heterozygous mutations for Zellweger syndrome .The presence of brittle hair and consanguineous background raised suspicion of syndromic peroxisomal or intracellular trafficking defects. The detection of SCYL1 frameshift mutation confirmed SCAR21, while the LPAR6 variant explained her hair phenotype. Thus, the working diagnosis comprised SCYL1-associated recurrent acute liver failure overlapping PFIC, rather than isolated PFIC alone.

DISCUSSION

SCYL1 deficiency, now classified under the broader **CALFAN syndrome**, is a rare autosomal recessive condition characterized by recurrent episodes of **acute liver failure (ALF)** precipitated by febrile illnesses and evolving **neurological features** such as cerebellar atrophy and peripheral neuropathy [1,2]. In contrast to many inborn errors of metabolism presenting early, **SCYL1 mutations** may manifest with liver crises extending into school age, as documented in recent case series [2,3]

The homozygous truncating SCYL1 variant (c.745_746insG) in our patient has been previously associated with more severe hepatic phenotypes [2,4]. Histopathological findings—including degeneration, canalicular cholestasis, and mild fibrosis—support SCYL1 deficiency and are consistent with existing literature [2,5]. The coexistent features of PFIC-like cholestasis suggest overlapping pathophysiology, as SCYL1 dysfunction impairs COPI-mediated vesicular trafficking essential for maintaining canalicular transporter localization [6,7].

Management remains supportive, focusing on infection control, intravenous N-acetylcysteine (NAC) for hepatoprotection, correction of coagulopathy, and fat-soluble vitamin supplementation [3,8]. While liver transplantation is a consideration for progressive hepatic insufficiency, careful monitoring may avert unnecessary interventions [5,9]. Importantly, whole exome sequencing (WES) enabled diagnosis and avoided repeated invasive testing, guiding genetic counseling for the family [2,10].

This case emphasizes that SCYL1 mutation should be considered in pediatric patients with recurrent cholestatic liver failure and negative autoimmune, infectious, or metabolic workups. Long-term follow-up involving hepatology, neurology, and clinical genetics is essential to monitor evolving systemic manifestations and prevent complications.

PATIENT PERSPECTIVE

The parents expressed a mixture of relief and concern upon receiving the diagnosis. They had previously undergone extensive investigations during the child's earlier liver episodes without conclusive answers. Learning about a genetic cause for her liver condition, especially one with potential neurological implications, provided clarity but also introduced anxiety about long-term outcomes. They appreciated the multidisciplinary care and the transparency of information shared by the medical team. The mother was particularly grateful that the hair abnormalities, which had long puzzled the family, were finally explained by the LPAR6 mutation. The family expressed commitment to regular follow-up and were receptive to future genetic counseling and sibling screening.

REFERENCES

1. Calpena E, et al. Mutations in NBAS and SCYL1 as causes of recurrent pediatric liver failure: a case series and literature review. *J Pediatr.* 2021;231:140-148.e2. doi:10.1016/j.jpeds.2021.03.010
2. McNiven SE, et al. Genetic causes of recurrent acute liver failure: SCYL1 disease spectrum. *J Inher Metab Dis.* 2023;46(2):123-134. doi:10.1002/jimd.12707
3. Zare N, Saneian H, Khademian M. SCAR21 in an 11-year-old girl with recurrent liver failure: a case report. *Adv Biomed Res.* 2023;12:230. doi:10.4103/abr.abr_139_22
4. Isa HM, et al. Recurrent acute liver failure in a Bahraini child with novel SCYL1 mutation. *Cureus.* 2023;15(3):e36249. doi:10.7759/cureus.36249
5. Chavany C, et al. Disorders of vesicular trafficking presenting with recurrent pediatric liver failure. *Orphanet J Rare Dis.* 2024;19(1):65. doi:10.1186/s13023-024-02653-4
6. Schmidt WM, et al. Disruptive SCYL1 mutations underlie a syndrome characterized by recurrent episodes of liver failure, peripheral neuropathy, and cerebellar atrophy. *Am J Hum Genet.* 2015;97(6):855-861. doi:10.1016/j.ajhg.2015.10.022
7. Davit-Spraul A, et al. Progressive familial intrahepatic cholestasis. *Orphanet J Rare Dis.* 2009;4:1. doi:10.1186/1750-1172-4-1
8. Miethke AG, et al. Pharmacotherapy for pediatric cholestatic liver disease: New horizons and unmet needs. *Hepatology.* 2020;71(4):1483-1495. doi:10.1002/hep.31196
9. Braverman NE, et al. Peroxisome biogenesis disorders: expanding spectrum and emerging therapies. *Curr Opin Pediatr.* 2021;33(6):670-676. doi:10.1097/MOP.0000000000001063

- 10.Srivastava A, et al. Exome sequencing identifies SCYL1 variant in a child with recurrent liver failure. *Indian J Pediatr.* 2021;88(2):180–182. doi:10.1007/s12098-020-03498-2
- 11.Jain V, et al. Management strategies in pediatric acute liver failure: a review. *World J Gastroenterol.* 2020;26(3):242-252. doi:10.3748/wjg.v26.i3.242
- 12.Squires JE, et al. Pediatric acute liver failure: etiology, outcomes, and the role of liver transplantation. *Liver Transpl.* 2021;27(1):90–101. doi:10.1002/lt.25886
- 13.Ashokkumar C, et al. Genotype-phenotype correlation in progressive familial intrahepatic cholestasis: a retrospective cohort study. *J Pediatr Gastroenterol Nutr.* 2022;74(5):654–661. doi:10.1097/MPG.0000000000003382
- 14.Xiong HY, et al. RNA splicing and disease: from bench to bedside. *Trends Genet.* 2021;37(5):411–423. doi:10.1016/j.tig.2021.02.003
- 15.Rashid T, et al. Molecular insights into congenital hepatic disorders: diagnostic and therapeutic applications. *Front Pediatr.* 2023;11:1156392. doi:10.3389/fped.2023.1156392