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Case Report

# Infantile Liver Failure as the Initial Manifestation of SCYL1-Related CALFAN Syndrome: A Case Report and Literature Review

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**Abstract:**

***Background:*** CALFAN (Cholestasis, Acute Liver Failure, and Neurodegeneration) syndrome is a rare autosomal recessive disorder caused by biallelic pathogenic variants in SCYL1 (SCY1-like pseudo-kinase 1). It is classically associated with low or normal gamma-glutamyl transpeptidase (GGT) cholestasis, infection-triggered acute liver failure (ALF), and progressive neurodegeneration. Because neurological and skeletal manifestations may be absent during the first hepatic presentation, early diagnosis can be missed unless the hepatic phenotype is recognized.

***Case*:** We describe a 9-month-old female infant born to third-degree consanguineous parents who developed fever-triggered cholestatic jaundice and ALF. Structural biliary disease, viral hepatitis, and common metabolic disorders were excluded. Whole-exome sequencing revealed a homozygous pathogenic nonsense variant in SCYL1 (c.1567C>T; p.Arg523*), consistent with autosomal recessive CALFAN syndrome. No neurological, neuroimaging, or skeletal abnormalities were present at initial presentation. The clinical course was notable for persistent hyperbilirubinemia and a family history of sibling death from infantile liver failure.

***Discussion*:** This case adds to the SCYL1 spectrum by demonstrating isolated infantile ALF without neurological features at presentation, a severe hepatic phenotype with persistent cholestasis, and a novel homozygous null variant in a consanguineous family.

***Conclusion:*** SCYL1 deficiency should be considered in infants with fever-triggered ALF and low/normal-GGT cholestasis, even when neurological and skeletal signs are absent. Early genomic testing, systematic exclusion of low-GGT cholestasis mimics, longitudinal neurological surveillance, timely transplant referral, and recurrence-risk counselling are essential.

**Keywords:** calfan syndrome, infantile liver failure, SCYL1

## Introduction

Cholestasis, Acute Liver Failure, and Neurodegeneration (CALFAN) syndrome is an exceptionally rare autosomal recessive disorder caused by biallelic pathogenic variants in the SCYL1 gene. It is characterized by recurrent episodes of pediatric acute liver failure, low or normal gamma-glutamyl transpeptidase (GGT) cholestasis, and progressive neurodegeneration, with marked phenotypic variability.[1, 2] Acute onset of liver disease without evidence of chronic liver disease with biochemical evidence of severe liver injury, coagulopathy not corrected by vitamin K defined as international normalized ratio (INR) ≥ 1.5 with evidence of hepatic encephalopathy (HE) or INR >2 with or without HE was the defining criteria for ALF.[3]

SCY1-like pseudo-kinase 1 (SCYL1) encodes a protein involved in Golgi-endoplasmic reticulum trafficking. Recent studies have shown that SCYL1 deficiency leads to endoplasmic reticulum stress and increased hepatocellular vulnerability, providing a mechanistic explanation for infection-triggered hepatic decompensation and progressive neurological involvement.[4, 5]

Clinically, SCYL1-related CALFAN syndrome usually presents during infancy or early childhood with episodic cholestatic hepatitis or ALF, often following febrile illnesses or upper respiratory tract infections (URTIs). Liver biochemistry may normalize between episodes, which can delay diagnosis and lead to misclassification as self-limited viral hepatitis. Neurological manifestations-including developmental delay, tremor, peripheral neuropathy, optic atrophy, and cerebellar atrophy-may emerge later in childhood or adolescence.[1, 2, 6]

CALFAN syndrome is exceedingly rare, with fewer than 25 reported cases worldwide to date. Because it overlaps clinically with other causes of low/normal-GGT cholestasis, particularly progressive familial intrahepatic cholestasis (PFIC), bile acid synthesis defects, neuroblastoma amplified sequence (NBAS) related recurrent acute liver failure (ALF), and mitochondrial hepatopathy, so early genetic testing is essential for diagnosis, management, and genetic counselling.[2, 6-8]

## Case

A 9-month-old female infant born to parents in a third-degree consanguineous marriage was admitted for evaluation of cholestatic jaundice and liver dysfunction. She was born at term by normal vaginal delivery, with no history of neonatal intensive care unit admission. The mother was hepatitis B surface antigen (HBsAg) positive; however, the infant received hepatitis B immunoglobulin and appropriate hepatitis B vaccination at birth.

At 9 months of age, the child developed an acute febrile illness lasting three days, associated with upper respiratory tract symptoms. Four days after the onset of fever, the child developed jaundice with high-colored urine and pigmented stool (stool color chart 5-6).

There was no history of bleeding manifestations, ecchymotic patches, seizures, or altered sensorium. Mild pruritus developed two days after hospitalization. On examination, the child was icteric and undernourished. Anthropometry revealed severe wasting and stunting, with weight 6 kg (Z-score −3.15), length 66 cm (Z-score −2.72), weight-for-length Z-score −3.09, and preserved head circumference of 45 cm (Z-score −0.15). Developmental milestones were appropriate for age. Abdominal examination revealed hepatomegaly, with the liver palpable 3 cm below the right costal margin, soft in consistency; the spleen was not palpable.

Initial evaluation revealed significant liver dysfunction with total bilirubin of 14 mg/dL (direct 10.6 mg/dL) and markedly elevated aminotransferases (AST 1513 IU/L, ALT 348 IU/L). GGT was within the age-appropriate range (109 IU/L). Serum albumin was preserved (3.94 g/dL). Coagulation studies showed a prolonged INR of 3.56, which was not responsive to parenteral vitamin K. Complete blood count demonstrated anemia with leukocytosis.

Etiological evaluation showed normal thyroid function, negative viral serologies (hepatotropic viruses, Epstein-Barr virus (EBV), cytomegalovirus (CMV), Human herpesvirus 6 (HHV-6), Adenovirus, and human immunodeficiency virus (HIV)), normal immunoglobulin levels, and a negative sepsis screen. Serum bile acids were raised (214umol/L). Serum alpha-fetoprotein, ammonia, lactate, and creatine phosphokinase (CPK) were within normal limits. The lactate/pyruvate ratio was 15:1, which was normal, and the acylcarnitine profile was within normal limits. Ultrasonography of the abdomen showed an altered echotexture and hypoechoic with enlargement of the liver (8.4cm). No dilatation of the intrahepatic biliary tree and common hepatic duct. The gallbladder showed a normal lumen (length 21mm) with a normal wall. The common bile duct (CBD) was normal, 1.8mm. Portal vein diameter was 5.7mm and hepatic veins were normal. The spleen was normal (size 5.5cm). No ascites was seen **(Figure 1)**.

The family history was significant for a sibling who had died in infancy due to liver failure without any identified etiology. Given the combination of normal-GGT cholestasis, fever-triggered hepatic dysfunction, consanguinity, and sibling death from liver disease, a genetic etiology was suspected. Whole-exome sequencing (WES) identified a homozygous pathogenic nonsense variant in the SCYL1 gene (c.1567C>T; p.Arg523*; NM_020680.4), located in exon 11. This variant was classified as

pathogenic according to ACMG criteria and was associated with autosomal recessive CALFAN syndrome.

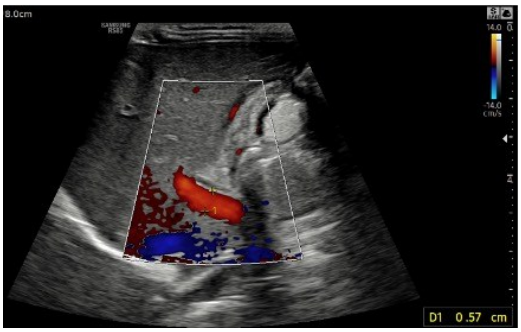


**Figure 1.** Abdominal ultrasonography showing hepatomegaly with altered liver echotexture. No intrahepatic biliary dilatation, gallbladder abnormality, or ascites is seen.

Imaging evaluation, including skeletal survey and brain magnetic resonance imaging (MRI), revealed no neurological or skeletal abnormalities at presentation. The child was managed conservatively with supportive care, including nutritional rehabilitation with calorie supplementation of 150-180kcal/kg/day, a protein target of 2-3g/kg/day, medium chain triglyceride (MCT)-containing feeds along with night feeds. She also received fat-soluble vitamin supplementation (vitamins A, D, E, and K), parenteral vitamin K for coagulopathy, ursodeoxycholic acid at 20 mg/kg/day, symptomatic treatment for pruritus with antihistamines, and close monitoring with prompt treatment of intercurrent infections. Coagulopathy gradually resolved with supportive management during hospital stay and INR was 1.1 at discharge. However, bilirubin showed an increasing trend, with total/direct bilirubin rising from 14/10.6 mg/dL at presentation to 16/13.5 mg/dL during hospital stay. The family was counselled regarding the risk of recurrent hepatic crises, the need for early liver-transplant evaluation if hepatic dysfunction persisted or recurred, possible future neurological deterioration, and recurrence risk in future pregnancies. Bilirubin trend remained static in follow-up with total/direct bilirubin-13.8/9.6 mg/dL without any further episodes of ALF. The patient remains under close follow-up for growth, liver function, and surveillance for potential neurological manifestations, with a current follow-up duration of 6 months.

**Diagnostic Evaluation and Exclusion of Differential Diagnoses**

The diagnostic approach was guided by the presence of infantile ALF with cholestasis and normal/low GGT. Structural biliary disease was unlikely because the infant had pigmented stools, a normal-sized gallbladder and CBD, and no sonographic evidence of biliary obstruction. Viral hepatitis and systemic infection were excluded by negative hepatotropic and non-hepatotropic viruses (EBV, CMV, HHV-6, Adenovirus) and sepsis screen. PFIC was considered because of low/normal-GGT cholestasis,

pruritus, raised serum bile acid levels; however, the acute fever-triggered liver failure, consanguinity, sibling death, absence of a typical PFIC phenotype at presentation, and diagnostic SCYL1 variant supported CALFAN syndrome. Bile acid synthesis defects were considered, but were less likely because serum bile acids were raised. Mitochondrial hepatopathy was evaluated by serum lactate, lactate/pyruvate ratio (15:1), ammonia, creatine phosphokinase, and acylcarnitine profile; these did not support a primary mitochondrial or fatty-acid oxidation disorder.[9]. Recurrent ALF associated with mutations like NBAS, Leucyl-tRNA Synthetase 1(LARS 1), tRNA mitochondrial 2-thiouridylase (TRMU) was considered in view of fever-triggered episode and WES identified a pathogenic homozygous SCYL1 variant explaining the phenotype **(Figure 2)**.

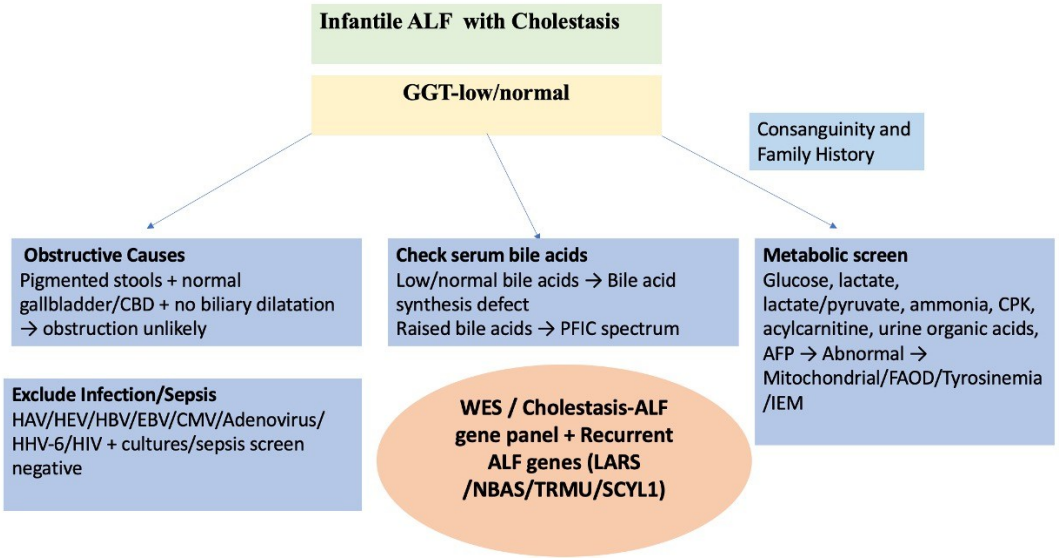


**Figure 2.** Diagnostic algorithm for infantile acute liver failure with low/normal-GGT cholestasis.

ALF = acute liver failure; GGT = gamma-glutamyl transferase; CBD = common bile duct; HAV = hepatitis A virus; HEV = hepatitis E virus; HBV = hepatitis B virus; EBV = Epstein–Barr virus; CMV = cytomegalovirus; HHV-6 = human herpesvirus 6; HIV = human immunodeficiency virus; PFIC = progressive familial intrahepatic cholestasis; CPK = creatine phosphokinase; AFP = alpha-fetoprotein; FAOD = fatty acid oxidation disorder; IEM = inborn error of metabolism; WES = whole-exome sequencing; LARS = leucyl-tRNA synthetase 1; NBAS = neuroblastoma amplified sequence; TRMU = tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase; SCYL1 = SCY1-like pseudokinase 1.

## Discussion

The SCYL1 gene encodes SCY1-like pseudokinase 1, a ubiquitously expressed protein involved in coat protein complex I (COPI)-mediated retrograde trafficking between the Golgi apparatus and endoplasmic reticulum (ER), with a critical role in neuronal

integrity and hepatocellular homeostasis.[4] Loss of SCYL1 impairs COPI-dependent retrograde transport, leading to intracellular accumulation of secretory and membrane proteins, chronic ER stress, and activation of the unfolded protein response. During periods of increased metabolic demand, such as intercurrent infections, this adaptive response may become maladaptive, progressing to hepatocellular apoptosis. A similar vulnerability of cerebellar Purkinje cells likely accounts for progressive neurological involvement in older patients, providing a unifying mechanistic explanation for the combined hepatic-neurological phenotype.[4, 5]

The present case adds clinically useful information to the reported SCYL1 spectrum. First, the disease presented as isolated infantile ALF without neurological, neuroimaging, or skeletal abnormalities. Second, the hepatic phenotype was severe, with persistent cholestasis after the first recognized febrile trigger rather than complete inter-episodic normalization. Third, a homozygous null SCYL1 variant (c.1567C>T; p.Arg523*) in a consanguineous family. Fourth, the family history of sibling death from infantile liver failure suggests that some families carrying null SCYL1 variants may have reduced hepatic reserve and a more aggressive early hepatic course. Therefore, the absence of neurological findings at the first presentation should not delay SCYL1 testing when the hepatic phenotype is compatible.

Pathogenic variants in SCYL1 were initially described in 2015 as the cause of autosomal recessive spinocerebellar ataxia type 21 (SCAR21; OMIM #616719), characterized predominantly by progressive neurodegeneration.[1] Subsequent reports expanded the phenotypic spectrum to include a prominent hepatic presentation, leading to recognition of CALFAN syndrome, defined by low/normal-GGT cholestasis, recurrent acute liver failure, and anticipated neurodegeneration.[2, 6-8] Most reported cases involve homozygous pathogenic variants, frequently in settings of consanguinity, whereas compound heterozygosity has also been documented. Marked inter- and intrafamilial variability has been reported, including differences in the age of hepatic onset—most commonly during infancy—the frequency of hepatic crises, neurological progression, and the need for liver transplantation.[6-8, 10, 11] **(Table 1)**.

The genotype-phenotype correlation remains incomplete. Truncating/null variants, including p.Arg 523*, plausibly result in marked loss of protein function, but published cases show that genotype alone does not fully predict outcome. Kazem et al. reported variable severity of the hepatic phenotype among affected members of the same family carrying the same mutation **(Table 1)**.[6] Environmental triggers such as fever/URTI, diarrhea, nutritional state, age at first decompensation, and modifier genes may influence severity. In the present family, the proband and a deceased sibling with infantile liver failure support a severe familial hepatic phenotype. This observation should be interpreted cautiously because sibling molecular confirmation was not

available; nevertheless, it strengthens the need for genetic counselling and prenatal/preimplantation options in future pregnancies.

Clinically, SCYL1-related liver disease has classically been described as episodic, with normalization of liver biochemistry between episodes of ALF or cholestasis. This pattern, reported in early cohorts, often led to diagnostic delays as transient improvement was misattributed to self-limited viral hepatitis. However, accumulating evidence indicates that hepatic involvement can follow a more aggressive or progressive course in some patients requiring liver transplantation, with no reports of graft failure post liver transplant.[2, 7, 11]

**Table 1.** Genotypic and phenotypic characteristics of patients with CALFAN syndrome

| Study | Gender / No of patients | SCYL1 Variant | Clinical Features<br>- **Hepatic Features (Age of onset).**<br>- **Neurological Features (Age of onset)**<br>- **Skeletal Features (Age of onset)** | Treatment / Outcome |
|---|---|---|---|---|
| Schmidt et al., 2015[1] | 1 Male & 2 Female | Compound heterozygosity family1: gene deletion (Exon 2) family2: frameshift mutation (Exon 8) | - Recurrent low-GGT cholestasis, ALF (early infancy)<br>- Delayed motor milestones, tremors, ataxia (variable)<br>- Scoliosis, joint contractures | Supportive care/ survived |
| Incecik et al., 2018[12] | 1 Female | Homozygous/ Exon 1: C.1420C>T | - Recurrent cholestasis (9 months)<br>- Delayed motor development, mild learning disability, ataxia (infancy)<br>- No skeletal features | Supportive care/ survived |
| Lenz et al., 2018[8] | 7 Patients (5 families) | SCYL1 variants (missense, nonsense, splice-site) | - Recurrent cholestasis, low-GGT, transient liver failure (infancy)<br>- 1/7 Seizures, 6/7 microcephaly, 4/7 motor dysfunction (infancy), 2/7 cerebellar atrophy<br>- 5 out of 7 had skeletal features (short stature, failure to thrive, lumbar lordosis, hip dysplasia, clefting of ribs | Liver transplant in one patient at 23 months of age and satisfactory post-transplant course. Other patients were on supportive care/ all survived |
| Li et al., 2019[7] | 1 Female | Homozygous /Exon 1/ Homozygous SCYL1 exon 1 (NM_020680): c.92_93insGGGC | - Recurrent low-GGT cholestasis, three ALF episodes (14 Months)<br>- Developmental delay, cerebellar ataxia (later childhood) | Supportive care/ survived |

| Study | Gender / No of patients | SCYL1 Variant | Clinical Features<br>- Hepatic Features (Age of onset).<br>- Neurological Features (Age of onset)<br>- Skeletal Features (Age of onset) | Treatment / Outcome |
|---|---|---|---|---|
| | | CCT, p.(H32Gfs*20) | - Bilateral femoral head necrosis, bilateral hip joint dysplasia | |
| Shohet et al., 2019[13] | 1 Male & 2 Female | homozygous/ exon 4: c.459C>T p. (Gly153Gly) | - Recurrent cholestasis (onset at 5 months)<br>- Pt 1: Developmental delay<br>Pt 2: Motor deterioration<br>- Pt 1: Abnormal thoracic vertebrae<br>Pt 2: Short stature, delayed bone age, small, femoral epiphyses | Supportive care/ survived |
| Chavany et al., 2020[14] | 1 Male | Compound heterozygous: (c.2356_2357insGA p.) (c.1386 + 1G > A | - Recurrent ALF episodes (infancy)<br>- No neurological features<br>- No skeletal features | Supportive care/ survived |
| Campos et al., 2020[15] | 1 Female | Exon 12, homozygosity: c.1636C>T (p.Gln546*) | - ALF (at 13 months)<br>- Tremors and apathy (28 months), severe tremors (6 years), cerebellar ataxia<br>- None | Supportive care/ survived |
| McNiven V et al., 2021[11] | 1 Male and 1 female | pt 1: Exon 3, 7–8, compound heterozygous: (c.399delC; p.Asn133Lysfs*136) | - Pt 1: Recurrent ALF (4 Months).<br>Pt 2: Severe ALF (5 Months)<br>- GDD, cognitive decline, hypotonia, motor weakness, tremors, cerebellar signs<br>Pt 1: 18 months.<br>Pt 2: Age of onset not defined<br>- Short stature, scoliosis, abnormal chest shape, lumbar spine abnormalities | Liver transplant<br>Pt 1:21 months age (diagnosed at 13 years)<br>Pt 2:7 months old (diagnosed at 9 years)<br>Both siblings had satisfactory post-LT courses |
| Isa et al., 2023[16] | 1 Male | Homozygous/ Exon 7: (NM_020680.4):c.895A>T (p.lys299Ter) | - Recurrent cholestasis, three episodes (2 years 8 months)<br>- Intellectual disability, motor delay (toddlerhood)<br>- None | Supportive care/ survived |
| Youssef et al., 2023[2] | 1 Female | Exon 8/ compound heterozygous: c.937delG and c.1509 1510delTG | - Recurrent cholestasis, 3 ALF episodes (9 months)<br>- Mild deficits; progressive ataxia (post-transplant)<br>- None | Liver transplant (at 20 years of age) and satisfactory results |

| Study | Gender / No of patients | SCYL1 Variant | Clinical Features<br>- **Hepatic Features (Age of onset).**<br>- **Neurological Features (Age of onset)**<br>- **Skeletal Features (Age of onset)** | Treatment / Outcome |
|---|---|---|---|---|
| Kazem et al., 2025[6] | 1 Male and 1 female | Exon11 Homozygous SCYL1 (NM_020680.4):c. 1386+1G > A. (in both siblings) | - Pt 1: Recurrent cholestasis, ALF (16 months) Sibling 2: Asymptomatic<br>- Pt 1: Mild developmental delay; Sibling 2: Normal<br>- None | Supportive care/ survived |
| Suenera et al., 2025[10] | 1 Female | Exon 6/ homozygous: frameshift mutation, c.745_746insG p.lys249ArgisTer58 | - Recurrent cholestasis (8 months)<br>- Fine tremors (1 year), developmental delay<br>- None | Supportive care/survived |
| Present case | Female | Homozygous SCYL1 c.1567C>T (p. Arg523*) nonsense variant | - Fever-triggered infantile ALF (9 Months), sibling death<br>- None at presentation<br>- None at presentation | Supportive care/survived |

ALF = acute liver failure; GDD = global developmental delay; GGT = gamma-glutamyl transpeptidase; LT = liver transplant

Low-to-normal GGT cholestasis remains a key diagnostic feature of CALFAN syndrome. Recognition of this biochemical signature is crucial in infants with febrile illness-triggered ALF, especially when associated with consanguinity, family history of unexplained infantile liver failure, pigmented stools, absent biliary obstruction, and negative viral/metabolic evaluation. In such cases, targeted cholestasis with ALF panels or rapid WES should be considered early rather than after repeated hepatic crises.

Liver biopsy findings in SCYL1-related disease are nonspecific and may include variable portal/lobular inflammation, fibrosis, cholestasis, steatosis, and giant-cell hepatitis.[2, 8, 11, 15] In our patient, a liver biopsy could not be performed because of significant coagulopathy. The absence of a biopsy did not preclude diagnosis because the clinical phenotype and homozygous pathogenic SCYL1 variant provided molecular confirmation.

**Neurological Evolution and Surveillance**

Neurological involvement is a defining but evolutionary component of SCYL1 disease. Progressive cerebellar ataxia, tremor, hypotonia, peripheral neuropathy, optic atrophy, seizures, microcephaly, and variable cognitive impairment have been documented, often emerging after recurrent hepatic decompensations or later in

childhood.[12, 13, 16] Importantly, neurological manifestations may be absent in early infancy, as in our patient, who had normal development and normal brain MRI at presentation. A normal initial neurological examination should therefore be viewed as a baseline, not as evidence against CALFAN syndrome.

After diagnosis, follow-up should include periodic developmental assessment, neurological examination for tremor/ataxia/hypotonia, assessment for peripheral neuropathy when age-appropriate, ophthalmic evaluation for optic nerve involvement, and repeat neuroimaging if symptoms emerge. This counselling is particularly important before liver transplantation because transplantation may stabilize the hepatic disease, but is not expected to prevent later neurological progression.[2]

Beyond the hepatic–neurological axis, extrahepatic manifestations-particularly skeletal abnormalities-further broaden the phenotypic spectrum of CALFAN syndrome. Skeletal findings reported across cohorts include short stature, failure to thrive, scoliosis, vertebral anomalies, hip dysplasia, and delayed bone age.[1, 7, 8, 11] The absence of skeletal involvement in our patient, as well as in several other reported cases, suggests that these features may be age-dependent or influenced by genotype-specific modifiers. Given their reported frequency, routine longitudinal orthopedic assessment is advisable in all affected individuals.

Management of CALFAN syndrome remains largely supportive, focusing on nutritional optimization, fat-soluble vitamin supplementation, cholestasis/pruritus management, prevention and early treatment of intercurrent infection, and close monitoring of bilirubin, INR, transaminases, glucose, ammonia, and encephalopathy.[2, 8]

Referral for liver transplantation should be considered early when there is persistent synthetic dysfunction, recurrent ALF, worsening cholestasis despite supportive care, failure to thrive due to chronic cholestasis, or inability to maintain hepatic stability between infections.[2, 7, 11] In SCYL1 disease, transplantation may reduce hepatic crises and stabilize liver function, but families must be counselled that neurological progression can still occur because the disorder is multisystemic. Therefore, transplant decisions should be individualized and made jointly by hepatology, transplant surgery, neurology, genetics, nutrition, and the family.

This mutation has not been described previously in the literature and only one case has been reported from India till now. Our patient has been under close follow-up for the last 6 months. The family was advised to seek early medical care during febrile illnesses, maintain adequate nutrition and hydration, avoid unnecessary hepatotoxic medications, and continue serial liver and neurological monitoring. Genetic

counselling was provided regarding autosomal recessive inheritance and recurrence risk.

## Conclusion

SCYL1-related CALFAN syndrome should be suspected in infants with fever-triggered ALF and low/normal-GGT cholestasis, particularly when there is consanguinity or a family history of unexplained infantile liver failure. The present case emphasizes that neurological and skeletal manifestations may be absent at first presentation, and that a severe hepatic course with persistent cholestasis can occur. Early genomic testing, systematic exclusion of low-GGT cholestasis differentials, proactive nutritional and infection-related supportive care, timely transplant referral for persistent severe hepatic dysfunction or recurrent ALF, and long-term neurological surveillance are the key practical lessons from this case.

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Written informed consent has been obtained from the patient

## Conflict of Interest

None to disclose

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None

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