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Case Report

SCYL1 deficiency and intrafamilial variability: Two cases from Kuwait

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ABSTRACT

Introduction: Biallelic pathogenic variants in *SCYL1* have been reported in 22 individuals to date. Also referred to as CALFAN syndrome (cholestasis, acute liver failure, and neurodegeneration), this condition is characterized by recurrent episodic acute liver failure (ALF) with low-GGT cholestasis and variable neurological manifestations. *SCYL1* deficiency disrupts intracellular vesicular trafficking, leading to hepatopathy and, in some cases, abnormal glycosylation.

Results: We report two Kuwaiti siblings homozygous for a pathogenic splice site variant in *SCYL1*(NM_020680.4): c.1386 + 1G > A p.?. The younger sibling, an 8-year-old female presented at 16 months with ALF, hepatosplenomegaly, global developmental delay, hypotonia, and gait instability. During liver crises, she demonstrated biochemical features including low-GGT cholestasis, coagulopathy, and transient glycosylation abnormalities. Liver biopsy revealed peri-sinusoidal fibrosis and mild steatosis. She experienced two additional ALF episodes at 26 months and 3 years, both resolving completely. Follow-up biochemical testing at age 5.5 years showed normalization of glycosylation patterns following hepatic recovery. In contrast, her 9-year-old brother, who carries the same homozygous variant, remains asymptomatic, with normal development, liver function and imaging.

Conclusion: To our knowledge, this is the first description of an asymptomatic individual homozygous for a pathogenic *SCYL1* variant. Our findings highlight striking intrafamilial variability in *SCYL1*-deficiency and emphasize the reversibility of glycosylation abnormalities and liver dysfunction upon clinical recovery.

1. Introduction

The etiology of pediatric acute liver failure (ALF) encompasses a wide range of causes, including infectious agents, metabolic disorders, drug-induced liver injury, and autoimmune diseases. However, in up to 50 % of cases, the cause remains indeterminate [1]. The increasing accessibility of exome sequencing has enabled the identification of monogenic etiologies in some of these previously unexplained ALF with pathogenic variants in genes such as *DGUOK*, *HMGCL*, *TRMU*, *EI*, *F2AK3*, and *NBAS* [2,3]. More recently, biallelic pathogenic variants in the *SCYL1* gene have been associated with recurrent, episodic ALF typically preceded by a febrile illness. This condition is also described in literature as CALFAN syndrome (low γ-glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration) [4]. It is characterized by a variable spectrum of neurological involvement, ranging from mild developmental delay to severe neurological phenotypes including spinocerebellar ataxia and neurodegeneration [5]. The hepatic manifestations are similarly heterogenous, ranging from self-limited episodes to progressive liver disease requiring liver transplantation in infancy [6]. Skeletal abnormalities have been documented in more than half of reported cases [6].

SCYL1- related disorder was initially identified in *SCYL1* knockout mouse models, which exhibited progressive motor neuron degeneration and spinocerebellar ataxia [7]. Subsequent studies revealed that *SCYL1* functions as a regulator of intracellular vesicular transport and maintains Golgi apparatus morphology [5]. Defective vesicular trafficking

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results in increased endoplasmic reticulum stress that predisposes hepatocytes to cytolysis, thereby providing a molecular explanation for the hepatic dysfunction observed in *SCYL1*-deficient individuals [8].

There have been 22 cases reported worldwide since it was first described in 2015 by Schmidt et al. [5] Here, we describe two additional cases: Kuwaiti siblings born to consanguineous parents, with a homozygous pathogenic variant in *SCYL1*. Interestingly, only the younger female sibling presented with developmental delay and recurrent episodes of acute liver failure, while her older brother remains phenotypically unaffected with no health issues.

2. Case description

2.1. Case 1

An 8-year-old Kuwaiti girl was born full-term to consanguineous parents via spontaneous vaginal delivery, with a birthweight of 2.9 kg. She developed neonatal jaundice on day 2 of life, which resolved spontaneously. She was noted to have poor feeding since birth. At 4 months of age, she was admitted for poor oral intake and abdominal distention. An abdominal ultrasound at that time was unremarkable. At 16 months, during a febrile illness, she developed yellow discoloration of the eyes and was admitted for three weeks, including a one-week stay in the pediatric intensive care unit for ALF and cholestasis. Extensive evaluation for ALF revealed direct hyperbilirubinemia, low albumin, deranged coagulation profile, and transaminitis with low gamma-glutamyl transferase (*GGT*). Infectious, metabolic, and immunologic workup failed to identify a cause. Further investigations showed abnormal glycosylation patterns with Type I and Type II abnormalities, consistent with congenital disorders of glycosylation (CDG). A liver biopsy at that time revealed peri-sinusoidal and perivenular fibrosis with mild steatosis. On physical examination at 16 months, she was noted to have hypotonia and delayed motor milestones including failure to walk, but no other neurological manifestations.

She subsequently experienced two additional episodes of cholestasis hepatitis associated with febrile illness: at 26 months and at 3 years of age. Both episodes required hospitalization but resolved completely with conservative management.

Clinical exome sequencing on DNA extracted from peripheral blood, as described by Bamshad et al. [9], revealed a homozygous pathogenic variant *SCYL1*(NM_020680.4): c.1386 + 1G > A p.?. This variant was previously reported by Chavany et al. in a compound heterozygous state [3]. Segregation analysis was performed to support the pathogenicity of the identified variant, particularly given that *SCYL1* deficiency is a recently described disorder and this specific splice-site variant has only been reported once previously. Testing of both parents confirmed heterozygous carrier status, and, notably, the patient's asymptomatic 8-year-old brother was also found to be homozygous for the same variant.

Following her last cholestasis episode at age 3 years, she made a full clinical recovery, with normalization of liver transaminases and liver function tests. However, developmental delays persisted, particularly in speech as well as fine and gross motor milestones. Although not ataxic, she exhibited gait abnormalities, including frequent falls and delayed motor acquisition. She began walking after age 2 years and continue to experience mild difficulty with activities such as climbing stairs, running, and jumping. At age 5-years-9-months, a follow-up carbohydrate-deficient transferrin (CDT) and N-glycan testing (performed as previously described) [10] showed normalization of the glycosylation pattern in the context of hepatic recovery (Table 1). A non-contrast brain MRI was unremarkable. Abdominal ultrasonography revealed mild hepatosplenomegaly (liver size = 13 cm) with mild residual periportal fibrosis. A repeat abdominal ultrasound at age 7-years revealed normalization of the liver and spleen sizes with no abnormalities. At her most recent evaluation at age 8-years, she demonstrated failure to thrive with weight at the 1st percentile, height at the 7th percentile, and head circumference at the 4th percentile. Academically, she is enrolled in third grade at a mainstream school and is performing well overall, though she demonstrates difficulty in mathematics. Her speech has improved through social interactions, though it remains mildly delayed. Importantly, her gait and motor development have also improved spontaneously over time without the need for physical or occupational therapy interventions.

Table 1
N-glycan analysis of case 1 in the setting of hepatic recovery.

N-glycan	Case 1	Ref. low	Ref. high
	%Total glycan	$N = 100$	
HexNAc2 (Man 0)	0.04	0.01	0.07
Hex1HexNAc2 (Man1 or Gal1)	0.08	0.01	0.10
Hex1HexNAc2n (Man2)	0.13	0.00	0.24
NeuAc1Hex1HexNAc2 (Tetra)	0.01	0.00	0.05
Hex3HexNAc (Man3)	0.26	0.02	0.42
Hex4HexNAc2 (Man4)	0.75	0.22	1.20
Neu5Ac1Hex4HexNAc4 (Mono-gal)	1.71	0.67	1.88
Neu5Ac2Hex5HexNAc4 (Di-sialo)	31.89	25.55	55.21

Serum N-glycan profile for case 1 measured at age 5 years 9 months after clinical recovery showing no glycosylation abnormalities.
Abbreviations: Ref: reference; Man: mannose; Gal: galactose; Tetra: tetrasaccharide.

2.2. Case 2

The second case her older male sibling, a 9-year-old who remains completely asymptomatic. He has exhibited normal developmental milestones, and his physical examination has been unremarkable. He has never experienced any episodes of ALF, and his liver enzymes and functions tests, including transaminases, bilirubin, and coagulation profile, have consistently remained within normal limits. Abdominal ultrasound and brain MRI obtained at age 7 years were both unremarkable. Despite being homozygous for the same pathogenic *SCYL1* variant identified in his sister, he has not demonstrated any clinical manifestations of the disorder despite history of mild febrile illnesses. A comparative summary between the clinical characteristics of the two siblings is shown in Table 2.

3. Discussion

We report two siblings with identical biallelic pathogenic variants in the *SCYL1* gene, bringing the total number of cases to 24. While the older male sibling remains completely asymptomatic with normal developmental milestones, the younger female sibling presents with recurrent ALF episodes and delayed development. These episodes were characterized by normal to mildly elevated GGT, consistent with prior reports [4,6,11,12], along with direct hyperbilirubinemia, transaminitis, hypoalbuminemia and coagulopathy.

Case 1 experienced three episodes of ALF, the last of which occurred at age 3-years. During one of these episodes, glycosylation testing revealed abnormal characteristics of both Type I and Type II patterns, consistent with CDG (Table 1). Follow-up testing at age 5, after complete hepatic recovery, showed normalization of these patterns. Similar transient glycosylation abnormalities, resembling a CDG- II pattern were reported by Lenz et al. in one of seven *SCYL1*-deficient individuals, exclusively during liver crises [4]. These findings suggest that the glycosylation abnormalities are secondary to hepatic dysfunction, possibly reflecting temporary Golgi dysfunction, rather than being a permanent feature of *SCYL*-1 deficiency [4].

This pattern supports the interpretation that glycosylation defects in *SCYL1* deficiency are secondary to hepatic dysfunction, rather than a primary feature of the disease. Mechanistically, liver injury can impair ER-Golgi trafficking, leading to temporary Golgi dysfunction and disrupted glycoprotein processing. *SCYL1* encodes a protein involved in coat protein complex I (COPI)-mediated vesicular transport, essential for

Table 2
Clinical comparison of siblings with identical SCYL1 variants.

	Sibling 1	Sibling 2
Date of Birth	Sep, 2016	Aug, 2015
Gender	Female	Male
Nationality	Kuwaiti	
Homozygous *SCYL1* variant	*SCYL1*(NM_020680.4):c.1386 + 1G > A	
Hepatology		
No. of acute liver failure episodes (age at each episode)	3 (16 m, 26 m, 3 y)	0
Hepatosplenomegaly	Yes (resolved by age 7 y)	No
Liver Biopsy (age at liver biopsy)	Peri-sinusoidal and periventricular fibrosis with mild steatosis (2 y)	Not performed
Neurology		
Walking independently	>2 years	12 months
Cognition	Normal	Normal
Neurological examination	Hypotonia, low muscle bulk, mild gait instability (resolved in childhood), normal reflexes	Unremarkable
Development	Speech and gross motor delay Failure to thrive	Normal
Skeletal Manifestations	No	No
MRI		
Cerebellar vermis atrophy	No	No
Optic nerve thinning	No	No

Genetic and clinical characteristics of case 1 and her unaffected sibling (case 2) with identical homozygous mutation SCYL1 c.1386 + 1G > A. Ages refer to time of assessment indicated in the text.
Abbreviations: ALF: acute liver failure; GGT: gamma-glutamyl transferase; MRI: magnetic resonance imaging; y: years; m: months.

recycling glycosylation enzymes within the Golgi. Disruption of this pathway can result in mislocalization of glycosyltransferases and defective glycan maturation. Similar transient glycosylation defects have been observed in related vesicular trafficking disorders, such as *NBAS* and *RINT1* deficiencies, further supporting a common stress-induced mechanism during hepatic decompensation [8,13].

Taken together, these findings support the hypothesis that transient glycosylation defects in SCYL1 deficiency reflect secondary Golgi dysfunction during liver crises, rather than a constitutive congenital disorder of glycosylation. Further studies are needed to clarify the mechanisms underlying these transient defects.

By age 7, Case 1 also exhibited resolution of previously documented hepatosplenomegaly. Hepatomegaly or hepatosplenomegaly appear to be a common feature in *SCYL1* deficiency, occurring in approximately 90 % of reported cases [3–6,11,12,14–17]. However, its progression varies: in some, it is transient and linked to acute liver crises [4], while in others, it persists despite recovery. For instance, Schmidt et al. described persistent hepatosplenomegaly in a 17-year-old, long after ALF episode had resolved [5]. Case 1 demonstrated a favorable outcome with complete hepatic recovery and no further episodes after age 3, supporting the notion of a self-limiting hepatic phenotype in some individuals. Nevertheless, disease severity remains highly variable, with approximately 4 of 22 previously reported cases requiring liver transplantation [4,6,14].

Neurologically, intrafamilial variability is also evident. Brain MRI in both Case 1 and her older asymptomatic brother was unremarkable. Case 1 exhibited hypotonia and delays in motor and speech development. By age 8, her gait instability had resolved, however, she continued to exhibit mild speech delay, reduced muscle bulk and tone and academic challenges, particularly in mathematics. This mild neurological involvement contrasts with more severe phenotypes reported in the literature, which have included learning difficulties, intellectual disabilities, stuttering, intention tremor, cerebellar signs, muscle atrophy, peripheral neuropathy, oculomotor abnormalities, and epilepsy [3–6,11,12,14–19]. Notably, no skeletal abnormalities were observed in either sibling.

The striking intrafamilial discordance in phenotype highlights the complexity of *SCYL1* deficiency. The brother, despite being homozygous for the same variant, remains completely asymptomatic, an observation not previously reported. This suggests a possible role for modifying genetic, epigenetic, or environmental factors. Environmental triggers, such as infections or febrile illnesses, may act as stressors that precipitate hepatic crises in genetically susceptible individuals. Lenz et al. reported transient glycosylation abnormalities in *SCYL1*-deficient patients during liver crises and proposed that such environmental stressors might unmask latent hepatic vulnerability in affected individuals [4]. On the genetic level, McNiven et al. described two *SCYL1*-deficient individuals and emphasized the importance of reassessing sequencing data to uncover additional contributing variants. They proposed that secondary genetic hits, regulatory variants, or polymorphisms in interacting pathways could modulate clinical severity [6]. A comparative study of vesicular trafficking disorders involving *NBAS*, *RINT1*, and *SCYL1* further suggested that host-specific stress response pathways, such as those regulating endoplasmic reticulum (ER) stress and autophagy, may serve as genetic modifiers contributing to interindividual variability in phenotype [8]. Epigenetic mechanisms may also play a role, though they remain underexplored in the context of *SCYL1* deficiency. Differential DNA methylation or histone modifications—potentially influenced by early-life exposures—could affect *SCYL1* expression or that of downstream effectors in hepatic or neural tissues.

The limited availability of long-term follow-up data in the existing literature complicates interpretation of disease progression and variability. Our findings emphasize the need for continued surveillance of both symptomatic and asymptomatic individuals with biallelic *SCYL1* variants, as well as longitudinal studies to define the natural history, identify predictive biomarkers, and guide future clinical management.

4. Conclusion

This report contributes to the limited but growing body of literature on *SCYL1* deficiency (CALFAN Syndrome), particularly regarding its natural history and genotype-phenotype correlation. Despite identical biallelic pathogenic variants, only one sibling exhibited recurrent cholestatic ALF and developmental delay, while the other remains asymptomatic, representing the first such intrafamilial discordance reported. Furthermore, our findings confirm that the glycosylation abnormalities associated with this condition are reversible following recovery of liver function.

Editorial policies and ethical considerations

This study was performed in accordance with ethical principles for medical research outlined in Declaration of Helsinki. This study was approved by the institutional review board of the Kuwait Ministry of Health and Kuwait Medical Genetics Center. Informed consent was obtained from all individuals for being included in the study. This article does not contain any studies on animal subjects.

CRediT authorship contribution statement

Laila Kazem: Writing – review & editing, Writing – original draft, Data curation. **Wafaa Al-Qabandi:** Writing – review & editing, Data curation. **Buthaina Albash:** Writing – review & editing, Data curation. **Reem Elshafie:** Writing – review & editing, Investigation, Formal analysis. **Miao He:** Writing – review & editing, Investigation, Formal analysis. **Hind Alsharhan:** Writing – review & editing, Data curation, Conceptualization.

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Declaration of competing interest

Laila Kazem, Wafaa Al-Qabandi, Buthaina Albash, Reem Elshafie, Miao He, and Hind Alsharhan declare that they have no conflicts of interest.

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Data availability statement

All data included in this study can be de-identified and shared upon reasonable request to the corresponding author.

References

[1] M.R. Narkewicz, D.D. Olio, S.J. Karpen, et al., Pattern of diagnostic evaluation for the causes of pediatric acute liver failure: an opportunity for quality improvement, J. Pediatr. 155 (6) (2009) 801–806.e1, https://doi.org/10.1016/j.jpeds.2009.06.005.

[2] D. Lenz, L.D. Schlieben, M. Shimura, et al., Genetic landscape of pediatric acute liver failure of indeterminate origin, Hepatology 79 (5) (2024) 1075–1087, https://doi.org/10.1097/HEP.0000000000000684.

[3] J. Chavany, A. Cano, B. Roquelaure, et al., Mutations in NBAS and SCYL1, genetic causes of recurrent liver failure in children: three case reports and a literature review, Arch. Pediatr. 27 (3) (2020) 155–159, https://doi.org/10.1016/j.arcped.2020.01.003.

[4] D. Lenz, P. McClean, A. Kansu, et al., SCYL1 variants cause a syndrome with low γ-glutamyl-transferase cholestasis, acute liver failure, and neurodegeneration (CALFAN), Genet. Med. 20 (10) (2018) 1255–1265, https://doi.org/10.1038/gim.2017.260.

[5] W.M. Schmidt, S.L. Rutledge, R. Schüle, et al., Disruptive SCYL1 mutations underlie a syndrome characterized by recurrent episodes of liver failure, peripheral neuropathy, cerebellar atrophy, and ataxia, Am. J. Hum. Genet. 97 (6) (2015) 855–861, https://doi.org/10.1016/j.ajhg.2015.10.011.

[6] V. McNiven, D. Gattini, I. Siddiqui, et al., SCYL1 disease and liver transplantation diagnosed by reanalysis of exome sequencing and deletion/duplication analysis of SCYL1, Am. J. Med. Genet. A 185 (4) (2021) 1091–1097, https://doi.org/10.1002/ajmg.a.62079.

[7] W.M. Schmidt, C. Kraus, H. Höger, et al., Mutation in the Scyl1 gene encoding amino-terminal kinase-like protein causes a recessive form of spinocerebellar neurodegeneration, EMBO Rep. 8 (7) (2007) 691–697, https://doi.org/10.1038/sj.embor.7401001.

[8] B. Peters, T. Dattner, L.D. Schlieben, T. Sun, C. Staufner, D. Lenz, Disorders of vesicular trafficking presenting with recurrent acute liver failure: NBAS, RINT1, and SCYL1 deficiency, J. Inherit. Metab. Dis. 48 (1) (2025) e12707, https://doi.org/10.1002/jimd.12707.

[9] M.J. Bamshad, S.B. Ng, A.W. Bigham, et al., Exome sequencing as a tool for Mendelian disease gene discovery, Nat. Rev. Genet. 12 (11) (2011) 745–755, https://doi.org/10.1038/nrg3031.

[10] H. Alsharhan, M. He, A.C. Edmondson, et al., ALG13 X-linked intellectual disability: new variants, glycosylation analysis, and expanded phenotypes, J. Inherit. Metab. Dis. 44 (4) (2021) 1001–1012, https://doi.org/10.1002/jimd.12378.

[11] A. Shohet, L. Cohen, D. Haguel, et al., Variant in SCYL1 gene causes aberrant splicing in a family with cerebellar ataxia, recurrent episodes of liver failure, and growth retardation, Eur. J. Hum. Genet. 27 (2) (2019) 263–268, https://doi.org/10.1038/s41431-018-0268-2.

[12] J.Q. Li, J.Y. Gong, A.S. Knisely, M.H. Zhang, J.S. Wang, Recurrent acute liver failure associated with novel SCYL1 mutation: a case report, World J. Clin. Cases 7 (4) (2019) 494–499, https://doi.org/10.12998/wjcc.v7.i4.494.

[13] T.M. Witkos, W.L. Chan, M. Joensuu, et al., GORAB scaffolds COPI at the trans-Golgi for efficient enzyme recycling and correct protein glycosylation, Nat. Commun. 10 (2019) 127, https://doi.org/10.1038/s41467-018-08044-6.

[14] M. Youssef, K.L. Mascia, B. McGuire, et al., CALFAN (low γ-glutamyl transpeptidase [GGT] cholestasis, acute liver failure, and neurodegeneration) syndrome: a case report with 3-year follow-up after liver transplantation in early adulthood, Case Rep. Hepatol. 2023 (2023) 3010131, https://doi.org/10.1155/2023/3010131.

[15] C. Spagnoli, D. Frattini, G.G. Salerno, et al., On CALFAN syndrome: report of a patient with a novel variant in *SCYL1* gene and recurrent respiratory failure, Genet. Med. 21 (2019) 1663–1664, https://doi.org/10.1038/s41436-018-0389-6.

[16] H.M. Isa, J.F. Alkaabi, W.H. Alhammadi, K.A. Marjan, Recurrent acute liver failure in a Bahraini child with a novel mutation of spinocerebellar ataxia-21, Cureus 15 (3) (2023) e36249, https://doi.org/10.7759/cureus.36249.

[17] D. Suenera, D. Navinumapathy, D.G. Chaudhary, S D., Acute on chronic liver disease in a child with *SCYL1* mutation: a rare pediatric case report, TPM Test Psychometr. Methodol. Appl. Psychol. 32 (S1) (2025) 1209–1214. Available from: https://tpmap.org/submission/index.php/tpm/article/view/755.

[18] T. Campos, E. Leão Teles, E. Rodrigues, C. Nogueira, L. Vilarinho, M. Leão, Two genetic disorders (TRMU and *SCYL1*) explaining transient infantile liver failure in one patient, Integr. Mol. Med. 7 (2020) 1–4, https://doi.org/10.15761/IMM.1000399.

[19] F. Incecik, O.M. Herguner, P. Willems, N.O. Mungan, Spinocerebellar ataxia-21 in a Turkish child, Ann. Indian Acad. Neurol. 21 (1) (2018) 68–70, https://doi.org/10.4103/aian.AIAN_415_17.