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A novel homozygous *NR1H4* mutation in idiopathic elevated transaminases

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ABSTRACT

We describe a patient with a homozygous loss-of-function mutation in *NR1H4*, presenting with idiopathic mild elevation of transaminases. His presentation differs from the limited previously reported cases of progressive familial intrahepatic cholestasis type 5 (PFIC5).

Case report: A 7-year-old boy was admitted to our outpatient clinic due to persistently elevated transaminases since 12 months of age. While PFIC5 is typically a rapidly progressive disease requiring liver transplantation, this patient's laboratory results showed normal gamma-glutamyl transferase (GGT), international normalized ratio (INR), albumin, and alpha-fetoprotein (AFP) levels. Liver biopsy revealed only mild fibrosis. Over a two-year follow-up, he has remained stable with mild transaminase elevation.

Conclusion: Infants with cryptogenic liver disease should be evaluated for *NR1H4* mutations-associated PFIC5. This mutation may represent a novel metabolic etiology of idiopathic, mildly elevated transaminases.

***Keywords**: child; transaminases; loss of function mutation; genes;* NR1H4.

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INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of rare inherited disorders characterized by defects in bile transport and secretion, leading to intrahepatic cholestasis during infancy or childhood.[1] PFIC types are classified from 1 to 6 based on the affected gene.[2,3] Mutations in the ATP-transporter genes *ATP8B1, ABCB11*, and *ABCB4* are responsible for the most common subtypes, PFIC types 1, 2, and 3, respectively.[3,4] More recently described subtypes include PFIC4 (tight junction protein 2 mutation, *TJP2*), PFIC5 (*NR1H4* mutations), and PFIC6 (*MYO5B* related cholestasis), as well as undefined forms associated with *SLC51A, USP53, KIF12, LSR*, and *WDR83OS* mutations.[2] PFIC5, one of the PFIC variants, was first described in 2016 and is caused by mutations in *NR1H4* gene, which encodes the farnesoid X receptor (FXR), a bile acid-activated transcription factor required for bile acid homeostasis.[5] However, data on FXR-related PFIC5 in children are scarce, with only a few case reports in the literature.[4-6] Here, we report a patient with homozygous *NR1H4* loss-of-function mutation diagnosed through genetic panel testing.

CASE REPORT

A 7-year-old boy was admitted to our outpatient clinic with persistently elevated transaminase levels since he was 12 months old. He was born to consanguineous parents (first cousins). His older sister had a history of neonatal cholestasis, elevated alpha-fetoprotein (AFP), splenomegaly, ascites, bilateral hydronephrosis, and nephrocalcinosis. Genetic testing was not performed at the time, and she died at 8.5 months due to end-stage liver failure *(Table 1)*. Initial laboratory findings for the patient showed elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), low gamma-glutamyltranspeptidase (GGT), and normal total bilirubin (TB), conjugated bilirubin (CB), albumin (ALB), and alpha-fetoprotein (AFP) levels. Screening for toxoplasmosis and viral infections, including hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, rubella, and human immunodeficiency virus (HIV), was negative. Autoimmune hepatitis was ruled out due to repeatedly normal titers of antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver/kidney microsome antibodies, as well as normal serum immunoglobulin G levels for age. Liver histology revealed mixed portal inflammation, periportal interface hepatitis, confluent and focal necrosis. No hepatocellular accumulation was seen with periodic acid–Schiff stain. Reticulin staining showed a normal reticulin roof. Masson's trichrome staining showed portal area fibrosis with short fibrous septa. According to the Ishak score system, necroinflammatory activity was 5/18, and fibrosis was scored 2/6 *(Table 1)*. Due to the family history, Next-Generation Sequencing (NGS) and Whole Exome Sequencing (WES) analysis were performed, identifying a homozygous c.526C>T (p.Arg176*, NM_001206979.2, dbSNP rs113090017) nonsense variant in *NR1H4* gene. This variant introduces a premature stop codon and is classified as a pathogenic mutation in the National Center for Biotechnology Information (NCBI) ClinVar database. Sequencing of *ATP8B1* and *ABCB11* genes was normal. Despite the homozygous mutation, the patient has not shown clinical deterioration in the follow-up. Both parents were heterozygous for the variant but had normal liver function, and there were no signs of cholestasis during either maternal pregnancy. Written informed consent was obtained from the parents for publication of this case.

DISCUSSION

A heterozygous *NR1H4* mutation was first described in 2012 in a patient from China. That patient presented with high levels of bilirubin, alanine aminotransferase, gamma-glutamyltransferase, cirrhosis, and ascites. The data suggest that *NR1H4* mutations may lead to FXR loss of function and impaired regulation of bile production and secretion. However, the heterozygous parents of our patient had normal liver biochemistry and showed no signs of liver dysfunction. The mother did not experience cholestasis in either of her two pregnancies. Our findings differ from a previous report of severe infantile cholestasis in an individual heterozygous for the same mutation.[5,6] In 2016, pathogenic variants in *NR1H4* were first associated with low GGT cholestasis and later classified as PFIC5.[5] To date, only 13 patients from 10 unrelated families have been reported. Most cases presented as rapidly progressive liver failure, vitamin K-independent coagulopathy, high AFP levels, and ultimately required liver transplantation to preserve their life. Eight patients were male, four were female, and one patient's sex was unknown. All were born at term without maternal or fetal complications. Twelve of the 13 patients

Table 1. Summary of clinical and laboratory findings of the patient and his sister

	Patient		Patient's sister
Sex	Male		Female
Age at onset	12 months		2 days
First evaluation	7 years		28 days
Signs	Mildly elevated transaminases		Nefrocalcinosis, splenomegaly, ascites, encephalopathy
Symptoms	-		Jaundice
Laboratory	***Initial***	***Actual***	***Before death***
ALT (U/L)	87	182	109
AST (U/L)	58	93	390
GGT (U/L)	9	9	31
Direct bilirubin (mg/dl)	0.15	0.1	16
AFP (ng/ml)	2.16	2	425 572
INR	1.06	1.05	3.3
PLT (/mL)	295 000	336 000	99 000
Histopathology	Non-specific inflammation, mild fibrosis		Ductopeny, fibrosis
Outcome	Alive; 9-year-old		Died at 8.5-month-old before liver transplantation

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; AFP: alpha-fetoprotein; INR: international normalized ratio; PLT: platelet.

presented with neonatal jaundice, with a median age of onset of 7 days after birth.[3-5,7] At initial evaluation, all reported patients had conjugated hyperbilirubinemia, elevated aminotransferases, elevated AFP, low to normal GGT, and prolonged INR.[3-5,7]

Clinical manifestations included cholestasis (13/13), persistently elevated AFP (11/11), coagulopathy (11/11), hypoglycemia (9/13), splenomegaly (7/13), hyperammonemia (7/13), failure to thrive (8/13), and hepatomegaly (6/13). Six patients underwent liver transplantation at a median age of 6.2 months. Only one patient died from acute infection one year after transplantation, while the other seven, who did not receive transplantation, died at a median age of 5 months (range 1.2-8). Eight patients had homozygous genotype and five had compound heterozygous genotypes.[3-5,7] Our case shows different characteristics from the previously reported cases. PFIC5 has been described as a rapidly progressive disease, whose natural history is unaffected by medical interventions and leading to liver transplantation. However, our 9-year-old patient did not experience neonatal cholestasis, developmental delay, respiratory distress, or liver failure. His laboratory findings have consistently shown normal GGT, INR, albumin, and AFP levels, with only persistent mild hypertransaminasemia. He has remained clinically stable over the past two years. These findings suggest that a strict genotype-phenotype correlation may not be present in all cases. Accurate diagnosis of PFIC5 is critical for optimal management, timely therapeutic intervention, and prevention of complications before end-stage liver disease develops. Infants with cryptogenic liver disease should be evaluated for *NR1H4* mutations. This mutation may represent a novel metabolic genetic cause of idiopathic mild transaminase elevation. ■

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