Journal of Clinical and Translational Hepatology **2025** vol. 13(2) | 173–177
DOI: 10.14218/JCTH.2024.00304

Illuminating and Instructive Clinical Case

Ferrochelatase Gene Variants Associated with Cholestasis in Adults: A Case Report

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Received: August 23, 2024 | **Revised:** October 21, 2024 | **Accepted:** November 05, 2024 | **Published online:** November 28, 2024

Abstract

We reported a case of recurrent liver dysfunction in an adult patient with a history of abnormal liver enzymes persisting for over ten years. The primary abnormalities included elevated levels of gamma-glutamyl transferase and alkaline phosphatase. Despite conducting a series of extensive etiological tests to identify common causes of liver disease, the diagnosis remained unclear. However, whole-exome next-generation sequencing revealed a homozygous intronic mutation in the ferrochelatase gene (c.315-48T>C), which may be associated with the patient's cholestasis.

Citation of this article: Lu X, Liu K, Zheng W, Zhang X, Shi J, Yu S, *et al*. Ferrochelatase Gene Variants Associated with Cholestasis in Adults: A Case Report. J Clin Transl Hepatol 2025;13(2):173–177. doi: 10.14218/JCTH.2024.00304.

Introduction

Ferrochelatase (FECH) is the terminal enzyme in the heme biosynthetic pathway, catalyzing the insertion of iron into protoporphyrin to form heme. In the pathological condition, the activity of FECH is markedly decreased or even absent due to the abnormality of gene regulation, which causes excessive accumulation of protoporphyrin in erythrocytes, plasma, skin and liver, leading to the corresponding clinical symptoms.[1,2] Its typically characterized by cutaneous photosensitivity with burning, tingling, and itching within minutes of sun or UV exposure, followed later by erythema and swelling.[3] Liver complications only occur in a very small number of patients.[4] Here, we report a case of adult-onset cholestasis possibly caused by *FECH* mutation, which exhibited recurrent liver dysfunction, especially elevated γ-glutamyl transpeptidase.

Case presentation

A 43-year-old male presented to the hepatology clinic with recurrent abnormal liver enzymes: γ-glutamyl transpeptidase (GGT) 890 U/L (normal 10–60 U/L), alkaline phosphatase (ALP) 171 U/L (normal 45–125 U/L), and alanine aminotransferase 105 U/L (normal 9–50 U/L). Blood lipid tests showed total cholesterol 7.58 mmol/L (normal < 5.81 mmol/L), triglycerides 4.12 mmol/L (normal < 1.70 mmol/L), low-density lipoprotein cholesterol 4.64 mmol/L (normal < 3.37 mmol/L), and high-density lipoprotein cholesterol 0.92 mmol/L (normal 1.16–1.42 mmol/L). The patient was diagnosed with obvious cholestasis and hyperlipidemia. Clinical examination findings are shown in Table 1. Routine tests, including blood, urine, stool, iron, transferrin, 25-OH-vitamin D, renal function, thyroid, and coagulation tests, were within normal limits. An extensive etiological examination was performed to investigate common causes of liver disease. Serological tests for viral markers, autoimmune markers, humoral immune markers, ceruloplasmin, and α1-antitrypsin were negative, ruling out viral infections, autoimmune hepatitis, Wilson's disease, and α1-antitrypsin deficiency. The physical examination was unremarkable. The electrocardiogram and cardiac ultrasonography showed normal results. Ultrasonography indicated the presence of fatty liver. Liver magnetic resonance elastography showed increased liver stiffness, with an elastic value of approximately 2.76 kPa, corresponding to a fibrosis stage of F2. Abdominal magnetic resonance cholangiopancreatography revealed no biliary abnormalities. The patient had no history of smoking, alcohol consumption, or other drug abuse, no history of blood transfusion or exposure to epidemic water or areas, no cholestasis in childhood, and no relevant family history.

Further H&E staining of liver biopsy tissue obtained by puncture sampling revealed a clear lobular structure with approximately six portal areas, partial loosening of hepatocytes within the lobule, scattered focal necrosis, and occasional cholestasis. Additionally, fatty degeneration of some hepatocytes (mixed type, accounting for about 40% of the sample) was observed, along with mild chronic inflammatory cell in-

Keywords: FECH; Cholestasis; Liver dysfunction; Adult patient; Case report.
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Table 1. Clinical examination results of the patient

Parameter	Value	Normal range
Liver function		
ALT (U/L)	105	7–40
AST (U/L)	32	13–35
ALP (U/L)	171	35–100
GGP (U/L)	890	7–45
Total bilirubin (μmol/L)	12.5	0–23
Albumin (g/dL)	47.4	40–55
Kidney function		
Serum creatinine (μmol/L)	71	41–73
Blood urea nitrogen (mmol/L)	6.3	2.6–7.5
Blood lipids		
Total cholesterol (mmol/L)	7.58	<5.81
Triglyceride (mmol/L)	4.12	<1.70
Low-density lipoprotein cholesterol (mmol/L)	4.64	<3.37
High-density lipoprotein cholesterol (mmol/L)	0.92	1.16–1.42
Virological indicators		
Hepatitis A virus	(−)	(−)
Hepatitis B virus	(−)	(−)
Hepatitis C virus	(−)	(−)
Hepatitis D virus	(−)	(−)
Hepatitis E virus	(−)	(−)
Syphilis	(−)	(−)
Herpes virus	(−)	(−)
Cytomegalovirus	(−)	(−)
Rubella	(−)	(−)
Toxoplasmosis	(−)	(−)
Parvovirus	(−)	(−)
Human immunodeficiency virus	(−)	(−)
Autoimmune liver disease antibodies		
Antinuclear	(−)	(−)
Antimitochondrial	(−)	(−)
Anti-smooth muscle	(−)	(−)
Anti-liver-kidney microsomal antigen-1	(−)	(−)
Anti-liver cytosol-1	(−)	(−)
Gamma globulin	(−)	(−)
Humoral immune markers		
IgG (g/L)	12.4	8.6–17.4
IgA (g/L)	2.27	1.0–4.2
IgM (g/L)	1.23	0.3–2.2
IgE (U/mL)	25.6	0–100
C3 (g/L)	1.06	0.7–1.4
C4 (g/L)	0.3	0.1–0.4

(continued)

Table 1. *(continued)*

Parameter	Value	Normal range
Iron (μmol/L)	18.2	10.6–36.7
Transferrin (g/L)	2.69	2.0–3.6
Ceruloplasmin (mg/L)	272	150–600
α1-antitrypsin (U/L)	1.15	0.85–2.13
Thyroid functions		
Free triiodothyronine (pmol/L)	4.94	3.1–6.8
Free thyroxine (pmol/L)	17.7	12–22
Thyroid stimulating hormone (mIU/L)	1.71	0.27–4.20
Thyroglobulin (ng/mL)	10.74	3.5–77
Thyroglobulin antibody (IU/mL)	12.05	0–115
Thyroid peroxidase autoantibody (IU/mL)	12.50	0–34
Coagulation functions		
Prothrombin time (s)	11.4	10.4–12.7
INR	0.96	0.85–1.15
Imaging examination		
Electrocardiogram	Normal	N/A
Cardiac ultrasonography	Normal	N/A
Abdominal ultrasonography	Fatty liver	N/A
Liver magnetic resonance elastography	Fibrosis (METAVIR F2), Fatty liver	N/A
Abdominal MRCP	Normal	N/A

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; INR, international normalized ratio; MRCP, magnetic resonance cholangiopancreatography; N/A, not applicable.

filtration in the portal areas. No abnormalities were noted in the small bile ducts or small blood vessels, but fibrous tissue hyperplasia was observed, with some extending into the lobules, indicating a fibrosis stage of S1-2 (Fig. 1A–C). Masson staining further confirmed collagen fiber deposition (Fig. 1D). Immunohistochemical staining showed CK7 (bile duct +), CK19 (bile duct +), CD34 (vessel +), CD8 (lymphocyte +), HBsAg (−), and HBcAg (−). These pathological examination results were consistent with the imaging findings, confirming fatty liver, but the cause of cholestasis remained undetermined. Upon further questioning, the patient revealed that abnormal liver function had been detected 16 years ago, but he exhibited no clinical symptoms such as fatigue, loss of appetite, abdominal distension or pain, or other extrahepatic manifestations. During this period, he sought treatment at multiple hospitals, but the underlying cause remained unclear. For over ten years, he has intermittently taken compound glycyrrhizin tablets and other similar drugs for liver protection and enzyme lowering, but liver enzyme levels remained consistently elevated. The current serological, imaging, and pathological results did not adequately explain the elevated biliary enzymes. Consequently, gene variant analysis of the patient's whole exome and adjacent splicing regions revealed a homozygous intronic variation in the *FECH* gene: c.315-48T>C. Verification through both second-generation and first-generation sequencing confirmed the accuracy and reliability of this variation (Fig. 2). We recommended that the patient's relatives undergo pedigree verification and receive genetic counseling.

The patient was treated with ursodeoxycholic acid to stimulate bile flow, along with liver protection and lipid-lowering therapies, resulting in partial improvement of symptoms and liver function test results (Fig. 3).

Discussion

Complete or partial deficiency of FECH due to mutations can result in erythropoietic protoporphyria (EPP, OMIM: 177000).[5] EPP is a rare genetic disorder with autosomal recessive inheritance (very rare) and autosomal dominant incomplete penetrance.[6] The primary symptom of EPP is painful skin photosensitivity, typically manifesting in early childhood. Many patients also experience chronic anemia, iron deficiency, and low vitamin D levels. Liver complications are rare and occur in only a small subset of patients. When protoporphyrin accumulates in the liver, it can lead to protoporphyrin liver disease, which may cause severe abdominal pain, particularly in the upper right quadrant, and jaundice. Since protoporphyrin is fat-soluble, it must be excreted from the liver into the intestinal tract via bile. Excessive accumulation can disrupt bile excretion, resulting in intrahepatic protoporphyrin mixed with cholestasis and the formation of microbiliary plugs. Pathological examination often reveals numerous brown-yellow to brown granular deposits in hepatocytes, Kupffer cells, hepatic sinusoids, and microbiliary ducts, accompanied by microbiliary plug formation. Polarizing microscopy shows characteristic red birefringence and Maltese crosses.[7,8] In our case, the patient presented with liver dysfunction, particularly elevated GGT, but did not exhibit abdominal pain, cutaneous photosensitivity, or hematological manifestations.

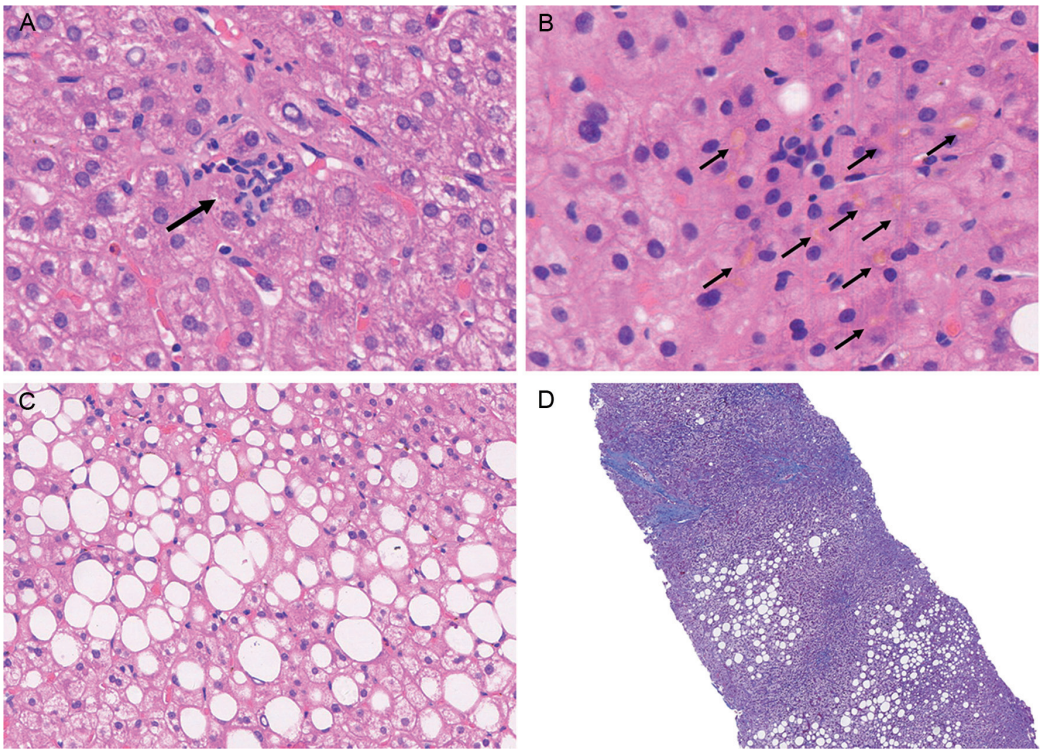

Fig. 1. Microphotographs showing (A) focal necrosis (black arrow; 400×); (B) cholestasis (black arrows; 400×); (C) fatty degeneration of hepatocytes (200×); (D) Masson stain positive (4×).

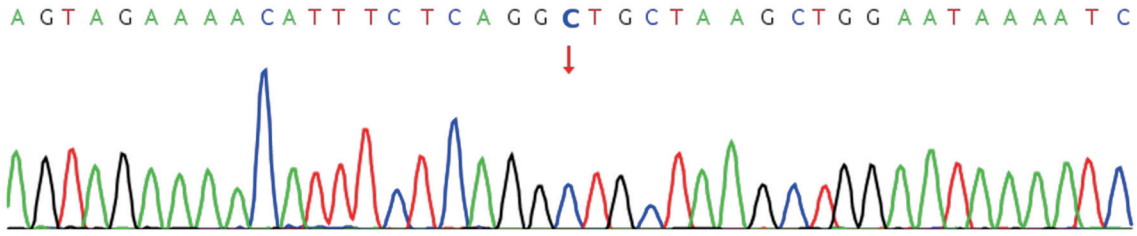

Fig. 2. First-generation sequencing peak map. The peak marked with an arrow indicates the homozygous nucleotide variant c.315-48T>C.

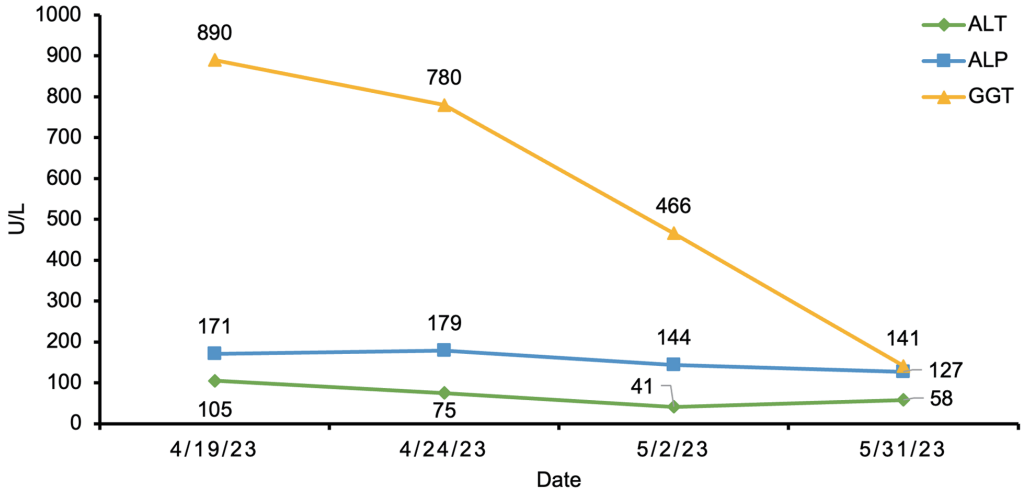

Fig. 3. Liver function test results. ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase.

Furthermore, the liver biopsy did not show protoporphyrin deposits in hepatocytes. Due to the lack of specific symptoms and typical indicators, we are currently unable to determine the patient's diagnosis.

Numerous mutations in the *FECH* gene have been identified, primarily consisting of null allelic mutations, with a small number of missense mutations. *Minder et al*. established a significant genotype-phenotype association between *FECH* "null allele" mutations and liver complications.[9] However, accumulated evidence suggests that these mutations alone do not fully explain the severe liver disease phenotype, as the same mutations have been observed in asymptomatic family members of patients with liver disease, as well as in patients who did not develop liver disease.[10,11] Among these mutations, c.315-48T>C (also referred to as IVS3-48T>C), a known hypomorphic allele located within intron 3, results in residual ferrochelatase activity and is considered a necessary but insufficient pathogenic variant for overt clinical symptoms.[12,13] Current cases indicate that individuals carrying the c.315-48T>C mutation are typically asymptomatic or exhibit only mild symptoms, while significant clinical manifestations tend to arise only when other variants that severely disrupt FECH activity are present. In contrast, our patient exhibited recurrent abnormal elevations of ALP and GGT. This observation, along with similar findings from other studies, highlights the heterogeneity and specificity of *FECH* gene mutations. Further research is essential to elucidate these complexities.

As a rare genetic mutation, there is currently no specific treatment available. Consequently, patient management primarily focuses on symptom relief. Ursodeoxycholic acid (UDCA) is a medication commonly used to treat cholestatic hepatopathies. This hydrophilic dihydroxy bile acid enhances the secretion of endogenous bile acids, increases the proportion of hydrophilic bile acids, and mitigates the cytotoxic effects of hydrophobic bile acids, thereby offering protective benefits to liver and bile duct cells.[14] Following UDCA treatment, the patient's ALP and GGT levels, key indicators of cholestasis, showed significant reduction, and the patient's symptoms improved partially. We anticipate the development of more therapeutic strategies involving gene regulation in the future to address patients' conditions more effectively.

Conclusions

We present a case of a patient with unexplained, long-term recurrent liver enzyme abnormalities that improved with UDCA treatment. The patient's symptoms may be associated with the c.315-48T>C variant of the *FECH* gene. This observation contributes new insights into the relationship between *FECH* allele abnormalities and clinical symptoms.

Funding

This work was supported by grants from the National Natural Science Foundation of China (82222074, 82074154), the Shuguang Program of the Shanghai Education Development Foundation and the Shanghai Municipal Education Commission (23SG38), the Youth Tip-top Talent Program in Shanghai, and the High-Level Key Discipline of the State Administration of Traditional Chinese Medicine (ZYYZDXK-2023060).

Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Study concept and design (XL, WZ), acquisition of data (SY, XZ), drafting of the manuscript (XL, JS), critical revision of the manuscript (HF, KL), administrative, technical, or material support (ZY), and study supervision (YG). All authors have approved the final version and publication of the manuscript.

Ethical statement

The study was performed in accordance with the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report.

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