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Case Report

# Dubin-Johnson Syndrome and Familial Hypercholanemia Type 2 in Infant Patient - Impact of Two Genes on Liver Cholestasis: Case Report and Literature Review

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## Abstract

**Background:** Dubin-Johnson syndrome (DJS) and familial hypercholanemia (FHC) are rare hereditary cholestatic liver diseases affecting bilirubin and bile acid metabolism, respectively. DJS is characterized by chronic conjugated hyperbilirubinemia without significant liver dysfunction, whereas FHC leads to elevated serum bile acids and potential malabsorption of fat-soluble vitamins. While both conditions have been individually reported, their coexistence in a single patient is extremely rare. This case report describes a pediatric patient diagnosed with both conditions, highlighting the unique genetic findings and clinical presentation. It contributes to the understanding of overlapping cholestatic disorders and emphasizes the role of genetic testing in early diagnosis and management.

**Case Summary:** We report the case of a 13-month-old Chinese male who presented with persistent jaundice since birth, scleral icterus, and clay-colored stools. Liver function tests showed direct hyperbilirubinemia with mild transaminases and preserved synthetic liver function. Imaging studies, including hepatobiliary scintigraphy, ruled out biliary atresia. A comprehensive genetic panel identified two heterozygous variants in the ABCC2 gene, suggestive of DJS, and a heterozygous pathogenic variant in the SLC10A1 gene, associated with FHC2. Our patient remained asymptomatic, with only transitory peaks of mildly elevated transaminases. Treatment with ursodeoxycholic acid and fat-soluble vitamin supplementation led to improvement.

**Conclusion:** This case highlights the clinical implications of coexisting DJS and FHC2. It underscores the importance of genetic testing in pediatric cholestatic liver diseases for accurate diagnosis and tailored management. The coexistence of DJS and FHC2 suggests that multiple genetic defects may contribute to disease severity, necessitating long-term follow-up and monitoring for potential complications.

**Keywords:** Dubin-Johnson Syndrome; Familial Hypercholanemia; Cholestatic Liver Disease; Genetic Liver Disorders; Pediatric Hepatology; Case Report

## Core Tip

This case report describes a rare paediatric patient with coexisting Dubin-Johnson syndrome (DJS) and familial hypercholanemia type 2 (FHC2), both contributing to neonatal cholestatic liver disease. Genetic testing revealed two heterozygous ABCC2 variants linked to DJS and a heterozygous pathogenic *SLC10A1* variant associated with FHC2. The patient remained asymptomatic with transitory peaks of mild liver enzyme elevation, improving with ursodeoxycholic acid and vitamin supplementation. This case highlights the significance of genetic testing in diagnosing rare cholestatic disorders and the potential impact of dual genetic mutations on disease presentation and management.

## Introduction

Cholestatic liver disease encompasses a variety of conditions in which bile flow from the liver is disturbed, reduced, or blocked, leading to a buildup of bile acids and bilirubin in the liver [1]. This condition can result in jaundice, liver damage, and issues with fat-

soluble vitamin absorption [2]. Among hereditary cholestatic disorders in children, Dubin-Johnson syndrome and familial hypercholanemia are two distinct forms of cholestatic liver disease in pediatric patients.

Dubin-Johnson syndrome (DJS) and familial hypercholanemia (FHC) are very rare hereditary conditions impacting bilirubin and bile acid metabolism, respectively [3]. DJS causes chronic conjugated hyperbilirubinemia, often with minimal symptoms, and distinct dark pigmentation in the liver due to pigment deposition [4]. FHC, associated with high serum bile acid levels, leads to persistent itching, fat malabsorption, and complications from fat-soluble vitamin deficiencies [5].

We report a child diagnosed with two genetic disorders, Dubin-Johnson syndrome and familial hypercholanemia, both of which manifested as cholestatic liver disease during the neonatal period.

## Case Presentation

Our patient is a 13-month-old Chinese male who presented with jaundice and scleral icterus since birth. He was born at 38 weeks via elective C-section, and is exclusively breastfed baby. The patient has no history of ABO or Rh incompatibility, and newborn screening result is normal. The jaundice persisted beyond two weeks of age, associated with clay-coloured stools and normal bowel movements. Clinical examination revealed jaundice discolouration and scleral icterus. Cardiac, respiratory, and neurological examinations are normal. Abdomen is soft and lax, with no hepatosplenomegaly, ascites, or oedema. There is no family history of liver disease. The liver function test showed direct hyperbilirubinemia, and mild Liver transaminases, with preserved protein synthetic function, PT-PTT, and albumin levels. Findings indicated neonatal cholestasis, biliary atresia was ruled out [6] after a normal liver ultrasound and a normal HIDA scan, which showed timely bile excretion [7]. A comprehensive diagnostic workup was performed, which excluded congenital infection, metabolic disorders, and endocrinopathies as causes of cholestatic liver disease. Patient started on Ursodeoxycholic acid and vitamins A, D, E, K supplementation.

Genetic liver panel testing (a 53-gene panel) revealed two heterozygous variants (c.577-3C>T and c.2620+3A>G) of unknown significance in the ABCC2 gene. Defects in the ABCC2 gene cause disorders, including Dubin-Johnson syndrome [MIM: 237500]. Additionally, a heterozygous likely pathogenic variant c.729_730del (p.Phe244LeufsTer33) in the SLC10A1 gene is also detected. Defects in the SLC10A1 gene cause disorders, including familial hypercholanemia 2 [MIM: 619256].

## Discussion

Dubin-Johnson syndrome (DJS) is a rare hereditary condition characterized by a chronic elevation of conjugated bilirubin levels due to a defect in bilirubin excretion by hepatocytes. This condition leads to persistent, often asymptomatic hyperbilirubinemia, typically without liver dysfunction. A hallmark feature of Dubin-Johnson syndrome is the accumulation of a melanin-like pigment within liver cells, giving the liver its characteristic dark, almost black appearance [8]. Additionally, it affects the metabolism of coproporphyrin, specifically causing increased excretion of coproporphyrin I in the urine [9], a unique diagnostic marker for the syndrome. Dubin-Johnson syndrome is caused by a defect in the multidrug resistance protein 2 gene (ABCC2), located on chromosome 10 [10].

Our patient was found to have two heterozygous variants of uncertain significance in the ABCC2 gene: c.577-3C>T and c.2620+3A>G. This double heterozygosity of the ABCC2 gene is suggestive of Dubin-Johnson syndrome in our patient, a condition characterized by asymptomatic hyperbilirubinemia without liver dysfunction. However, given the classification of these variants as variants of uncertain significance (VUS), a definitive diagnosis cannot be established. Furthermore, next-generation sequencing (NGS) of the ABCC2 gene may help detect additional mutations associated with DJS. While the presence of these variants in our patient suggests a possible genetic predisposition, their clinical significance remains inconclusive at this time.

Familial hypercholanemia (FHC) is a very rare autosomal recessive disorder marked by elevated serum bile acid levels, leading to persistent itching, fat malabsorption, and related health issues. Due to bile acid build-up, patients often experience poor nutrient absorption, particularly of fat-soluble vitamins like A, D, E, and K. This deficiency can result in complications, including growth delays, rickets, and coagulation issues [5]. FHC typically follows an autosomal recessive inheritance pattern and shows genetic heterogeneity with three reported types. FHC1 is linked to six genes associated with familial hypercholanemia type 1, with the TJP2 and BAAT genes most commonly implicated [11], especially in Amish populations. FHC2 (NTCP deficiency) is linked to the SLC10A1 gene (Solute Carrier Family 10 Member 1) [12], while FHC3 is linked to the BAAT gene (Bile Acid-CoA: Amino Acid N-Acyltransferase) [13].

Our patient was found to have a heterozygous likely pathogenic variant, c.729_730del (p.Phe244LeufsTer33), in the SLC10A1 gene. Defects in the SLC10A1 gene cause disorders, including familial hypercholanemia type 2 [MIM: 619256]. SLC10A1 encodes a protein that belongs to the sodium/bile acid cotransporter family. This protein plays a role in bile acid reabsorption [14]. In our patient,

a heterozygous pathogenic variant, c.729_730del in the SLC10A1 gene, was detected. For diseases with autosomal recessive inheritance, both copies of the gene are expected to have causal variants; however, a second variant in the gene was not detected in this patient, although the possibility of a variant not detectable by NGS cannot be excluded. Furthermore, FHC has been reported to have a complex inheritance pattern [13]. In familial hypercholanemia 2 (FHCA2) (NTCP deficiency), most patients are asymptomatic and show no liver dysfunction, although some neonates may present with transient jaundice or transiently elevated liver enzymes. These abnormalities improve with age. The bile acid defect can result in impaired absorption of fat-soluble vitamins, including vitamins D and K, potentially causing reduced bone mineral density or prolonged prothrombin time (PT) [5].

Our patient remained asymptomatic, with normal bilirubin levels and reduced serum bile acid after ursodeoxycholic acid treatment; however, he continued to have transitory peaks of mild elevated transaminases (less than 100 U/L) throughout the course of the disease, with preserved synthetic liver function. In the literature, approximately 25 patients have been reported to have familial hypercholanemia type 2 (FHCA2), most of whom are of Chinese ethnicity and have different mutations in the SLC10A1 gene [13]. A search of PubMed and Wanfang databases retrieved 11 studies, including 60 paediatric NTCP deficiency patients, from January 2015 to November 2020. In one center, hypercholanemia was documented in 12 out of 12 patients (100%) with prolonged neonatal jaundice [15].

## Conclusion

We report an infant patient with two defective genes – a double heterozygous mutation for Dubin-Johnson syndrome and a heterozygous mutation for familial hypercholanemia type 2 – representing two rare and distinct cholestatic liver diseases, DJS and FHC2. Furthermore, the presence of two genetic liver disorders in the same patient may have a greater impact on liver disease progression. Our case report contributes to the existing literature and aids in phenotype-genotype distinction for these rare liver diseases in children. Early genetic testing can guide treatment strategies, including targeted therapies and monitoring for complications. This case underscores the need for further research into the combined impact of multiple genetic defects on liver disease progression, management, and long-term outcomes.

## Conflict of Interest Statement

The authors declare no conflict of interest.

## Ethics Statement

Informed patient consent was obtained from the family for the publication of this manuscript.

## Bibliography

1. Memon N., *et al*. "Inherited disorders of bilirubin clearance". *Pediatric Research* 79.3 (2016): 378-386.
2. Shah R and John S. "Cholestatic Jaundice. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing (2025).
3. Memon N., *et al*. "Inherited disorders of bilirubin clearance". *Pediatric Research* 79.3 (2016): 378-386.
4. Talaga ZJ and Vaidya PN. "Dubin-Johnson Syndrome". In: StatPearls. Treasure Island (FL): StatPearls Publishing (2025).
5. Hypercholanemia, familial, 2 - NIH Genetic Testing Registry (GTR) - NCBI (2025).
6. Liu T., *et al*. "Neonatal Dubin-Johnson Syndrome and its Differentiation from Biliary Atresia". *Journal of Clinical and Translational Hepatology* 11.1 (2023): 163-173.
7. Brahee DD and Lampl BS. "Neonatal diagnosis of biliary atresia: a practical review and update". *Pediatric Radiology* 52.4 (2022): 685-692.
8. Zhao C., *et al*. "Clinical and pathological features of Dubin-Johnson syndrome]". *Zhonghua Bing Li Xue Za Zhi* 50.8 (2021): 929-933.
9. Kondo T., *et al*. "Coproporphyrin isomers in Dubin-Johnson syndrome". *Gastroenterology* 70.6 (1976): 1117-1120.
10. Sharma P and Sharma S. "In silico screening and analysis of single-nucleotide polymorphic variants of the ABCC2 gene affecting Dubin-Johnson syndrome". *Arab Journal of Gastroenterology* 23.3 (2022): 172-187.
11. Carlton VEH., *et al*. "Complex inheritance of familial hypercholanemia with associated mutations in TJP2 and BAAT". *Nature Genetics* 34.1 (2003): 91-96.
12. Qiu JW., *et al*. "Sodium taurocholate cotransporting polypeptide (NTCP) deficiency: Identification of a novel *SLC10A1* mutation in two unrelated infants presenting with neonatal indirect hyperbilirubinemia and remarkable hypercholanemia". *Oncotarget* 8.63 (2017): 106598-106607.

13. PubChem. "BAAT - bile acid-CoA:amino acid N-acyltransferase (human) (2025).

14. Barbara Döring., *et al*. "The SLC10 carrier family: transport functions and molecular structure". *Current Topics in Membranes* 70 (2012): 105-168.

15. Ting-Ting Zou., *et al*. "Clinical features of sodium-taurocholate cotransporting polypeptide deficiency in pediatric patients: case series and literature review". Translational Pediatrics 10.4 (2021): 1045-1054.