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CASE REPORT

Hepatology

A novel genetic variant associated with progressive familial intrahepatic cholestasis type 3: A case series

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Abstract

Progressive familial intrahepatic cholestasis type 3 (PFIC-3) is a rare disorder characterized by chronic cholestasis usually progressing to end-stage liver disease (ESLD) within the first two decades of life. PFIC-3 is caused by pathogenic genetic variants of the ATP-binding cassette 4 (ABCB4) gene with variable inheritance; the most common is autosomal recessive. We present two cases of PFIC-3 with genetic testing confirming a novel genetic variant in ABCB4 with homozygous genotype c.779 T > C, p.L260P. Both individuals are from mainland Southeast Asia and have a clinical picture consistent with cholestasis progressing to ESLD.

KEYWORDS

cirrhosis, end-stage liver disease, whole exome sequencing

1 | INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) is a class of rare disorders characterized by impairment in the secretion of bile acids leading to intrahepatic cholestasis. Originally only three forms were recognized, but today, over 10 variants have been described. There is significant variability of disease phenotype even among patients with the same genetic variant.[1] PFIC-3 is caused by a defective protein encoded by the ATP-binding cassette 4 (ABCB4) gene on chromosome seven. This protein is responsible for the transport of phosphatidylcholine to the outer canalicular membrane, neutralizing bile salts and protecting the bile ducts from cellular injury.[2] PFIC-3 often presents with chronic cholestasis progressing to end-stage liver disease (ESLD) within the first two decades of life, but milder phenotypes exist. The spectrum of PFIC-3 includes cholesterol gallstones, refractory pruritis, drug-induced cholestasis, adult idiopathic cirrhosis, intrahepatic cholestasis of pregnancy, transient neonatal cholestasis, intestinal failure-associated liver disease, and there may also be a risk factor in certain primary hepatobiliary malignancies.[3] Cholestatic injury is the consequence of variants hindering the function a phospholipid transporter encoded by this gene.[4,5] Any variant altering the tertiary or quaternary structure of the protein can cause cholestasis. Heterozygous variants predispose individuals to hepatic injury, but the effect is generally more severe in homozygous variants.[3,6] Treatment generally involves medical management of associated symptoms and clinical sequelae, but liver transplantation may be required if symptoms are refractory to medical management or if there is progression to ESLD.[1]

In this report we discuss two children of Southeast Asian descent, one in the United States and one in Thailand, with ESLD who share a novel genetic variant

in ABCB4 with homozygous genotype c.779 T > C, p.L260P.

1.1 | Case presentation 1

A 6-year-old female presented to our emergency department with hypoxia, jaundice, hepatosplenomegaly, and mild ascites.

Originally from Burma, she developed jaundice, abdominal distension, oily stools, and easy bruising at the age of 9 months. Little is known about her medical care between the age of 9 months and 5 years, until the family relocated to Malaysia. Initial work-up at that time revealed an abdominal ultrasound concerning for multifocal hypodense lesions, portal vein thrombosis, and splenic infarcts. Liver biopsy was consistent with cirrhosis with lobular and portal inflammation, and esophagogastroduodenoscopy revealed grade one esophageal varices. While in Malaysia, her ascites was treated with diuretics. Lactulose was initiated for prevention of hyperammonemia.

Upon arrival to our emergency department at the age of 6 years, laboratory evaluation was obtained and is shown in Table 1. Liver biopsy was performed and is shown in Figure 1. Lesions and cirrhotic liver were biopsied and both samples showed lymphocytic infiltration of the portal/septal areas and evidence of hepatocyte damage. Due to chronic changes, etiology of ESLD was not determined based upon liver biopsy. Repeat workup for etiologies of liver disease was consistent with reports from Malaysia. As transplantation was being considered without a unifying diagnosis, whole exome sequencing was performed and revealed homozygosity with a novel variant in ABCB4 c.779 T > C, p.L260P. In consultation with a medical geneticist, we determined this gene variant is likely to be associated with her clinical presentation.

The child ultimately received a deceased donor liver transplant and is doing well. At explant, a normal gallbladder was identified.

TABLE 1 Initial laboratory evaluation.

Laboratory studies	Patient 1	Patient 2	Reference range
ALT (u/L)	88	143	0–19
AST (u/L)	39	115	26–45
Total bilirubin (mg/dL)	22.9	1.9	0–0.3
Direct bilirubin (mg/dL)	11.7	1.75	0–0.1
GGT (u/L)	83	111	6–16
Hgb (g/dL)	10.3	11.1	11.4–15.5
Platelets (cells/mcL)	74,000	474,000	150,000–400,000
INR	2.3	1.12	0.8–1.1
ANA	<1:40	—	<1:40
IgG (mg/dL)	2593	—	540–1360

Note: —: value not obtained.

Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; Hgb, hemoglobin; IgG, immunoglobulin G; INR, international normalized ratio.

1.2 | Case presentation 2

A 16-month-old female presented to a hepatology clinic in Thailand with a history of ecchymosis, coagulopathy, and elevated liver enzymes. The patient had been adopted at 3 months of age and family history was unknown. The initial laboratory evaluation is shown in Table 1. At that time, initial investigation for chronic liver disease, including viral hepatitis and autoimmune hepatitis profiles, were unremarkable. By the age of 2, she had visible jaundice and hepatomegaly. A liver biopsy performed at age 5 was consistent with cirrhosis, moderate cholestasis, and ductular proliferation (Figure 2). Cholestasis gene panel revealed homozygosity for a novel variant in ABCB4 c.779 T > C, p.L260P.

The child is now 10-years-old and has been intermittently hospitalized for spontaneous bacterial peritonitis, variceal bleeding requiring endoscopic intervention, hypoalbuminemia requiring intravenous albumin with diuretic infusion, and malnutrition requiring intravenous lipid infusion. She is not a candidate for liver transplant due to a lack of caregiver and financial support and is receiving palliative care in Thailand.

2 | DISCUSSION

We present two cases of young females with ESLD, both from Southeast Asia, who were found to have a novel homozygous variant in the ABCB4 gene presenting with severe cholestasis progressing to ESLD. As this was a novel variant, we contacted the genetic laboratory asking if this had been reported previously, who connected us with the medical team in Thailand caring for a similar patient. The two children are from the same geographical area and had similar clinical presentations. Both children had histological findings of mixed portal inflammation and abnormal bile ducts which are consistent with other reports of PFIC-3, although MDR3 staining was not performed.[7] There are no current reports of this genetic variant in other individuals in Southeast Asia, and the family members of these individuals did not undergo genetic testing.

Notably, PFIC-3 can share features with biliary atresia, thus, a normal gallbladder at explant for the first case is important in distinguishing these conditions.

The availability of genetic testing has led to the recognition of a myriad of clinical phenotypes associated with ABCB4 genetic variants and their descriptions are important for further understanding

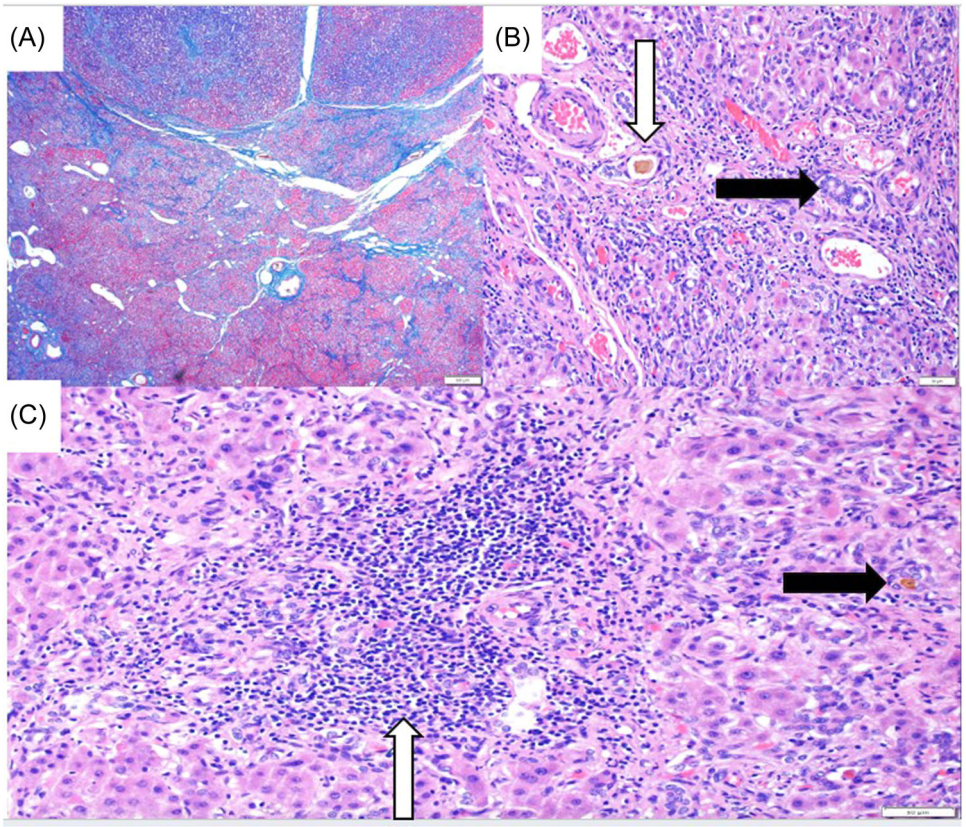

FIGURE 1 Liver biopsy images from patient 1. (A) Masson's trichrome reveals cirrhosis. (B) There are rare bile duct plugs (white arrow) as well as bile duct proliferation (black arrow). (C) Portal and lobular lymphocytic inflammation (white arrow) with lobular disarray. There is one area of intracellular cholestasis (black arrow).

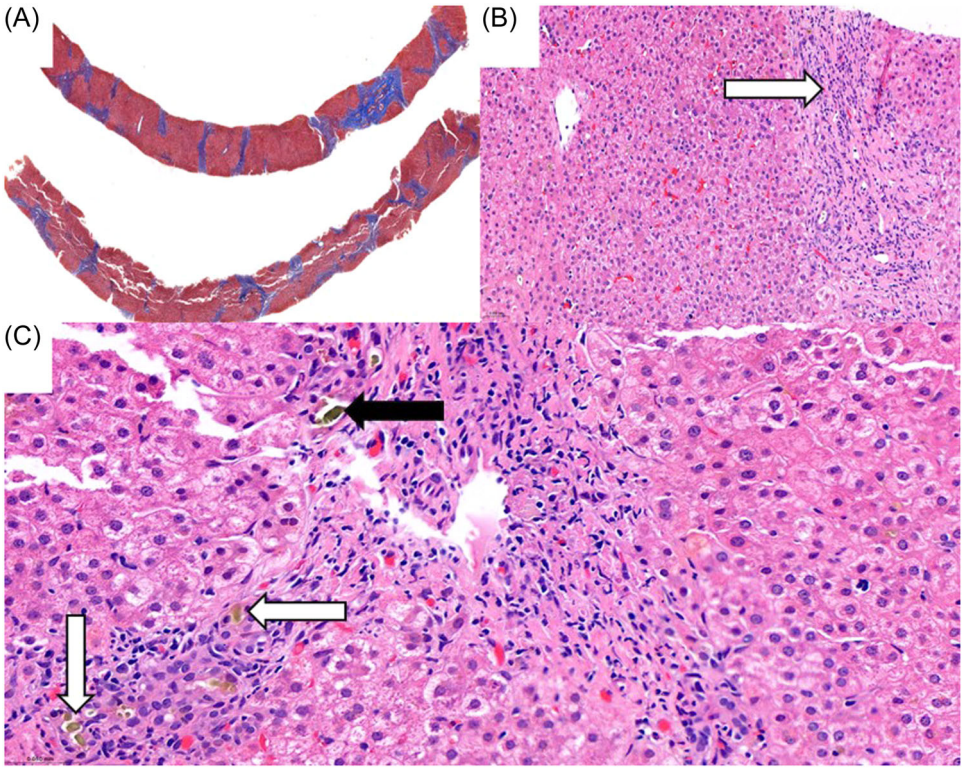

FIGURE 2 Liver biopsy images from patient 2. (A) Masson's trichrome reveals bridging fibrosis. (B) Portal inflammation is noted (white arrow). (C) The hepatic lobules reveal hepatocellular and canalicular cholestasis (white arrows) with bile duct proliferation and occasional bile plugs (black arrow).

of this spectrum of disease. As genetic testing becomes more common, collaboration with testing laboratories who may have significant unpublished data is also critical.

In our case, it allowed us to connect with clinicians with a similar patient and provided some insight into the prognosis of these children. With improved understanding of the gene variants involved in PFIC-3, we can more effectively and accurately anticipate morbidity, mortality, and need for transplant, as well as provide tailored and refined genetic counseling to patients and their families.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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