

# Intrahepatic cholestasis in two Omani siblings associated with a novel homozygous *ATP8B1* mutation, c.379C>G (p.L127V)

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## Abstract

We report two Omani brothers with intrahepatic cholestasis that resolved with supportive care. In one, cholestasis began in infancy; in the other, only at the age of 18 months. Whole exome sequencing identified a novel homozygous variant, c.379C>G (p.L127V) in *ATP8B1*. Those attending patients with cholestasis from the Arabian peninsula should be aware of this mutation and of the variation in its phenotypic effects.

**Keywords:** *ATP8B1*, benign recurrent intrahepatic cholestasis, progressive familial intrahepatic cholestasis, whole exome sequencing

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## INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) is a clinical designation for several autosomal recessive disorders often apparent in infancy.<sup>[1-3]</sup> In PFIC1, hepatic dysfunction manifests as malabsorption with failure to thrive, pruritus, and cholestatic jaundice. It ultimately develops into severe and permanent liver disease with progressive fibrosis. Patients with less severe manifestations and without liver fibrosis are said to have “benign” recurrent intrahepatic cholestasis (BRIC1).

One form of PFIC1/BRIC1 is caused by defects in familial intrahepatic cholestasis 1 (FIC1) protein, expressed in the apical membrane of a variety of epithelial cells, including hepatocytes, and is encoded by *ATP8B1*. It is an aminophospholipid transporter

responsible for the enrichment of the inner leaflet of the plasma membrane in phosphatidylserine and phosphatidylethanolamine. Functional deficiency of FIC1 results in disordered membrane composition, with instability and disturbed function of various membrane proteins. Deafness, diarrhea, pancreatitis, elevated sweat electrolyte concentrations, and hypothyroidism are among the extrahepatic sequelae of *ATP8B1* disease. Distinct *ATP8B1* mutations cause PFIC1 in particular demes: in Amish [c.923G>T (p.G308V)], Inuit and Athabaskan [c.1660G>A (D554N)] and Indian children (c.[589\_592inv; 592\_593insA]) or BRIC in northern European children and adults [c.1982T>C (p.I661T)].<sup>[4-6]</sup> The full range of mutations associated with PFIC1/BRIC1 remains undescribed in the various populations of the Middle East and Arabian peninsula.

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We report two Omani brothers in whom intrahepatic cholestasis was associated with the novel homozygous c.379C>G (p. L127V) mutation in *ATP8B1*. We describe the clinical phenotype associated with that mutation, with mild, resolving disease suggestive of BRIC1.

## CASE REPORTS

### Case 1

A previously healthy 18-month-old Omani boy, born at term to healthy consanguineous parents, presented with several weeks' history of worsening jaundice, dark-colored urine, and frequent large, pale, smelly, and greasy stools, accompanied by reported itching.

During pregnancy, complicated by gestational diabetes managed by diet, no pruritus was reported. His birth weight was 3.1 kg; the neonatal period was uneventful and without hyperbilirubinemia. His growth and developmental milestones were appropriate. On examination, his weight was 11 kg (25<sup>th</sup> percentile), height 83 cm (50<sup>th</sup> percentile), and head circumference 47 cm (25<sup>th</sup> percentile). He was mildly jaundiced and had cutaneous scratch marks. Abdominal organomegaly was not found. Laboratory test results included total bilirubin 27  $\mu\text{mol/L}$  (expected, 5–22), direct bilirubin 15.3  $\mu\text{mol/L}$  (1.7–8.6), alkaline phosphatase 789 IU/L (110–302), gamma-glutamyl transpeptidase (GGT) 8 IU/L (6–16), aspartate aminotransferase 112 IU/L (22–58), alanine aminotransferase 98 IU/L (11–39), prothrombin time 27.6 s (8.1–12.3), and international normalized ratio 2.76 (0.88–1.24), without hypoproteinemia. The absence of elevated serum GGT activity despite jaundice with conjugated hyperbilirubinemia and pruritus, in conjunction with the family history (see Case 2), led to the presumptive diagnosis of familial intrahepatic cholestasis. Serum and urine bile acids analyses were not performed. Liver biopsy was not done. Medium-chain triglyceride formula was added to the diet and therapy was started with ursodeoxycholic acid (300 mg/day), fat-soluble vitamins E, D, K, and A daily supplements, and weekly subcutaneous injections of 2.5 mg vitamin K. During the first 4 weeks of treatment, jaundice and itching worsened, total and direct bilirubin values rose but progressively declined into expected ranges, and coagulopathy normalized. By the age of 20 months, jaundice and itching resolved completely and urine and stool color normalized. Serum GGT activity always remained within expected range.

### Case 2

An older brother, now 15 years old, developed intrahepatic cholestasis during infancy. The information available in

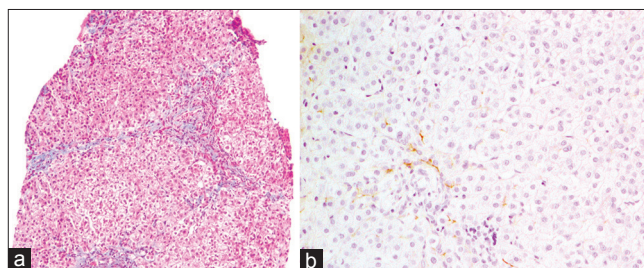
his chart was incomplete because of frequent loss to follow-up. Light microscopy of a liver-biopsy specimen obtained at age 6 months found intralobular cholestasis, mainly canalicular, and mild portal-tract fibrosis with focal portal-portal bridging fibrosis [Figure 1a]. GGT normally outlines all bile canaliculi crisply. Expression of GGT was deficient [Figure 1b], suggestive of *ATP8B1* disease.<sup>[7]</sup> Intrahepatic cholestasis lasted until 4 years of age, and was managed with supportive care. Resolution was spontaneous; he has remained well.

### Whole exome sequencing

Whole exome sequencing (Baylor Miraca Genetics Laboratories, Houston, TX) revealed that both brothers were homozygous for the novel *ATP8B1* variant c.379C>G (p. L127V), predicted by SIFT/PolyPhen2 analysis to be tolerated but possibly damaging. Sanger sequencing confirmed the mutation. Each parent was a heterozygote for the variant, supporting autosomal recessive Mendelian inheritance. Another brother and sister were both heterozygotes for this mutation. They complain occasionally of pruritus, but icterus and clinical-biochemistry abnormalities, including hypercholanemia, have not been documented.

## DISCUSSION

We report intrahepatic cholestasis in two Omani brothers homozygous for the novel c.379C>G (p. L127V) variant in *ATP8B1*. Although the clinical course of the older brother is not well documented, mild liver fibrosis at age 6 months: precludes BRIC. Yet cholestasis remitting around the age of 4 years is atypical for PFIC1. The phenotype appears to be an intergrade. Disease in the younger brother, with remission after a briefer bout of cholestasis, appears clinically to represent BRIC1 but without confirmatory clinicopathologic criteria in the



**Figure 1:** Liver biopsy specimen of the proband's older sibling at the age of six months. (a) Intralobular cholestasis, mainly canalicular; mild portal-tract fibrosis with focal portal-portal bridging fibrosis. Chromotrope aniline blue stain. (Magnification,  $\times 100$ ). (b) Deficiency of canalicular expression of gamma-glutamyl transpeptidase (GGT); the canalicular network marks only in immediately periportal regions. Anti-GGT antibody, diaminobenzidine chromogen, hematoxylin counterstain. (Magnification,  $\times 200$ )

absence of liver histopathology. The mutation common to both brothers thus appears, in homozygous form, to be associated with mild, resolving disease more suggestive of BRIC1. Given both clinical courses, this mutation seems to be associated with a favorable prognosis, although long-term consequences cannot yet be assessed.

Many mutations in *ATP8B1* have been described.<sup>[4-6]</sup> The mutation type sometimes predicts the cholestasis phenotype. For example, nonsense and frame-shift mutations are more often detected in PFIC1, whereas missense mutations are more frequently identified in BRIC1.<sup>[4]</sup> However, phenotypic presentation varies greatly even among patients with the same mutation.<sup>[8]</sup> BRIC1 and PFIC1 caused by *ATP8B1* mutation are therefore considered part of a clinical continuum spectrum of intrahepatic-cholestasis disorders and are therefore preferably referred to as *ATP8B1* deficiency disease.<sup>[7,9,10]</sup> Variation in background (coexistent mutation in other genes predisposing to cholestasis) may contribute to phenotypic variation, but without clear explanation so far.<sup>[4,8-10]</sup>

The c.379C>G (p. L127V) variant in *ATP8B1* in our patient and sibling has not been previously reported. Comprehensive studies of *ATP8B1* in patients with BRIC1 or PFIC1 from the Middle East are lacking. Until more variants are reported from the Middle East, expensive whole genome sequencing studies will be needed for individual patients. Only when results of such studies are shared, collated, and coordinated with tribal and regional origin can diagnosis and screening be conducted more rapidly and cheaply.

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### Conflicts of interest

There are no conflicts of interest.

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