The cholangiographic features of severe forms of ABCB4/MDR3 deficiency-associated cholangiopathy in adults

Caractéristiques cholangiographiques des formes sévères de cholangiopathie associée aux anomalies du gène ABCB4/MDR3

R. Poupon\textsuperscript{a,b,c,*}, L. Arrive\textsuperscript{d}, O. Rosmorduc\textsuperscript{a,b,c}

\textsuperscript{a} Université Pierre-et-Marie-Curie Paris-6, UMR S938, 75012 Paris, France
\textsuperscript{b} Inserm, UMR S938, 75012 Paris, France
\textsuperscript{c} Service d’hépato-gastro-entérologie, hôpital Saint-Antoine, AP–HP, 184, rue du Faubourg-Saint-Antoine, 75012 Paris, France
\textsuperscript{d} Service de radiologie, hôpital Saint-Antoine, AP–HP, 75012 Paris, France

Available online 27 May 2010

Summary

We previously reported the association of ABCB4/MDR3 gene variants with a peculiar form of cholelithiasis in European adults, currently referred to as the LPAC syndrome. ABCB4/MDR3 deficiency is also now thought to be related to some forms of hepatolithiasis in Japan. We herein report in eight patients a new phenotype associated with ABCB4 gene mutations, characterized by a typical LPAC symptomatic disease associated with large uni- or multifocal spindle-shaped dilations of the intrahepatic bile ducts without any bile duct stenosis, and filled of gallstones. We excluded from this series, the patients with minimal intrahepatic bile duct dilations, with bile duct stenosis, with focal or diffuse irregular bile ducts compatible with the diagnosis of sclerosing cholangitis, with bile duct dilations that did not contain stones or alternatively with stones in bile ducts without large dilations. The prevalence of this phenotype does not exceed 5 to 10% of the patients with LPAC syndrome. Importantly, the ABCB4/MDR3 mutations observed in this series did not differ from those observed in patients with LPAC syndrome with no or minimal intrahepatic bile duct dilations that could suggest a specific genetic background in this setting. This variant shows similar sensitivity to ursodeoxycholic acid and may be partly reversible under long-term therapy. In summary, we describe here a peculiar cholangiographic phenotype of the LPAC syndrome characterized by single-shaped large bile duct dilations filled with cholesterol or brown-pigment stones. This phenotype is not associated with a peculiar type of ABCB4 mutation.

© 2010 Elsevier Masson SAS. All rights reserved.

* Corresponding author.
E-mail address: raoul.poupon@sat.aphp.fr (R. Poupon).

0399-8320/$ - see front matter © 2010 Elsevier Masson SAS. All rights reserved.
The cholangiographic features of severe forms of ABCB4/MDR3 deficiency

Introduction

Intrahepatic lithiasis is characterized by the presence of stones above the convergence of the right or left hepatic bile ducts. The disease is rare in the Western world but has a high prevalence in East Asian countries where it is often referred to as oriental cholangiopathtis [1,2]. Pathogenesis of primary intrahepatic stones, seen primarily in East Asian countries, probably involves a combination of bile stasis, bile infection, malnutrition, and parasitic infestation [3]. Intrahepatic stone formation in both East Asia, Japan and Western countries is affected by congenital and acquired risk factors. Congenital factors include anatomical anomalies such as biliary strictures associated with sclerosing cholangitis, and extrahepatic anomalies such as choledochal cyst or Caroli’s disease and genetic conditions such as haemolytic diseases and ABCB4/MDR3 deficiency [4–6].

The overall prevalence of left versus right hepatic lithiasis is relatively high. This is usually explained by the anatomical difference between the left and right hepatic ducts, the left hepatic duct forming an acute angle at the junction with the common bile duct tend to induce bile stasis when associated with biliary strictures. We previously reported the association of ABCB4/MDR3 gene variants with a peculiar form of cholelithiasis in adults now referred to as the LPAC syndrome, characterized by the following clinical features: age at the onset of symptoms lower than 40 years; association with cholecystitis, cholangitis or acute pancreatitis; recurrence of symptoms despite cholecystectomy; intrahepatic gallstones or sludge evidenced by ultrasonography (US); onset of symptoms at the end of or following pregnancy; history of cholesterol gallstones amongst first-degree relatives; increased serum gamma-glutamyl transferase (GGT) activity; prophylactic therapeutic activity of ursodeoxycholic acid (UDCA) [5,7]. Our results have been reinforced by data in the literature showing an increased cholesterol saturation index and a defect in the hepatic transport and biliary secretion of phospholipids in patients with an intrahepatic cholesterol and brown-pigment gallstone disease from Japan [8].

We herein report in eight patients a new phenotype associated with ABCB4 gene mutations, characterized by a typical LPAC symptomatic disease associated with large uni- or multifocal spindle-shaped dilations of the intrahepatic bile ducts without any bile duct stenosis, and filled of gallstones. We excluded from this series, the patients with minimal intrahepatic bile duct dilations, with bile duct stenosis, with focal or diffuse irregular bile duct compatible with the diagnosis of sclerosing cholangitis, with bile duct dilations that did not contain stones or alternatively with stones in bile ducts without large dilations.

Patients

The clinical features of the eight caucasian patients with a French ancestry are summarized in Table 1.

Patient 1 (AK)

This 27-year old woman presented with recurrent cholangitis since she was aged 24. Apart from the recurrent episodes of cholangitis, the liver biochemical tests remained constantly but moderately elevated: serum GGT activities ranged from 150 to 200 UI/ml and ALT activities from 55 to 65 UI/l. US showed multiple intrahepatic stones associated with a thickening of the left intrahepatic bile ducts. ERCP and Magnetic resonance imaging (MRI) showed large intrahepatic bile duct spindleshaped dilatations filled with stones, the liver segments V VII and VIII (Fig. 1 A and B). The liver biopsy showed only mild portal inflammation without significant fibrosis. ABCB4 gene analysis showed a compound heterozygous mutation in exon 4 (Arg47Gln) and exon 11 (Arg406Gln). In familial background, her mother (at the age of 40), her sister (at the age of 30) and her brother (at the age of 24) had cholecystectomy for symptomatic gallbladder cholelithiasis (the respective genotypes are presented on Fig. 1 C). The analysis of a fresh bile sample showed a low phospholipid content (10% of total biliary lipid concentration). UDCA therapy was started at 600 mg/d. During the subsequent weeks, she experienced recurrent episodes of cholangitis. A percutaneous biliary drainage was performed and a stent was placed in the bile duct of the segment V but the stones could not be extracted nor fragmented. The biliary stent had to be withdrawn a few months later because of recurrent of biliary pains. An endoscopic retrograde cholangiography (ERCP) was carried out to remove stones from the common bile duct. After 1 year of intermittent ursodeoxycholic acid (UDCA) treatment, US showed unmodified intrahepatic bile duct dilatations full of stones and associated with multiple intrahepatic biliary crystals. After 3 additional years of sustained UDCA therapy, she experienced less than one slight and transient biliary pain per month without recurrent cholangitis. The current MRI shows a dramatic improvement in both the number of the dilated bile duct gallstones and the size of the bile duct dilations (Fig. 2). The liver tests remained normal under UDCA treatment (AST 5 UI, ALT 10 UI, GGT 38 UI, alkaline phosphatase 55 UI, serum bilirubin 8 μmol/l). Since the end the year 2009, the frequency of biliary pain and cholangitis episodes has dramatically increased leading to the proposition of surgical treatment (partial hepatectomy).

Patient 2 (AR)

This 30-year old patient had a similar sequence of clinical, biochemical and radiologic manifestations as his sister presented above (patient 1). He experienced the first biliary symptoms at the age of 23 by the occurrence of biliary pain associated with multiple gallstones in the common bile duct. He underwent cholecystectomy and extraction of the common bile duct stones. At the age of 29, he had one episode of biliary pain with abnormal biochemical liver tests (AST 691 UI, ALT 68 UI, GGT 343 UI; serum bilirubin 72 μmol/l; alkaline phosphatase 129 UI). Two years later, he was hospitalized for a recurrence of the biliary symptoms associated with biochemical abnormalities (AST 208 UI, ALAT 512 UI, serum bilirubin 48 μmol/l, alkaline phosphatase 178 UI, GGT 237 UI and amylase 62 UI). US examination showed several stones in the common bile duct as well as several intrahepatic gallstones of 5 mm in diameters. He underwent an ERCP that allowed the extraction of cholesterol and brown-pigment stones (sized up to 15 mm in diameters) from the
Table 1  Clinical features of the eight caucasian patients.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Age of the diagnosis (years)</th>
<th>Clinical presentation</th>
<th>ABCB4 gene mutation</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>F</td>
<td>24</td>
<td>Cholestasis</td>
<td>Arg47Gln Arg406Gln</td>
<td>Recurrent cholangitis under UDCA</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>M</td>
<td>24</td>
<td>Cholestasis</td>
<td>Arg47Gln Arg406Gln</td>
<td>Recurrent cholangitis under UDCA</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>M</td>
<td>47</td>
<td>Cholestasis</td>
<td>Ala287Val</td>
<td>Free of symptoms under UDCA during 5 years. Two episodes of cholangitis since 2008</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>48</td>
<td>Cholecystectomy</td>
<td>Thr775Met Ala946Thr</td>
<td>Recurrent cholangitis Resection of segment VI</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>F</td>
<td>24</td>
<td>Cholecystectomy</td>
<td>Ala934Thr</td>
<td>Free of symptoms under UDCA</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>M</td>
<td>24</td>
<td>Cholecystectomy</td>
<td>Gly384Arg</td>
<td>Free of symptoms under UDCA</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>F</td>
<td>30</td>
<td>Cholecystectomy</td>
<td>Tyr1086Stop Val526Phe</td>
<td>Free of symptoms under UDCA</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>M</td>
<td>18</td>
<td>Cholecystectomy</td>
<td></td>
<td>Free of symptoms under UDCA</td>
</tr>
</tbody>
</table>

UDCA: ursodeoxycholic acid.

common bile duct. ABCB4 gene analysis showed the same compound heterozygous mutation as observed in patient 1 (e.g. in exon 4 (Arg47Gln) and in exon 11 (Arg406Gln) (Fig. 1C). The patient was asymptomatic without treatment during the further 3 years. Thereafter, he presented a biliary pain recurrence. US examination showed multiple intrahepatic biliary spots in the peripheral bile ducts associated with bile duct dilation in the central part of the liver. MRI confirmed the presence of a single spindle-shaped large bile duct dilation in the liver segment IV. This dilated

Figure 1  Imaging features (ERCP: panel A; MRCP [coronal MIP image from a 3D heavily T2-weighted sequence]: panel B) of patient 1. Family tree of patient 1 (panel C) with ABCB4 genotype and phenotype (attenuated form in white and severe form in red).
The cholangiographic features of severe forms of ABCB4/MDR3 deficiency

Figure 2  Comparison of bile duct imaging features of patient 1 (segment IV and segment VIII) by MR imaging [T2-weighted HASTE sequence] at the date of diagnosis (left) and at 3 years under ursodeoxycholic acid (UDCA) (right).

bile duct was filled with stones. Using ERCP, common bile duct gallstones up to 13 mm in diameters were extracted after endoscopic sphincterotomy. UDCA (8 mg/kg/d) was given. Recurrent biliary pain episodes were less frequent and intense during the 3 years of follow-up under UDCA treatment.

Patient 3 (BJL)

At the age of 47, the patient presented with recurrent episodes of cholangitis. Apart from these episodes, the liver tests were slightly abnormal (mainly GGT activity, 166 IU). A liver biopsy showed portal inflammation, extensive fibrosis and ductular proliferation. A diffuse spindle-shaped dilation of both the right and left intrahepatic bile ducts filled with many millimetric stones was evidenced by MRI (Fig. 3). In addition, two other gallstones were disclosed in the common bile duct. ABCB4 gene analysis showed a heterozygous mutation in exon 9 (Ala287Val). UDCA treatment was started (600 mg/d). Biliary pain did not recur during the first 5 years of follow-up. Under UDCA treatment, the patient is still asymptomatic and the liver biochemistries are normal. The last MRI shows unchanged diffuse intrahepatic bile duct dilatation filled of stones. Of note, the 28-year-old daughter of this patient is asymptomatic with normal hepatic tests (e.g. AST 24 IU, ALT 37 IU, GGT 27 IU) but with multiple intrahepatic hyperechoic foci along the small intrahepatic bile ducts without large bile duct dilatation at US examination. ABCB4 gene analysis in this daughter as well as in the asymptomatic father shows the same heterozygote mutation found in the index case. More recently, two episodes of cholangitis have occurred during the two last years and were easily controlled by antibiotics for 10 days.

Patient 4 (KG)

This 58-year old patient presented with recurrent episodes of cholangitis for several years. MRI examination showed a stone of 20 mm in the gallbladder associated with a single spindle-shaped bile duct dilatation filled with gallstones (Fig. 4A) in the segment VI. A cholecystectomy was performed followed by extraction of a cholesterol stone from

Figure 3  Bile duct imaging features (MR imaging [T2-weighted HASTE sequence]) of patients 3.
the common bile duct and resection of the liver segment VI which was atrophic. Choledocoscopy and cholangiography confirmed the absence of residual gallstone in both the intrahepatic and the common bile ducts. Macroscopic examination of the resected segment confirmed the presence of a large bile duct dilatation filled with brown gallstones (Fig. 4B). Histologic features were as follows: no liver fibrosis or cirrhosis; low-grade cell dysplasia in the dilated bile duct epithelium; moderate inflammatory infiltration with a few giant cells in contact with multiple cholesterol needles (Fig. 5A). A single high-grade dysplasia area and proliferative cholangitis was also evidenced in one of the dilated bile duct (Fig. 5B). Biliary lipid composition analysis showed the following features: phospholipids 6.92 mmol/l; cholesterol 1.75 mmol/l and bile acids 50.215 mmol/l. \textit{ABCB4} gene analysis showed an heterozygous compound mutation in exon 19 (Thr775Met) and exon 23 (Ala946Thr). US examination was carried out one month after the surgery and

![Figure 4](image_url)  
**Figure 4.** Bile duct imaging features (ERCP) of patient 4 before surgery (panel A) and macroscopic examination of the segment VI after liver resection (panel B).  

![Figure 5](image_url)  
**Figure 5.** Bile duct histologic features of segment VI from patient 4. Areas of low-grade cell dysplasia (panel A) and of high-grade dysplasia (panel B).
showed multiple intrahepatic hyperchoic spots in almost all the right liver segments associated with two residual gallstones located at the origin of remaining origin of bile ducts of the resected segment VI. Two months after surgery, the patient presented with cholangitis and acute pancreatitis (e.g. ALT 1050 IU, AST 940 IU, GGT 175 IU, alkaline phosphatase 630 IU, amylase 5640 IU). MRI showed several gallstones of 2 to 10 mm in diameters in the common bile duct, which were extracted after endoscopic sphincterotomy. The patient remained thereafter asymptomatic for more than 2 years under UDCA treatment (e.g. 800 mg/d). The last US did not find any residual material excepting the two unchanged known gallstones evidenced at the remaining origin of the bile ducts of the resected segment VI.

Patient 5 (YN)

This 51-year old woman had a cholecystectomy at the age of 27 for symptomatic gallstones. At the age of 30, she experienced recurrent cholangitis that required the extraction of gallstones from the common bile duct using ERCP and endoscopic sphincterotomy. The cholangiography did not show any dilation of the bile ducts. At the age of 47, she presented with recurrent biliary pain. The US and MRI examination showed a multifocal spindle-shaped dilatation of the intrahepatic bile ducts in five liver segments (e.g. segment III, V, VI, VIII and the left hepatic duct) filled with many gallstones up to 2 cm in diameters. Surgical extraction of the gallstones was performed and was completed by a hepatico-jejunostomy. A liver biopsy showed only minimal periductal fibrosis with moderate inflammation. \(ABC\textit{B}4\) gene analysis showed a heterozygous mutation in exon 23 (Ala934Thr). The bile composition analysis showed a low phospholipids concentration of 0.32 mmol/l concentration together with a bile acid concentration of 12 mmol/l. UDCA treatment (800 mg/d) was given. Rare recurrent episodes of biliary pain without complication were observed during the first year under treatment. Thenceforth, she remained asymptomatic with normal liver tests. After 30 months under UDCA treatment, MRI showed a significant decrease of the intrahepatic bile duct dilatation (from 11 to 3 mm and 12 to 4.5 mm for the right anterior and posterior bile ducts respectively and from 15 to 4.5 mm for the left hepatic bile duct). Four years later, the patient remained asymptomatic and the liver tests were within normal range. Current US imaging and MRI remained unchanged.

Patient 6 (OA)

This 46-year old patient had cholecystectomy at the age of 24 because of symptomatic cholesterol gallstones. Of note, the brother’s patient had also a history of recurrent biliary pain. The patient is also followed for ankylosing spondylarthritis necessitating anti-TNF-alpha therapy. At the age of 43, he underwent an extraction of cholesterol gallstones from the common bile duct using ERCP and endoscopic sphincterotomy. The follow-up was characterized by recurrent episodes of cholangitis. Apart from the episodes of cholangitis, the liver tests were slightly abnormal (e.g. AST 58 IU, ALT 115 IU, GGT 312 IU, alkaline phosphatase 486 IU, serum bilirubin 13 \(\mu\)mol/l). MRI examination showed a multifocal spindle-shaped dilatation of intrahepatic bile ducts (liver segments I, III and the posterior segments) filled with many gallstones associated with common bile duct lithiasis. The extrahepatic gallstones were extracted using ERCP and endoscopic sphincterotomy. \(ABC\textit{B}4\) gene analysis showed a heterozygote mutation in exon 11 (Gly384Arg). The patient remained asymptomatic after the start of UDCA treatment (600 mg/d). The liver tests remained normal and the MRI was unchanged after 3 years under UDCA treatment.

Patient 7 (LC)

This 36-year old patient had an ERCP with endoscopic sphincterotomy followed by cholecystectomy for a symptomatic lithiasis of the common bile duct at the age of 30. At this time, the cholangiography did not show any intrahepatic bile duct dilation. At the age of 35, a slight increase in the values of liver biochemistries was noted and US showed a focal dilation of one intrahepatic bile duct. MRI confirmed the presence of a single large spindle-shaped dilatation of the bile duct in the liver segment VIII. This dilation was filled of gallstones. \(ABC\textit{B}4\) gene analysis showed a heterozygous mutation in exon 25 (Tyr1086Stop). UDCA treatment was started. Until now, the patient is asymptomatic with normal liver tests UDCA. Biliary MRI remains unchanged after more than one year under treatment. Of note, the mother of this patient experienced cholestasis during pregnancy with the occurrence of symptomatic common bile duct gallstones at the age of 24. She had recurrence of the biliary symptoms at the age of 31 and of 54 leading to a surgical extraction of biliary gallstones and choledoco-duodenal diversion. Three years later, the patient remained asymptomatic and the liver tests were within normal range. Current US imaging and MRI show that bile ducts are free of gallstones.

Patient 8 (LY)

This 37-year old man had several episodes of epigastric pain compatible with biliary colic since the age of 18. In 2006, the liver biochemistries (ALT, GGT) were found abnormal. US examination disclosed multiple dots with echogenic trails diffusely distributed in the liver. MRI disclosed a single large spindle-shaped dilatation of the intrahepatic bile ducts of the right anterior segments containing several stones. \(ABC\textit{B}4\) gene analysis revealed a heterozygous mutation in exon 14 (Val526Phe). Three years later, the patient remained asymptomatic and the liver tests were within normal range excepting a slight increase in GGT (157 UI; normal range less than 61 UI). Current US imaging and MRI are unchanged.

Discussion

We report here a series of patients presenting with typical LPAC syndrome related to \(ABC\textit{B}4\) gene mutations and associated with intrahepatic uni or multifocal noncystic large spindle-shaped bile duct dilations, filled with gallstones which, in a characteristic way, do not extend in periphery beyond certain segmentary or under-segmentary channels contrary to secondary dilation with an obstacle. The intrahepatic calculi that occur without morphological strictures of the intrahepatic bile ducts are generated in the periph-
eral intrahepatic bile ducts and are generally of small size. The bile is supersaturated with cholesterol, mainly because of a defect of biliary phospholipids secretion. In half of the cases, a mutation in the \textit{ABCB4} gene has been highlighted [5].

In this study we ruled out the causes of intrahepatic bile duct dilations due to downstream-acquired stenosis (iatrogenic, biliodigestive anastomosis, sclerosing cholangitis, cholangiocarcinoma). In obstructive bile duct dilatation, the dilatation is most marked centrally, tapers towards periphery in an organized pattern and lacks focal areas of cystic dilatation. Primary sclerosing cholangitis was eliminated by clinical history and imaging data showing the absence of bile duct stenosis, the bulky dilatations without obstacle, the regular aspect of the bile ducts, the negative pANCA and the absence of inflammatory bowel disease. Cholangiocarcinoma was eliminated by the clinical history, the sacciform type of the bile duct dilations without any obstacle and the long-term follow-up.

A Caroli’s syndrome, which complications may be similar to that found in our patients (cholangitis, choledocholithiasis, hepatic abscess, cholangiocarcinoma, portal hypertension) was eliminated by the age of occurrence of the biliary symptoms, the absence of associated congenital diseases (renal tubular ectasia, lesions of adult recessive polycystic kidney disease, congenital hepatic fibrosis). The imaging features of Caroli disease, e.g. intrahepatic cystic anechoic areas in which fibrovascular bundles (composed of portal vein and hepatic arteries, “the central dot sign”), stones and linear bridging or septum, congenital hepatic fibrosis, polycystic kidney disease) were absent in the patients herein reported. In addition, in Caroli’s disease, dilated bile ducts have a random bizarre pattern associated with focal areas of cystic ectasia.

Pseudo-dilations of the peribiliary glands were eliminated by the absence of cirrhotic liver or polycystic liver disease or post transplant biliary complications. In addition, these peribiliary cysts are characterized by their peculiar distribution (e.g. predominantly perihilar and on both sides of the bile ducts and the portal vein), small size, the cystic appearance and absence of communication with the bile duct. Finally, other causes of bile duct dilatation (e.g. choledochal cyst, biliary papillomatosis, cholangiocarcinoma) were eliminated by the MRI imaging.

While we and others did not find \textit{ABCB4} mutations nor abnormal SNP frequency in unselected patient presenting with primary sclerosing cholangitis [9], \textit{mdr2} \textit{−/−} mice develop liver lesions mimicking sclerosing cholangitis characterized by biliary strictures and dilatations [10]. According to the findings of the present study one can speculate that \textit{ABCB4} defects might however participate in some way in bile duct architecture remodelling in a subgroup of patients with primary sclerosing cholangitis.

We observed an improvement of the intrahepatic bile duct dilatation in parallel to the number of gallstones and biliary symptoms in some patients after long-term UDCA treatment (e.g. more than 3 years). Several mechanisms may be involved in the beneficial effect of UDCA in this peculiar setting. First, UDCA decreases the cholesterol saturation of bile, and may increase phospholipids secretion. Second, UDCA attenuates proinflammatory cytokine induced phospholipase A2-IIA expression [11,12]. Third, and importantly UDCA may prevent phospholipids degradation and attenuate biliary inflammation trough it capacity to enhance innate immunity in the biliary tree [13]. Since \textit{ABCB4}/\textit{MDR3} deficiency is now recognised as a major player in hepatolithiasis [4–6], adjuvant therapeutic options to UDCA, such as the use of PPAR alpha agonists to enhance phospholipids in bile and to curb biliary inflammation warranted further trials in this devastating setting [14–16].

The prevalence of the phenotype is largely unknown. We evidenced 8 patients presenting with this major phenotype in a series of 40 high quality MRI in our center (<17% of patients referred to our department with a typical LPAC syndrome. However, there was no other major dilated form in more than 132 additional patients (US and/or CT and/or MRI) suggesting that the prevalence of this phenotype does not exceed 5 to 10% of the patients with LPAC syndrome. Importantly, the \textit{ABCB4}/\textit{MDR3} mutations observed in this series did not differ from those observed in patients with LPAC syndrome with no or minimal dilations.

In summary, we have provided here a peculiar cholangiographic phenotype of the LPAC syndrome characterized by single-shaped large bile duct dilations filled with cholesterol or brown-pigment stones. This variant of the syndrome shows similar sensitivity to UDCA and may be partly reversible under long-term therapy. This phenotype is not associated with a peculiar type of \textit{ABCB4} mutation and thus may be linked to a specific genetic background.

Conflict of interest statement

None.

References

The cholangiographic features of severe forms of ABCB4/MDR3 deficiency


