

Liver disease and ABCB4/MDR3

ABCB4/MDR3 is a biliary transporter protein. It is a transmembrane 'floppase' located on the canalicular membrane of hepatocytes, transporting phosphatidylcholine into the bile where it stabilises bile salts into micelles, preventing their damaging detergent effect on the bile duct lining. Expression of the protein is modified by factors including sex hormones and inflammatory cytokines.

ABCB4 (ATP binding cassette B4) is the preferred nomenclature for the gene and protein (rather than MDR-3, multidrug resistance glycoprotein 3) as the protein is not known to transport any drugs.

It is well established that mutations in ABCB4/MDR3 are responsible for severe cholestatic disease in children (progressive familial intrahepatic cholestasis type 3-PFIC3). Recently, however, it has been discovered that mutations in ABCB4/MDR3 can also manifest in older individuals, often with a more indolent phenotype.

The disease phenotype associated with ABCB4/MDR3 mutation depends on the mutation present. Homozygous or compound heterozygous mutations lead to severe disease presenting in childhood (PFIC3) whilst heterozygous missense mutations may be clinically silent or can present in adulthood with less severe disease. The precipitating agents are often sex steroids (oestrogenic or androgenic). Several different disease manifestations may occur in one family.

Diseases associated with ABCB4/MDR3 mutations:

- Progressive familial intrahepatic cholestasis type 3 (PFIC3)
- Intrahepatic cholestasis of pregnancy (ICP) – about 15% of cases are ABCB4 related
- Drug-induced cholestasis (especially with sex hormones)
- Low phospholipid-associated cholelithiasis syndrome (LPAC) - this is early-presenting gallstones, often with later evidence of microlithiasis in the intrahepatic ducts
- Adult ductopenia
- Unexplained episodic jaundice
- Cryptogenic cirrhosis

When to suspect ABCB4/MDR3 mutations in adults?

- Evidence of unexplained biliary injury and persistently elevated gamma-GT
- Family history of biliary disease - this is very useful, and includes disorders such as jaundice of pregnancy, early cholecystectomy, or unexplained biliary cirrhosis
- Jaundice of pregnancy that does not resolve completely after delivery

The histological features on liver biopsy are often subtle and are usually a cholestatic injury pattern with bile duct injury, mild duct loss, mild portal fibrosis, canalicular cholestasis, hepatocyte rosettes or intraductal cholesterol crystals. Progressive fibrosis can be seen in severe cases.

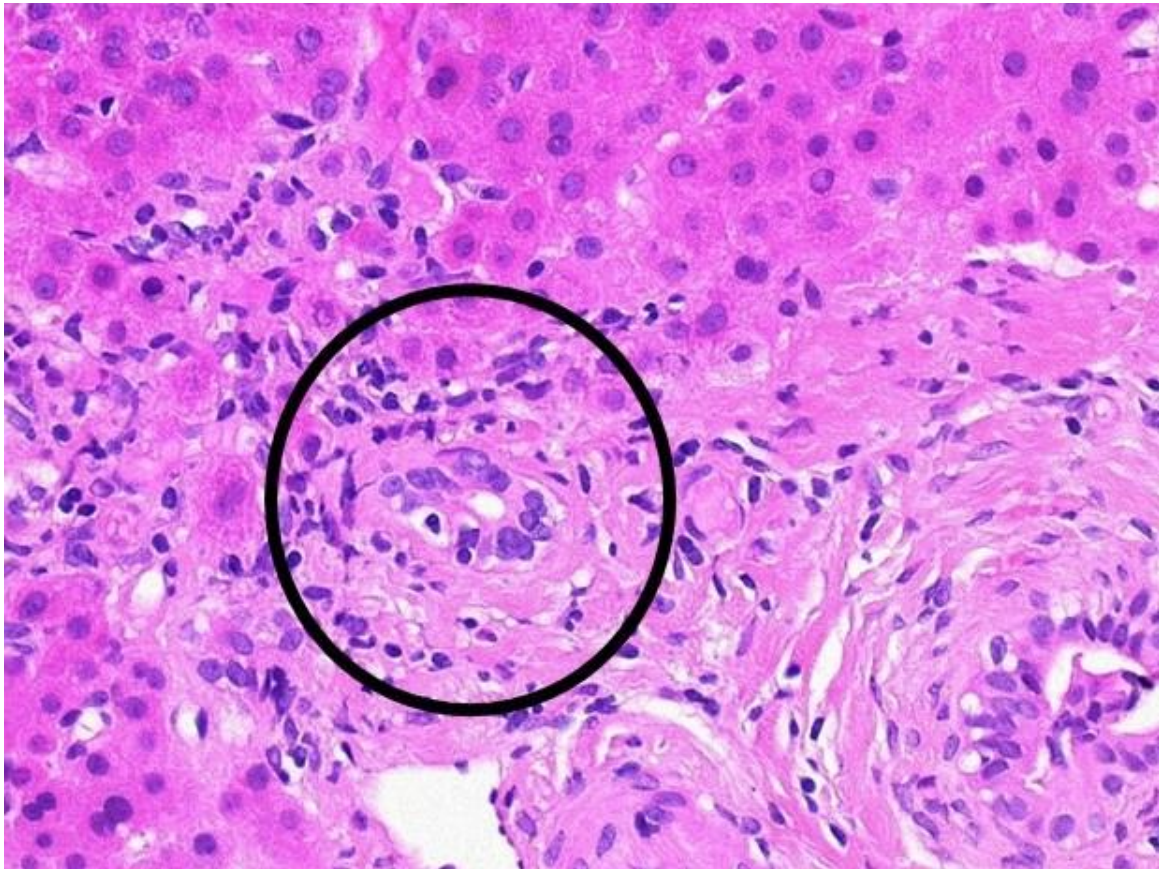


Figure 1. Damaged bile duct within a portal tract in a case of drug (OCP)-induced cholestasis with a heterozygous ABCB4/MDR3 mutation

The diagnosis can be challenging to make, as the full range of disease expression continues to evolve. The combination of mild biliary changes, an appropriate clinical setting and, in particular, a supporting family history (see earlier) will often suggest the diagnosis. The disease often improves if UDCA therapy is commenced. Genetic testing is only available at a few sites overseas (Paris and USA) and is expensive - our experience is that many suspect cases subsequently tested have demonstrated a heterozygous mutation.

Treatment of ABCB4/MDR3 mutation-associated liver disease includes ursodeoxycholic acid (UDCA) in mild cases, and transplantation in the rare cases that are severe. Experimental therapies have included fibrates, 6-ECDCA (farnesoid-X receptor agonist) and chaperone molecules (cyclosporin A).

Further reading:

Davit-Spraul A, *et al.* The spectrum of liver diseases related to ABCB4 gene mutations: pathophysiology and clinical aspects. *Semin Liver Dis.* 2010; 30:134-46.

Wendum D, *et al.* Aspects of liver pathology in adult patients with MDR3/ABCB4 gene mutations. *Virchows Arch.* 2012; 460:198-98.

Degiorgio D, *et al.* ABCB4 mutations in adult patients with cholestatic liver disease: impact and phenotypic expression. *J Gastroenterol.* 2016; 51:271-80