**ABC4 MUTATIONS CAN CAUSE A SPECTRUM OF CHOLESTATIC PHENOTYPES PRESENTING IN ADULTHOOD**

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**Background and Aims** The ABC4 gene encodes the floppase, multidrug-resistance p-glycoprotein 3 (MDR3), which transports phosphatidylcholine (PC) to the outer leaflet of the cell membranes lining the bile canaliculi. PC combines with bile acids in the canicular lumen to form micelles, thus preventing the emulsification action of bile acids damaging the canicular epithelium. Mutations in the ABC4 gene are associated with failure of this process leading to cholestatic liver disease. Presentations range from progressive familial intrahepatic cholestasis type 3 (PFIC3), most commonly presenting in childhood, to less severe forms typically presenting in adulthood. Adult phenotypes are poorly characterised hence we sought to examine in detail a series of patients with ABC4 variants presenting to our institution.

**Methods** Six unrelated adults with ABC4 variants (four female, mean age 39 years) presenting with a cholestatic liver disorder were identified. In addition, three sisters with adult-onset cholestasis (labelled as PFIC3), one of whom was compound heterozygous for ABC4, were studied. As well as case note review, detailed sequencing and histopathological analysis were performed.

**Results** Cases were sub-phenotyped as follows: drug-induced cholestasis, idiopathic adulthood ductopenia, refractory primary biliary cholangitis (PBC) and adult PFIC3. 6/9 had presented with gallstone complications and 5/7 females had a history of intrahepatic cholestasis of pregnancy (ICP). Liver transplantation was required for two out of these nine patients, with another currently wait-listed. Histologically, all cases demonstrated a degree of ductopenia, affecting the smallest interlobular ducts only, copper-associated protein and fibrosis. Portal inflammation was consistently present but of note non-duodenal.

**Conclusion** We describe a range of adult phenotypes associated with pathogenic variants, including novel, in the ABC4 gene. A distinct histological pattern was observed which differs from classical PBC and primary sclerosing cholangitis (PSC), in some cases overlapping with vanishing bile duct syndromes. Cholestatic liver disease in adults merits genetic analysis, particularly where there is a history of early gallstone disease or ICP, a relevant family history or where the histological profile described is present. Family members should be screened and liver transplantation may be required in more severe cases.