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Familial cholestasis: Progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis and intrahepatic cholestasis of pregnancy

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Progressive familial intrahepatic cholestasis (PFIC) type 1, 2 and 3 are due to mutations in *ATP8B1*, *ABCB11* and *ABCB4*, respectively. Each of these genes encodes a hepatocanalicular transporter, which is essential for the proper formation of bile. Mutations in *ABCB4* can result in progressive cholestatic disease, while mutations in *ATP8B1* and *ABCB11* can result both in episodic cholestasis, referred to as benign recurrent intrahepatic cholestasis (BRIC) type 1 and 2, as well as in progressive cholestatic disease. This suggests a clinical continuum and these diseases are therefore preferably referred to as ATP8B1 deficiency and ABCB11 deficiency. Similarly PFIC type 3 is designated as ABCB4 deficiency. Heterozygous mutations in each of these transporters can also be associated with intrahepatic cholestasis of pregnancy. This review summarizes the pathophysiology, clinical features and current as well as future therapeutic options for progressive familial- and benign recurrent intrahepatic cholestasis as well as intrahepatic cholestasis of pregnancy.

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Introduction

Familial intrahepatic cholestasis is a heterogeneous group of autosomal recessive liver disorders characterized by intrahepatic cholestasis, which can be divided in three main groups based on phenotypical differences: progressive familial intrahepatic cholestasis (PFIC), benign recurrent intrahepatic cholestasis (BRIC) and intrahepatic cholestasis of pregnancy (ICP). PFIC can be subdivided in three types with slightly different clinical, biochemical and histological features, associated with mutations in *ATP8B1* (PFIC1), *ABCB11* (PFIC2) and *ABCB4* (PFIC3) [1–3]. A small proportion of PFIC phenotypes are not due to mutations in these three genes and therefore additional genes might be involved. Mutations in *ATP8B1* and *ABCB11* can also result in the less severe phenotype of BRIC type 1 and 2, respectively, while heterozygous mutations in all three genes are associated with ICP. Occasionally the benign variant (BRIC) will progress to the more severe and permanent form of intrahepatic cholestasis (PFIC), indicative of a clinical continuum, with intermediate phenotypes between mild and progressive disease [4–6]. Therefore these diseases are preferably referred to as ATP8B1 deficiency and ABCB11 deficiency. Likewise, ABCB4 deficiency is used instead of PFIC3. The most prominent characteristics of these three genetic subtypes are summarized in Table 1.

Progressive familial intrahepatic cholestasis and benign recurrent intrahepatic cholestasis

ATP8B1 deficiency

Aetiology

ATP8B1 deficiency is an autosomal recessive disease caused by mutations in *ATP8B1* encoding ATP8B1 (formerly designated as FIC1), a P-type ATPase. ATP8B1 is abundantly expressed in a wide variety of tissues such as the small intestine, bladder and stomach and to a lesser extent also in the liver and pancreas. It is localized on the apical membrane of epithelial cells, including the canalicular membrane of hepatocytes [7–9]. The function of this P-type ATPase is not totally clear, but ATP8B1 appears to be no bile salt transporter itself. The most widely accepted hypothesis for ATP8B1 function is that of an aminophospholipid flippase, translocating phospholipids such as phosphatidylserine from the outer to the inner leaflet of the plasma membrane. In addition, a flippase-independent function of ATP8B1 in apical membrane organization was suggested recently [9]. Deficiency of ATP8B1 in the hepatocyte may result in the loss of asymmetric distribution of phospholipids in the canalicular membrane, decreasing both membrane stability and function of transmembrane transporters including the bile salt export pump, ABCB11 and, as such, causing cholestasis [10,11]. Extrahepatic manifestations such as the hearing loss, pancreatitis and diarrhoea, found in patients with ATP8B1 deficiency, suggest that perturbations in cellular membranes and/or a secondarily impaired function of transmembrane transporters can also be found in other organs [9,12–14].

To date, over 50 distinct mutations in *ATP8B1* are described [15–17]. The mutations G308V found in Amish, D554N found in Inuits and I661T are amongst the most frequently detected. The severity of ATP8B1 deficiency varies from benign remitting to progressive disease. A high variability in phenotypic presentation exists even in patients with the same mutation, so type and location of the mutation correlates only partially with the severity of clinical disease. Nevertheless mutations predicted to affect protein expression or function severely, such as nonsense and frameshift mutations, are more often detected in progressive disease, while missense mutations are more frequently identified in benign disease, possibly as a result of residual activity of ATP8B1 [16]. Recently genotype-phenotype correlations were further clarified by investigating the effects of several *ATP8B1* mutations on protein expression, localization and function. *In vitro*, it turned out that for common missense mutations such as G308V, D554N and I661T, ATP8B1 deficiency can be regarded as a protein folding disease, with different degrees of retention of the mutant protein in the endoplasmic reticulum, resulting in a decreased protein expression at the plasma membrane. Incubation at a reduced temperature could improve proper folding of some of the mutated proteins. Similarly, the