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Review Article

ATP-binding Cassette Transporter Defects and Their Roles in Hepatic Diseases

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Abstract

ATP-binding cassette (ABC) transporters are transmembrane proteins involved in the translocation of bilirubin, bile acids, phospholipids, and cholesterol into bile canaliculi. Mutations in particular genes encoding these transporters—including BSEP (*ABCB11* gene), MDR3 (*ABCB4* gene), sterolin-1 and sterolin-2 (*ABCG5/8* genes), and MRP2 (*ABCC2* gene)—result in a wide spectrum of liver diseases, ranging from benign conditions such as Dubin-Johnson syndrome to more severe presentations like progressive familial intrahepatic cholestasis. The severity of disease is influenced by many factors, including zygosity, mutation type, and environmental modifiers such as hormones, consanguinity, and founder effects. Homozygous and compound heterozygous mutations typically result in severe and early-onset diseases, while heterozygous single-allelic mutants generally result in milder diseases. Next-generation genetic testing has proven to have high diagnostic value and is important for prognostication. With knowledge of the underlying specific mutations, there is also potential for future targeted therapy for many severe diseases. The aim of this review is to update and discuss the hepatic diseases associated with ABC transporter mutations, the genetic and environmental effects that influence the severity of disease, typical presentations of these cholestatic hepatic diseases, diagnostic considerations, and treatment options.

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Introduction

ATP-binding cassette (ABC) transporters are transmembrane proteins that move substrates across lipid membranes. ABC transporter proteins are categorized into seven families encoded by *ABCA* through *ABCG* genes (Table 1). They are energized by ATP, which, when hydrolyzed, causes conformational change and induces transport.[1] In mammals, ABC transporters are primarily in the liver, intestine, blood-brain barrier, placenta, and kidney.[2]

The *ABCB11* gene on chromosome 2q24[3] encodes the bile salt export pump (BSEP) on the canalicular membrane.[4] Mutations can impair BSEP function, altering bile acid transport and causing cholestasis, as seen in Figure 1. More than 32,000 unique variants have been identified, including over 800 pathologic mutations of *ABCB11*.[5] *ABCB11* mutations have been linked to benign recurrent intrahepatic cholestasis (BRIC) type 2, intrahepatic cholestasis of pregnancy (ICP), oral contraceptive-induced cholestasis, and progressive familial intrahepatic cholestasis (PFIC) type 2.[6] In PFIC, an excess of toxic intrahepatic bile acids is thought to be responsible for hepatocellular damage and possible progression to chronic liver disease[7,8] as well as increased risk for hepatocellular carcinoma in the pediatric population.[9,10]

The *ABCB4* gene, located on chromosome 7, locus 21, encodes a phospholipid carrier protein, multidrug resistance 3 (MDR3), which is a "floppase" that translocates phospholipids from the inner to the outer leaflet of canalicular membrane lipid bilayers to be extracted by bile salts.[11–13] Biliary phosphatidylcholine typically serves as a carrier and solvent of cholesterol by forming mixed micelles. Over 20,000 *ABCB4* gene variants have been identified, of which more than 600 are considered pathologic mutations.[14,15] Mutations in the *ABCB4* gene result in decreased biliary phosphatidylcholine and decreased formation of simple micelles, as seen in Figure 1. *ABCB4* mutations in the adult population can present with intrahepatic cholelithiasis, PFIC3, ICP, or low phospholipid-associated cholestasis (LPAC) syndrome (Table 1). MDR3 dysfunction results in decreased solubility of cholesterol in bile, ultimately resulting in increased cholesterol precipitation and gallstones.[16] *ABCB4* mutations present with a broad spectrum of characteristics, including transient neonatal cholestasis, gallstones, liver cirrhosis, and end-stage liver disease.[17]

Because phosphatidylcholine is also protective to cholangiocyte epithelium, MDR3 dysfunction permits bile acid–mediated hepatocyte damage, which, if chronic, is associated with an increased risk of progression to secondary sclerosing cholangitis or biliary cirrhosis.[16,18–21] Rare cases of cholangiocarcinoma have also been reported.[22] Homozygous *ABCB4* cases usually present with more severe phenotypes, such as cirrhosis in pediatric patients. Heterozygous variants typically present in adults with features of PFIC.[23]

ABCG5 and ABCG8 genes in the *STSL* locus on chromo-

Keywords: ATP-binding cassette transporters; Cholestasis; Intrahepatic; Zygosity; Bile canaliculi; Next generation sequencing.

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Table 1. Relationship between zygosity of ABC mutations and corresponding phenotype(s)

Gene (Transporter)	Zygosity	Associated disease(s)	Progression to cirrhosis
ABCB11 (BSEP)	Homozygous/Compound Heterozygous	PFIC2 (severe cholestasis), early cirrhosis	High
	Heterozygous	BRIC2, ICP, OCC (transient/ mild cholestasis)	Low
	Biallelic Missense	BRIC2 (variable severity, dependent on mutation type)	Variable
ABCB4 (MDR3)	Homozygous/Compound Heterozygous	PFIC3, neonatal cholestasis, liver cirrhosis, end-stage liver disease	High
	Heterozygous	LPAC, ICP, DILI, ductopenic cholestasis	Low
	Heterozygous Missense (e.g., T175A, A250T, P352L)	MDR3 deficiency (variable protein dysfunction)	Variable (depends on variant and allele function)
ABCG5/8 (Sterolin1/2)	Homozygous/Compound Heterozygous	Sitosterolemia (with/without liver disease), chronic hepatitis	Possible (case-dependent)
ABCC2 (MRP2)	Homozygous	DJS (cosmetic, hyperbilirubinemia), risk for drug toxicity.	Rare
	Heterozygous	Mild abnormalities, altered excretion	Rare to possible (especially with drug exposures)

PFIC2, progressive familial intrahepatic cholestasis type 2; OCC, oral contraceptive-associated cholestasis; BRIC2, benign recurrent intrahepatic cholestasis type 2; DILI, drug-induced liver injury; ICP, intrahepatic cholestasis of pregnancy; LPAC, low phospholipid-associated cholestasis; DJS, Dubin-Johnson syndrome; MDR3, multidrug resistance 3; MRP2, multidrug resistance protein 2; sterolin 1/2, sterolin-1 and sterolin-2 heterodimer; BSEP, bile salt export pump.

some 2p21 encode proteins sterolin-1 and sterolin-2, respectively, which together form a heterodimer pair expressed on the canalicular hepatocyte membrane and are involved in the transport of hepatobiliary cholesterol from hepatocytes into the bile canaliculi.[24] Both sterolin-1 and sterolin-2 are synthesized in hepatocytes and form obligate heterodimers that translocate and embed in the hepatocyte apical membrane.[25] Over 8,800 variants of *ABCG5* and approximately 480 mutations have been identified, while over 20,000 variants and greater than 600 mutations of *ABCG8* have been reported.[26,27] Mutations in *ABCG5*/*ABCG8* result in elevated serum levels of cholesterol and other sterols, resulting in sitosterolemia (Fig. 1).[28] Mutations of *ABCG5*/*ABCG8* in mice have been shown to reduce biliary cholesterol and increase cholesterol in the liver.[29] Most patients with sitosterolemia have been found to have homozygous mutations.

The *ABCC2* gene is located on chromosome 10q24 and encodes the multidrug resistance-associated protein 2 (MRP2), a bile acid organic anion transporter involved in the transport of bilirubin and bile salts into bile (Fig. 1). MRP2 specifically excretes substances conjugated with glutathione, sulfate, and glucuronate and contributes to biliary flow.[30] Over 1,000 *ABCC2* mutations have been identified.[31] Deletion, missense, nonsense, and splice junction mutations have been identified as alterations to the *ABCC2* gene, leading to Dubin-Johnson syndrome (DJS). Autosomal recessive *ABCC2* mutations result in DJS with increased serum bilirubin glucuronides. Heterozygous individuals with *ABCC2* mutations are typically asymptomatic, whereas homozygous or compound heterozygous individuals developisolated elevation of conjugated hyperbilirubinemia.[7]

Zygosity of mutations in ABC genes appears to be a major determinant for the observed spectrum of disease (Table 1).[32,33] This refers to homozygous versus heterozygous genetic pairing of alleles, the former indicating two identical mutant alleles and the latter indicating a mutant and a normal allele. A compound heterozygote represents the presence of different (non-identical) mutant variants of alleles and can also lead to severe presentations. Genetic dosing refers to the number of mutant alleles (mono- versus biallelic), which often correlates with the severity of disease expression.

Severe cases of *ABCB11* defects that lead to PFIC2 are most often biallelic (homozygous or compound heterozy-

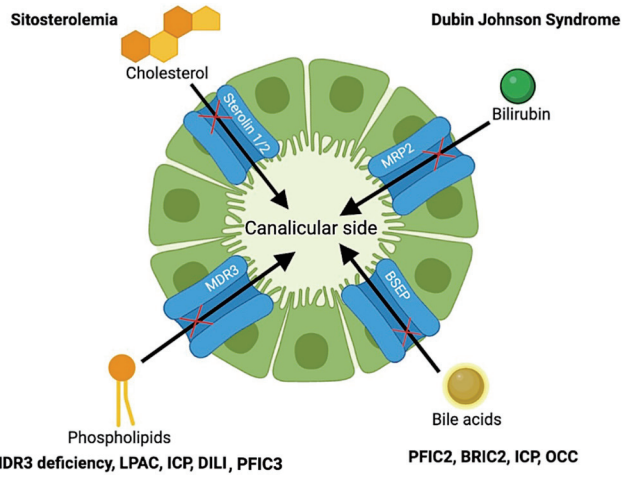

Fig. 1. A diagram showing ABC transporters, their substrates, and the associated diseases that result from mutations in specific ABC transporters. MDR3 defects are involved in the development of PFIC3, LPAC, ICP, and DILI. Sterolin 1/2 are cotransporters that transport plant sterols and can lead to sitosterolemia if mutated. MRP2 is responsible for the reuptake of conjugated bilirubin; mutations result in Dubin-Johnson syndrome. BSEP transports bile acids and is also located at the bile canalicular membrane. Mutations in this transporter are associated with PFIC2, BRIC2, ICP, and OCC. Created by BioRender. PFIC3, progressive familial intrahepatic cholestasis type 3; PFIC2, progressive familial intrahepatic cholestasis type 2; OCC, oral contraceptive-associated cholestasis; BRIC2, benign recurrent intrahepatic cholestasis type 2; DILI, drug-induced liver injury; ICP, intrahepatic cholestasis of pregnancy; LPAC, low phospholipid-associated cholestasis.

gous) variants.[34] In heterozygous (monoallelic) *ABCB4* transporter mutations, the phenotype is typically less severe, as in LPAC, ICP, ductopenic cholestatic liver disease, and drug-induced liver injury.[35–37] Gord-Gilart *et al*. studied heterozygous *ABCB4* missense variants in a pediatric population of 67 patients with chronic cholestasis and features of MDR3 deficiency and found various degrees of protein dysfunction. *ABCB4* variant T175A led to a 65.5% decrease in MDR3 activity, A250T had a 90% reduction of activity, and P352L resulted in reduced protein levels, suggesting different variants have specific functional consequences. Approximately 50% of MDR3 expression and function is presumed to be contributed by a normal allele in heterozygous individuals.[35] Homozygous (biallelic) *ABCB4* transporter mutations and compound heterozygous mutations lead to higher rates of progression to cirrhosis, as seen in PFIC3.[23]

Studies have shown that biallelic mutations do not always result in severe cholestatic disease, as they are dependent on the type of mutation (e.g., missense, truncating, splicing) and can be influenced by extrinsic environmental factors.[38,39] Biallelic missense mutations can sometimes result in less severe presentations compared to truncating and splicing mutations.[39] For example, Al-Hussaini *et al*. studied 65 pediatric patients with PFIC1–3 cholestatic disease and identified 27 different mutations that resulted in defective *ATP8B1*, *ABCB11*, and *ABCB4*. Of the 35 patients with *ABCB11* mutations, four with heterozygous missense mutations in *ABCB11* had transient PFIC2-associated cholestasis.[39] Compound heterozygous missense mutations, on the other hand, have been shown to cause early-onset, severe, and progressive PFIC2-associated liver disease.[40] Frameshift, homozygous splicing, and nonsense mutations developed severe phenotypes of PFIC2.[40]

The aim of this review is to provide an update on the diverse genetics, phenotypic presentations, diagnosis, and treatment of ABC transporter mutation-associated diseases.

Specific diseases caused by *ABCB11* mutations: ICP, BRIC, and PFIC2

Mutations of *ABCB11* encoding BSEP can give rise to a spectrum of cholestatic disorders of varying severity.

ICP

Epidemiology: The prevalence of *ABCB11* mutation is not certain. The incidence has been estimated to be between 1/50,000 and 1/100,000.[3] This accounts for 37.5%–90.0% of cholestatic patients.[41] *ABCB11* mutations have been primarily identified in European and American populations.[42,43]

The prevalence of ICP has been reported to range from 0.3%–5.6% and the incidence from 0.1% to 15.6%.[44,45] A meta-analysis showed a significantly increased risk for ICP in patients with pre-existing hepatobiliary disease (pooled risk ratio: 2.81, 95% confidence interval: 2.66–2.97, $P < 0.00001$).[46]

Presentation: ICP typically presents in the second trimester of pregnancy with generalized pruritus, more commonly located on the palms and soles in 25% of patients.[47] Symptoms of pruritus are typically worse in the evenings.[47] Only about 10% of patients with pruritus develop icterus.[47,48] Other symptoms, such as fatigue, nausea, vomiting, right upper quadrant abdominal pain, dark urine, and pale stools, may also be present.[49] Symptoms generally resolve after delivery of the fetus but can persist for up to one to two weeks.[47] Excoriation from pruritus in pregnant individuals is typically seen on physical exam.[49]

While maternal symptoms are troublesome, the main medical concern of ICP is poor fetal outcomes, including preterm delivery in 19%–60%,[21,50] fetal distress in 22%–41%,[50,51] and intrauterine fetal death in 0.8%–1.6% of ICP pregnancies.[48,50,51] Fetal risks increase with increasing levels of maternal serum bile acids.[52–54]

Diagnosis: ICP is diagnosed by the presence of pruritus in the second trimester. The combination of pruritus and an increase in serum bile acids is highly suggestive of ICP.[47] Blood tests, including total serum bile acid level greater than 10 μmol/L[54,55] and elevated aminotransferases, support the diagnosis of ICP in the absence of other causes of cholestasis.[54,56] Severe ICP, in which there is an increased risk for fetal complications, has been associated with higher levels of serum bile acids > 40 μmol/L.[52–54] Serum bile acid and alanine aminotransferase (ALT) due to ICP return to normal ranges within three weeks postpartum.[54] Ultrasound imaging is generally used to exclude other causes of cholestasis. Liver biopsy is rarely needed.[54] Genetic testing is not routinely recommended for the diagnosis of ICP.

Treatment: Ursodeoxycholic acid (UDCA) has been shown to significantly improve ICP-related pruritus and decrease mean bile acid levels by 79%, bilirubin levels by 50%, and ALT by 80%, $P \leq 0.01$.[57] In addition, because UDCA creates a more hydrophilic component to bile acids, bile acid-induced hepatotoxicity and mitochondrial integrity are ameliorated.[58,59] Bacq *et al*. found improvement of serum ALT in 65.9% of patients with ICP after UDCA treatment compared to 20% ($P < 0.0001$) for placebo, and normalization of serum ALT was observed in 27.8% with UDCA but only 14.3% with placebo ($P < 0.001$). Bile acid levels improved in 54.3% of ICP patients on UDCA treatment compared to 18.6% on placebo ($P < 0.01$).[57]

Cholestyramine binds to bile acids in the gut, preventing reabsorption of bile acids and reducing bile acid levels, and is recommended to treat pruritus. Recent evidence suggests that pruritogens such as lysophosphatidic acid, sulfated progesterone metabolites, and autotaxin bind to neuroreceptors such as MRGPRX4 that trigger pruritus.[60] Cholestyramine does not directly affect these receptors[60] and, therefore, only provides partial relief by preventing bile acid accumulation.[61] Cholestyramine has been reported to be less effective than UDCA in improving serum aspartate aminotransferase (AST) and ALT (21.4% compared to >70%, $P < 0.01$) and pruritus (66.6% vs. 19.0%, respectively; $P < 0.005$).[62]

BRIC

Epidemiology: Data on the prevalence of BRIC are not available, but it has been reported to be less prevalent than PFIC2.[63]

Presentation: BRIC can present at any age, though it typically presents by the age of 20 years with recurrent episodes lasting weeks to months.[64] BRIC is characterized by acute onset of recurrent bouts (at least two episodes) of cholestasis that present as jaundice and severe pruritus, with periods of no symptoms for weeks to years,[65] and normal laboratory and histology findings during the intervening periods.[59] Patients may have prodromal symptoms such as fatigue, poor appetite, and nausea, accompanied by weight loss.[65] The recurrence of symptoms in young patients with asymptomatic periods should raise suspicion for BRIC.

Diagnosis: BRIC is diagnosed by the presence of cholestasis with severe pruritus and at least two episodes of jaundice interspersed with asymptomatic periods. Typical laboratory findings include elevated serum conjugated bilirubin, alkaline phosphatase with normal GGT levels, and normal bile ducts on imaging. Liver biopsy is usually unnecessary.[66,67] Next-generation sequencing (NGS) remains the gold standard in

differentiating BRIC from PFIC2.[59]

Treatment: Cholestyramine and UDCA are common treatment options for pruritus from BRIC. Rifampicin has also been reported to reduce pruritus and abort cholestatic episodes by activation of the nuclear pregnane X receptor and induction of bile acid sulfation.[59,68] Alternatively, endoscopic nasobiliary drainage has been provided as a method to decompress bile in the common bile duct, resolving pruritus and jaundice.[59] Fibrates that inhibit bile acid synthesis and improve bile excretion may also be a treatment option.[69] Ileal bile acid transport inhibitors have recently also been used as BRIC therapy.[70,71]

PFIC2

Epidemiology: The incidence of *ABCB11* mutations has been estimated to be between 1/50,000 and 1/100,000, with approximately half of the cases represented by PFIC2.[3]

Presentation: The p.Val444A1a variant of *ABCB11* mutation accounts for 50% of BSEP transport dysfunction. Once BSEP activity falls below 20%–25%, liver damage usually occurs due to biallelic loss-of-function causing PFIC2. Onset can occur in adulthood, but PFIC2 typically presents in neonatal/early infancy.[72] Because of this early presentation, end-stage liver disease and development of hepatocellular malignancy may occur before the age of 1 year.[3] Heterozygous individuals are often spared chronic liver injury.[73] Baker *et al*. reported that jaundice, pruritus, hepatomegaly, splenomegaly, and discolored stools were the most common clinical presentations of PFIC2.[41] Davit-Spraul *et al*. studied 36 patients with PFIC2 and found that 100% of the patients developed pruritus, 97% developed hepatomegaly, and 41% had splenomegaly. Jaundice presented in 11% on presentation.[58] Symptoms have been reported to appear within the first month of life in 44% of PFIC2 patients.[58] Excoriation and hyperpigmentation of the skin were common physical findings. In severe cases, portal hypertension can develop by one year of age.[72] Early onset of jaundice is a commonly used indication for workup for possible PFIC2 after exclusion of common causes of hyperbilirubinemia in infancy.[74]

PFIC2 defects may result in fat-soluble vitamin deficiencies and coagulopathy (vitamin K), ataxia and peripheral neuropathy (vitamin E), rickets or osteomalacia (vitamin D), and/or night vision issues and xerophthalmia (vitamin A).[75] Compared to PFIC1 (*ATP8B1* mutation), PFIC2 presents with more severe and persistent cholestasis.[72]

Diagnosis: PFIC2 cases typically have elevated conjugated bilirubin levels without elevated GGT because PFIC2 affects the BSEP without damaging the bile duct epithelium, where GGT is produced. Ultrasonography is helpful in excluding surgical causes for cholestasis, such as choledochal cysts or biliary atresia.[76] NGS confirms the diagnosis and remains the gold standard for diagnosis.[59] Liver histology of PFIC2 may show hepatocellular necrosis, giant cell transformation, and evidence of cirrhosis.[58] Immunostaining for MDR3 and BSEP antibodies can permit differentiation between PFIC2 and PFIC3 because BSEP expression is markedly reduced in PFIC2, but preserved in PFIC3. The opposite would be expected for MDR3 staining.[58] While liver biopsy can be helpful in providing supportive findings, it is not required to diagnose PFIC2, as genetic testing remains the gold standard.[74,76]

Treatment: PFIC2 is often treated initially with UDCA. Phenobarbital can be used to treat neonatal hyperbilirubinemia through CYP enzyme UDP-glucuronosyltransferase induction.[74] Partial internal biliary drainage reduces the circulation of bile salts and decreases accumulation of bile salts. Partial internal biliary drainage is the gold standard therapy for non-cirrhotic, low-GGT cholestatic disease as seen in *ABCB11* mutations when unremitting pruritus is present. Partial external biliary diversion requires a permanent stoma. Therefore, ileal exclusion or partial internal biliary diversion methods have been proposed, but there are limited data on long-term outcomes.[77] Ileal bypass procedures have also been utilized in those with prior cholecystectomy. However, long-term efficacy remains unknown.[74] If these options fail, liver transplantation is the recommended alternative.[74]

Specific diseases caused by *ABCB4* mutations: ICP, LPAC, and PFIC3

Mutations in the *ABCB4* gene encoding MDR3 are responsible for several cholestatic liver diseases, including ICP, LPAC, and PFIC3.

ICP

As discussed above, predisposed women with mutations in *ABCB11* develop decreased BSEP activity due to elevated estrogens during pregnancy and share a similar mechanism with mono-allelic *ABCB4* mutations. The *ABCB4* biallelic form is generally a more severe form of ICP and is associated with progression to liver cirrhosis and end-stage liver disease.[18]

LPAC

Epidemiology: LPAC syndrome is rare, with prevalence reportedly less than 5% of patients with cholelithiasis.[78] Studies have suggested LPAC is present in 1% of adult patients with symptomatic cholelithiasis.[16,79] LPAC has been reported to occur in a female-to-male ratio of nearly 3:1.[80]

Presentation: LPAC presents with recurrent biliary symptoms, typically before age 40, and with persistent recurrent symptoms despite cholecystectomy.[23] In a study of 308 patients with LPAC, 95% experienced biliary colic.[79] Recurrence of biliary symptoms after cholecystectomy was reported in 86% of patients with LPAC, so this history should raise clinical suspicion for LPAC.[79] Patients diagnosed with *ABCB4* mutations as adults were observed to have less severe phenotypes, such as ICP and LPAC.[23]

Diagnosis: LPAC diagnosis is made based on two of three diagnostic criteria: recurrent symptoms despite cholecystectomy, presence of hyperechogenic intrahepatic foci, sludge or microlithiasis on ultrasound, and/or age of onset less than 40 years.[16] Imaging with ultrasonography of the liver is crucial in identifying intrahepatic sludge, microlithiasis, and hyperechoic foci with acoustic shadowing.[16] Biopsy findings are variable and nonspecific and not required for diagnosis.[16] Although *ABCB4* gene mutation identification with NGS is helpful in supporting diagnosis, its absence does not exclude LPAC, as 56%–65% of cases may lack *ABCB4* gene mutations.[16]

Treatment: UDCA is the preferred treatment for LPAC. Prevention by prophylactically treating with UDCA has proven effective in reducing recurrence.[80,81]

PFIC3

Epidemiology: The prevalence of PFIC3 has not been determined with certainty.[58] Nearly 1/3 of PFIC cases involve PFIC3.[82] There does not appear to be a sex predominance.[72]

Presentation: Biallelic mutations of *ABCB4* are associated with severe pediatric liver disease such as PFIC3. PFIC3 typically presents in infancy to early adulthood.[72] Schatz *et al*. studied 38 PFIC3 patients with homozygous or heterozygous *ABCB4* mutations and identified 26 patients with pruritus. Of these, 85% presented with hepatomegaly and 96% with

splenomegaly. Jaundice was seen in 62% of patients, and portal hypertension was noted in 69%.[33] PFIC3 can present with pruritus, although it is often less severe than PFIC2. Extrahepatic manifestations are uncommon.[33] Pediatric and early adult patients with unexplained cholestatic symptoms should be considered for a PFIC3 workup.[58]

Diagnosis: Diagnosis of PFIC3 is made by finding conjugated hyperbilirubinemia, including elevated serum ALT, alkaline phosphatase, and serum GGT. GGT was found to be increased in all patients; ALT was increased in 78.3%, AST in 91.3%, total bilirubin in nearly 70%, direct bilirubin in 73.9%, and total bile acid in 87%. Serum fasting bile acids were also typically elevated, while biliary concentrations remained in the normal range.[11] Cao *et al*. analyzed 23 patients, 14 of whom with *ABCB4* biallelic gene-related cholestatic liver disease were diagnosed as PFIC3, while the remaining variants were diagnosed with ICP, LPAC, or drug-induced liver injury. They also found liver fibrosis by abdominal ultrasound, CT, and/or MRI in all patients. Liver biopsies obtained in 19 patients revealed small bile duct hyperplasia in nearly 85%, copper staining in 42.1%, and cirrhotic changes in 63.2%.[14] Inflammatory infiltrates periportally with evidence of fibrosis and giant-cell transformation were also seen. Cholesterol crystals in bile ducts, with features of chronic cholangiopathy and cholesterol clefts, have been described.[11]

Using comprehensive bile acid profiling, tauro-tetrahydroxylated bile acid levels have been reported to be of value in predicting the clinical outcome of low-GGT intrahepatic cholestasis patients.[83] Genetic analysis utilizing[84] non-translated regions may be under-detected.[84]

Treatment: UDCA is the first-line therapy in PFIC3. Rifampicin and cholestyramine may also be used for management of pruritus.[33] Pharmacologic agents that target *ABCB4* gene transcription induction by farnesoid X receptor (FXR) agonists or peroxisome proliferator-activated receptor (PPAR)-α ligands have been suggested as potential second-line options.[33]

Management for *ABCB4* gene mutations includes ensuring dietary fat and fat-soluble vitamins are supplemented appropriately, particularly vitamin D, as studies have shown vitamin D deficiency in mouse models led to worsened liver fibrosis, suggesting possible protective benefit.[33]

Liver transplantation may be considered in patients with end-stage liver disease, HCC, or in those who are not responsive to medical therapies.

Specific diseases caused by *ABCG5* and *ABCG8* gene defects: Sitosterolemia

In contrast to bile acid and phospholipid transporters discussed above, *ABCG5* and *ABCG8* gene mutations primarily disrupt sterol homeostasis. Loss of function in the encoded transporters results in impaired biliary cholesterol efflux, clinically recognized as sitosterolemia.

Sitosterolemia

Epidemiology: *ABCG5* and *ABCG8* gene variants have been reported to range between 5% and 30% in the general population.[24] However, sitosterolemia is rare, with a reported prevalence of one in about 200,000 having homozygous or compound heterozygous mutations.[85]

Presentation: Sitosterolemia is characterized by elevated serum levels of plasma plant sterols and cholesterol. Patients may have the classic presentation of tendinous and tuberous xanthomas and premature coronary atherosclerosis.[86,87] Do *et al*. studied the presentations of 14 pediatric patients with sitosterolemia and observed xanthomas in 85.7% of patients, located in the elbow joint, buttocks, knees, ankle creases, wrist, and extensor surfaces. Arthralgia was present in 14.3% of patients.

This presentation may simulate that of familial hypercholesterolemia, although tendon xanthomas have been reported to be more severe in sitosterolemia than in heterozygous familial hypercholesterolemia. Patients with sitosterolemia may also present with hemolytic anemia, macrothrombocytopenia, and splenomegaly as a result of elevated sterol concentration in blood cell membranes.[88]

Diagnosis: Sitosterolemia can be diagnosed by clinical manifestations, a plasma concentration of sitosterol above 1 mg/dL, cerebrotendinous xanthomatosis, and confirmation of *ABCG5* and *ABCG8* mutations by NGS.[85,89] Kidambi *et al*. found sitosterol concentrations as high as 65 mg/dL.[58] Non-invasive coronary and carotid plaque management is often needed due to its significant impact on the cardiovascular system.[89,90]

Treatment: First-line treatment for sitosterolemia is avoidance of plant sterol-rich foods, including corn oil, sesame oil, margarine, avocado, peanuts, soybeans, among other fruits and vegetables. Cholesterol-rich foods should also be avoided.

Pharmacologic therapies such as ezetimibe and bile-acid sequestrant resins are recommended to help reduce sitosterol and lower LDL cholesterol levels. HMG-CoA reductase activity is inhibited in sitosterolemia. Therefore, statin therapy is not recommended for primary preventative therapy, although it can be used in possibly reducing atherosclerotic cardiovascular risks. Liver transplantation has been reported for treatment of sitosterolemia-induced liver cirrhosis.[91]

Specific diseases caused by *ABCC2* gene defects

DJS

Epidemiology: More than 50 mutations in MRP2 have been associated with DJS.[14,15] There is no known ethnic predisposition to DJS, although Sephardic Jews have been noted to have a higher frequency of disease burden.[92] The estimated prevalence of DJS is 1/1,300 individuals. DJS cases have primarily been reported as case reports.[93]

Presentation: DJS typically presents with asymptomatic mild jaundice and dark urine without pruritus. Abdominal pain and weakness have been rarely reported.[94,95]

Diagnosis: DJS presents with jaundice due to conjugated hyperbilirubinemia without hemolysis. Patients typically have elevated total bilirubin levels (2–5 mg/dL), while ALT, AST, alkaline phosphatase, and complete blood count remain normal. Although bilirubin levels are usually only mildly elevated, levels as high as 19 mg/dL have been reported.[96] Urinary coproporphyrin levels are elevated, of which 80% are coproporphyrin I isomers. Normally, 75% of urinary coproporphyrin consists of isomer III.[96] Cholescintigraphy can show delayed bromsulfthalein uptake and very slow excretion from hepatocytes, with visualization of the hepatobiliary tract. However, imaging is usually unnecessary to diagnose DJS. Liver biopsy is not required for the diagnosis of DJS. However, liver histology has been reported to reveal pigment deposits in lysosomes of hepatocytes.[97]

Treatment: DJS is a benign disease and, therefore, does not pose a risk for progressive disease. Phenobarbital and UDCA can be considered in the management of cholestasis in neonatal DJS.[98] Because many medications are normally eliminated by the hepatic MRP2 exporter, DJS patients should be advised regarding possible risk of excess blood levels of medications due to decreased hepatic elimination.[98]

Discussion

ABC transporter genetic defects, in combination with environmental factors, affect clinical presentations and disease severity.[99] For example, reproductive hormones such as estrogen and progesterone significantly influence the cholestatic presentation of ICP when hormone levels peak in the third trimester of pregnancy and in subsequent pregnancies.[100] Studies have demonstrated that progestin administration in patients with threatened preterm labor is associated with a significantly higher risk of ICP.[101–103] Tsur *et al*. studied over 800,000 pregnancies and found that vaginal progesterone use in the second and third trimesters was associated with a significantly increased risk for cholestasis compared to no progesterone therapy (odds ratio 3.16).[102] 17α-estradiol can also induce ICP by inhibiting the activity of BSEP.[104] Medications such as cyclosporine A, bosentan, oral contraceptives, and cyclosporine have been reported to inhibit ABC transporter BSEP or MDR3 function and lead to cholestatic patterns that present as drug-induced liver injury.[105]

ABC transporter mutations can be suspected based on clinical presentation and laboratory findings, but genetic testing is the gold standard for the diagnosis of most inherited cholestatic diseases. Studies have found that nearly half of patients with unexplained cholestatic liver disease after standard diagnostic workup had detectable gene variants for PFIC mutations in the *ABCB4* and *ABCB11* genes.[20,33,106]

Individuals with early-onset and progressive liver disease, unexplained cholestasis, ICP, LPAC, drug-induced cholestasis, or a family history of cholestatic diseases should consider genetic testing for ABC transporter mutations.[73,107]

Several genetic tests are available, ranging from targeted panels to more comprehensive genome testing. These include Sanger sequencing, NGS, and WES.[33] Commercial kits such as TaqMan assays and SmartAmp2 allow for rapid detection of single-nucleotide polymorphisms and specific variants of ABC transporters.[37,108] Full gene sequencing may be used when clinical suspicion for a pathologic variant is high but targeted testing is negative. WES has shown superior sensitivity in detecting pathogenic variants, particularly in non-coding or regulatory regions. By incorporating family history and biochemical markers, genetic testing can further enhance diagnosis and inform treatment options. Multigene panel testing or whole-genome testing can be used to screen and identify key genes such as ATP8B1, *ABCB11*, and *ABCB4*, among others.[109] Chen *et al*. studied three tiers of genetic analysis, including Sanger sequencing, panel-based NGS, and WES.[110] WES had significantly higher diagnostic sensitivity and identified almost 32% of patients with pathogenic variants who were negative for mutations on NGS.

Consanguinity has been shown to increase the risk for ABC transporter-related disease. Cheema *et al*. studied genetic cholestatic disorders in 171 children and identified consanguinity in 88.1% of cases, with a family history of at least one affected sibling in nearly 65% of cases.[111] Al-Hussaini *et al*. identified 65 patients, of whom 85% had consanguineous parents, with pathologic *ATP8B1* (n = 5), *ABCB4* (n = 25), or *ABCB11* (n = 35) gene mutations and early-onset cholestatic disease.[39] Other cases have been reported with severe PFIC in homozygous *ABCB4* mutations in children born to consanguineous parents.[112,113] Therefore, careful family histories can provide important indices of suspicion in cases of unexplained cholestasis. Xiao *et al*. performed large-scale population whole-exome and whole-genome sequencing on over 100,000 individuals across diverse ethnogeographic groups, suggesting that ABC transporter presentations may have population- and inter-ethnic genetic variability.[114] *ABCB4* and *ABCB11* gene mutations have not been studied in isolated communities such as Inuit or Amish groups, but there is evidence of a significantly increased presence of ABC transporter-related liver disease in ATP8B1 deficiency, likely due to "founder mutations," which result in high-frequency genetic alterations from a small ancestral cohort.[115,116] Other ABC transporter mutation variants have yet to be studied in these populations.

Because of evidence associating zygosity with severity of phenotype, genetic testing can provide important diagnostic and prognostic information and decrease the risk of biallelic offspring and severe disease through genetic counseling. It is recommended that diagnosis and genetic testing be done using a multidisciplinary approach, including genetic counseling to assist with family planning and provide the necessary psychosocial support.[117]

Clinical implications and future directions

Pregnancy-associated hormone changes and exogenous use of progesterone have been associated with cholestatic disease in predisposed patients. Certain pharmacologic agents, including antibiotics and chemotherapy agents, among others, have been shown to inhibit transporter activity, triggering symptoms.

Consanguinity and the founder effect have a significant impact on the incidence and severity of ABC transporter-associated cholestasis, as 85%–90% of affected individuals have parental consanguinity.

UDCA and rifampicin may provide symptomatic relief in mild disease presentations, but surgical interventions, including partial biliary diversion and liver transplant, may be needed in refractory or severe progressive disease.

Pediatric patients and those with delayed presentations of clinical cholestasis of undetermined etiology, or a family history of cholestatic disease, should be considered for NGS or WES genetic testing. Genetic counseling should be considered, particularly in consanguineous populations where homozygous or compound heterozygous mutations are more prevalent.

Cell culture and animal models have provided fundamental insight into ABC transporter–mediated hepatic disease mechanisms as well as potential novel therapies. The latter include targeted therapeutic interventions with FXR agonists[118] and PPAR ligands. Wagner *et al*. studied common bile duct–ligated wild-type (FXR +/+) and FXR knockout (FXR -/-) mice and observed preservation of *ABCB11* expression in wild-type mice but undetectable BSEP expression in knockout mice, suggesting BSEP dependence on FXR in mouse models.[119] Ogata *et al*. treated human THP-1 macrophage cells, human WI38 fibroblast cells, and mouse fibroblast cells with PPAR agonists such as fenofibrate, bezafibrate, and gemfibrozil, and observed increased *ABCA1* mRNA and protein levels. The effects of fenofibrate and PPAR ligand LY518674 on ABCA biogenesis decreased in the absence of PPARα, as studied in mouse fibroblasts.[120]

Gene-editing and adeno-associated viral (AAV)–mediated gene replacement techniques have been studied to restore *ABCB11* and *ABCB4* transporter function.[121,122] Aronson *et al*. administered AAV serotype 8-mediated gene therapy, derived by cloning hABCB4 cDNA into a modified AAV expression cassette, as a single dose to *ABCB4* knockout mice and found restoration of biliary phospholipid excretion with normalization of plasma alkaline phosphatase and bilirubin.[123]

Patient-derived hepatocyte and cholangiocyte models have also been studied and have shown the ability to use induced pluripotent stem cell-derived cells to study variant-specific targeted drug responses.[124] Induced pluripotent stem cells

were prepared from BSEP-deficient patients (*ABCB11* mutation) and differentiated into hepatocyte-like cells. Imagawa *et al*. utilized 4-phenylbutyrate (a potential PFIC2 treatment) in BSEP-deficient hepatocyte-like cells and found that the level of BSEP expression and the calculated biliary excretion index were preserved.[125]

Future research should be directed toward translating animal model findings into early-phase human trials to target and individualize the management of ABC transporter-associated cholestatic disease.

Conclusions

ABC transporters are vital for bile acid, phospholipid, cholesterol, and bilirubin excretion and can be involved in the export of toxins associated with pharmacotherapies. ABC transporter mutations are underrecognized causes of inherited hepatobiliary diseases that present as a spectrum of cholestatic disorders ranging from benign episodic cholestasis to progressive liver failure. *ABCB11*, *ABCB4*, ABCC2, and *ABCG5*/8 gene mutations can result in benign cholestatic syndromes such as BRIC, ICP, and DJS, or severe disease such as PFIC and sitosterolemia. Disease severity seems to be strongly influenced by zygosity, mutation type, and environmental triggers. Homozygous and compound heterozygous mutations, particularly in *ABCB11* and *ABCB4* genes, are associated with early-onset, severe, and progressive cholestatic disease. In contrast, heterozygous variants typically result in milder disease, such as ICP and LPAC.

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Conflict of interest

GYW has been an Editor-in-Chief of the *Journal of Clinical and Translational Hepatology* since 2013. He has no role in the publisher's decisions regarding this manuscript. DZ has no conflicts of interest related to this publication.

Author contributions

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