U.S. National Library of Medicine
National Center for Biotechnology Information

ATP8B1 Deficiency

Synonym: FIC1 Deficiency

Laura N Bull, PhD,[1] Raffaella Morotti, MD,[2] and James E Squires, MD, MS[3]

Created: October 15, 2001; Updated: September 9, 2021.

Summary

Clinical characteristics

The phenotypic spectrum of ATP8B1 deficiency ranges from severe through moderate to mild. Severe ATP8B1 deficiency is characterized by infantile-onset cholestasis that progresses to cirrhosis, hepatic failure, and early death. Although mild-to-moderate ATP8B1 deficiency initially was thought to involve intermittent symptomatic cholestasis with a lack of hepatic fibrosis, it is now known that hepatic fibrosis may be present early in the disease course. Furthermore, in some persons with ATP8B1 deficiency the clinical findings can span the phenotypic spectrum, shifting over time from the mild end of the spectrum (episodic cholestasis) to the severe end of the spectrum (persistent cholestasis). Sensorineural hearing loss (SNHL) is common across the phenotypic spectrum.

Diagnosis/testing

The diagnosis of ATP8B1 deficiency is established in a proband with suggestive clinical and laboratory findings and biallelic pathogenic variants in *ATP8B1* identified by molecular genetic testing.

Management

Treatment of manifestations: Cholestasis: pharmacotherapy is ineffective regardless of disease severity. In severe disease: the primary surgical therapy is interruption of the enterohepatic circulation which can reduce pruritus and slow or reverse the progression to hepatic fibrosis; when cirrhosis is present, liver transplantation may be the definitive therapy. Notably for some, secretory diarrhea can continue or worsen following liver transplantation. In mild-to-moderate disease, nasobiliary drainage and extracorporeal liver support may hasten the end of an episode of cholestasis. Pruritus: in severe disease pharmacotherapy has historically been ineffective; however, recent US Food and Drug Administration approval of ileal bile acid transporter inhibitors to treat pruritus introduces a novel therapeutic approach that holds great promise. Other options include UVB light therapy and plasmapheresis. In mild-to-moderate disease, pharmacotherapy may be efficacious. Secretory diarrhea can

Author Affiliations: 1 Liver Center Laboratory and Institute for Human Genetics Department of Medicine University of California, San Francisco San Francisco, California; Email: laura.bull@ucsf.edu. 2 Department of Pathology Yale School of Medicine New Haven, Connecticut; Email: raffaella.morotti@yale.edu. 3 UPMC Children's Hospital of Pittsburgh Department of Pediatric Gastroenterology and Hepatology Pittsburgh, Pennsylvania; Email: james.squires2@chp.edu.

require IV fluids or more palliative interventions. Poor growth may require medium-chain triglyceride-based formulas; fat-soluble vitamin deficiencies are treated symptomatically. SNHL is managed per standard protocols.

Surveillance: Routine monitoring of cholestasis, liver disease, pruritus, growth, and nutrition per treating hepatologist; routine audiograms for all individuals with ATP8B1 deficiency whether known to be symptomatic or not.

Agents/circumstances to avoid: Potentially ototoxic agents; oral contraceptive agent therapies can induce and/or exacerbate episodes of cholestasis.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment, surveillance, and awareness of agents and circumstances to avoid.

Genetic counseling

ATP8B1 deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ATP8B1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being a heterozygote (carrier), and a 25% chance of inheriting both normal alleles. Once the *ATP8B1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

ATP8B1 Deficiency: Phenotypic Continuum
• Severe ATP8B1 deficiency (progressive familial intrahepatic cholestasis type 1 [PFIC1])   • Mild-to-moderate ATP8B1 deficiency (benign recurrent intrahepatic cholestasis 1 [BRIC1])

For synonyms and outdated names see Nomenclature.

Diagnosis

No consensus clinical diagnostic criteria for ATP8B1 deficiency have been published.

Suggestive Findings

ATP8B1 deficiency **should be suspected** in individuals with the following clinical findings, laboratory findings, histologic findings on liver biopsy, and family history.

While mild-to-moderate and severe phenotype classifications have been proposed, ATP8B1 deficiency occurs along a continuous spectrum of severity.

Clinical Findings

Severe ATP8B1 deficiency. Unremitting cholestasis (typically beginning within the first few months of life) manifesting as [Davit-Spraul et al 2010, Pawlikowska et al 2010]:

- Jaundice
- Clinically significant diarrhea
- Failure to thrive
- Hemorrhage (due to the coagulopathy of vitamin K deficiency)
- Hepatosplenomegaly
- Pruritus

- Discolored and/or pale stools

The first episode of cholestasis in infancy may herald disease anywhere along the phenotypic continuum, including subsequent cirrhosis and end-stage liver disease or liver disease that appears likely to evolve to end stage if untreated.

Mild-to-moderate ATP8B1 deficiency (also sometimes termed benign recurrent intrahepatic cholestasis [BRIC])

- Episodes of cholestasis typically involve jaundice and pruritus; however, milder episodes may include pruritus only.
- Age at onset of the first episode of cholestasis, the length of episodes, and the duration of disease-free intervals between episodes vary greatly.
- "Benign" generally refers to lack of progressive liver disease; however, this may be a misnomer as quality of life and other health-related manifestations may be affected. Also, some individuals who initially experience episodic manifestations may eventually develop progressive liver disease.

Preliminary Laboratory Findings

Findings on standardized serum-based clinical-biochemistry tests used to evaluate cholestasis are summarized in Table 1.

Cholestasis as manifest by conjugated or direct hyperbilirubinemia and/or hypercholanemia in the setting of normal to low gamma-glutamyltranspeptidase (γ-GT) for age suggests ATP8B1 deficiency.

Note: Conjugated bilirubin levels may not be an accurate marker of cholestasis.

Findings consistent with severe ATP8B1 deficiency

- Serum γ-GT activity is low to normal despite conjugated hyperbilirubinemia and/or severe pruritus.

  Note: Because γ-GT activity is elevated in most types of cholestasis, forms of cholestasis in which γ-GT is not elevated are called "low-γ-GT cholestasis."

- Serum concentration of cholesterol is usually not elevated (an unusual finding in cholestasis).

- Serum concentration of total bile acids is elevated, often markedly so [Davit-Spraul et al 2010, Pawlikowska et al 2010].

Findings consistent with mild-to-moderate ATP8B1 deficiency. Serum γ-GT activity is low to normal despite conjugated hyperbilirubinemia (see Table 1).

Table 1. Serum Studies Consistent with ATP8B1 Deficiency

Phenotype	Serum γ-GT Activity	Serum Concentration of Cholesterol	Serum Concentration of Total Bile Acids	Serum Concentration of Conjugated Bilirubin
Severe	Low to nl [1]	Low to nl [1] (HDL low, oxidized LDL high, triglycerides high) [2]	Markedly ↑	High early w/resolution; subsequent ↑ w/end-stage liver disease

Table 1. continued from previous page.

Phenotype	Serum γ-GT Activity	Serum Concentration of Cholesterol	Serum Concentration of Total Bile Acids	Serum Concentration of Conjugated Bilirubin
Mild to moderate	Low to nl [3]	Usually low to nl during symptomatic periods [4]	Markedly ↑ during symptomatic periods; nl between episodes	Nl between episodes; variable increases during symptomatic periods

HDL = high density lipoprotein; LDL = low density lipoprotein; γ-GT = gamma-glutamyltranspeptidase; nl = normal

1. Usually elevated in cholestatic liver disease.
2. Nagasaka et al [2005], Nagasaka et al [2009], Pawlikowska et al [2010]
3. May be elevated at onset or at resolution of an episode of cholestasis.
4. Detailed study of one individual with mild ATP8B1 deficiency demonstrated low HDL and other lipid abnormalities during a bout of cholestasis [Nagasaka et al 2007].

Sweat chloride. Concentration of electrolytes in sweat may be elevated.

Liver imaging. Findings are generally variable and reflect disease severity. In progressive disease, findings consistent with liver cirrhosis including hepatomegaly, echotexture abnormalities, and secondary splenomegaly can be seen.

Liver Biopsy

Liver biopsy in the acute diagnosis and management of an infant with cholestasis helps to distinguish between biliary obstruction (including biliary atresia) and other possible diagnoses such as genetic disorders resulting in cholestasis.

- **ATP8B1 deficiency vs biliary atresia.** The characteristic histopathologic features that associate with severe ATP8B1 deficiency in infants include bland intracanalicular cholestasis in the setting of relatively preserved lobular architecture with "tidy"-appearing and sometimes small hepatocytes. While bile ducts are sometimes small and inconspicuous and may appear hypoplastic, paucity of interlobular bile ducts is not seen, nor is the significant ductular reaction that is associated with biliary obstruction (including biliary atresia).
- **Genetic disorders resulting in cholestasis.** Although molecular genetic testing is typically replacing more traditional histopathologic investigations to establish a monogenic cause of cholestasis, the option of liver biopsy remains when such genetic testing is not available. See Histologic Findings (pdf) for more information.

Family History

Family history is consistent with **autosomal recessive inheritance** (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of ATP8B1 deficiency **is established** in a proband with suggestive findings and biallelic pathogenic variants in *ATP8B1* identified by molecular genetic testing (see Table 2). If molecular genetic testing is not available, see the histologic findings associated with ATP8B1 deficiency in Histologic Findings (pdf).

Note: Identification of biallelic *ATP8B1* variants of uncertain significance (or identification of one known *ATP8B1* pathogenic variant and one *ATP8B1* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Molecular genetic testing approaches can include **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of ATP8B1 deficiency has not been considered may be more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A cholestatic liver disease multigene panel that includes *ATP8B1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in ATP8B1 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ATP8B1	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Klomp et al [2004], Wang et al [2016], Dröge et al [2017], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

ATP8B1 deficiency encompasses a phenotypic spectrum ranging from severe through moderate to mild. Severe ATP8B1 deficiency is characterized by infantile-onset cholestasis that progresses to cirrhosis, hepatic failure, and death. Mild-to-moderate ATP8B1 deficiency was initially thought to involve intermittent symptomatic cholestasis with a lack of hepatic fibrosis; however, some persons with clinically diagnosed mild disease have hepatic fibrosis on biopsy. Furthermore, in some persons with ATP8B1 deficiency the clinical findings can span the phenotypic spectrum, shifting over time from the mild end (episodic cholestasis) to the severe end of the spectrum (persistent cholestasis) [van Ooteghem et al 2002].

Family members with the same *ATP8B1* pathogenic variants do not always have disease of the same clinical severity. In addition, clinical severity can change over time: mild disease diagnosed in childhood may progress in adulthood to severe disease [Morris et al 2015, Squires et al 2017].

Severe ATP8B1 deficiency. The age and onset of manifestations of severe ATP8B1 deficiency vary among affected individuals. Affected children typically present in the first year of life, often with severe pruritus and jaundice [Pawlikowska et al 2010, Morris et al 2015]. The onset of pruritus is often difficult to pinpoint because detection depends on an infant's ability to scratch in a coordinated manner; thus, in some infants irritability may be an initial manifestation of pruritus. Some individuals have been treated for long periods for chronic dermatologic conditions because of longstanding pruritus without typical findings of liver disease.

Secondary manifestations such as coagulopathy (due to vitamin K deficiency), malabsorption, and poor weight gain may present earlier than age three months.

While onset in the first year of life with progression to cirrhosis by the end of the first decade of life is typical in severe ATP8B1 deficiency, both interfamilial and intrafamilial variability have been noted among affected individuals with the same pathogenic variants [Bourke et al 1996, Bull et al 1999, Klomp et al 2004, Morris et al 2015, Squires et al 2017, van Wessel et al 2021].

Mild-to-moderate ATP8B1 deficiency is characterized by intermittent episodes of cholestasis, severe pruritus, and jaundice in the absence of extrahepatic bile duct obstruction. Episodes may last from weeks to months. Symptom-free intervals may last from months to years. Individuals may have variable or unknown triggers for some or all bouts of cholestasis.

In truly mild disease, chronic liver damage does not develop; however, in some individuals in whom ATP8B1 deficiency initially appears mild, clinical monitoring over time or detection of fibrosis on liver biopsy may indicate disease of moderate severity [van Ooteghem et al 2002, van Mil et al 2004a]. More recently, *ATP8B1* pathogenic variants have been reported in some adults with cryptogenic cirrhosis, suggesting further broadening of the phenotypic spectrum of ATP8B1 deficiency to include development of liver disease beyond the first decades of life [Vitale et al 2018].

See Table 3 for an overview of the distinguishing features of the severe and mild-to-moderate phenotypes.

Table 3. ATP8B1 Deficiency: Comparison of Phenotypes by Select Features

	Feature	Severe	Mild to Moderate
Hepatic	Cholestasis	Near universal	Common/intermittent
	Pruritus	Near universal	Common/intermittent
	Nutritional deficiencies (incl vitamins A, D, E, K)	Common	Rare
	Poor growth	Common	Rare
	Diarrhea	Common	Rare
	Chronic liver disease	Common	Some
Extrahepatic	Sensorineural hearing loss	Common	Common
	Pancreatitis or pancreatic exocrine insufficiency	Some	Some

Cholestasis. Although children with the severe phenotype may initially experience episodes of severe cholestasis followed by disease-free intervals, cholestasis eventually becomes constant. Triggers that increase the risk of cholestasis may include intercurrent illness, drug exposure, shifts in hormonal milieu (including those resulting from ingestion of contraceptive drugs and/or pregnancy), and coexistent malignancy.

Pruritus is typically severe and persistent; jaundice is often intermittent. While pruritus is disproportionately severe for the degree of hyperbilirubinemia, it is proportional to the elevation in serum bile acids. Significant skin excoriations, caused by constant scratching, are frequent.

Nutritional deficiencies. Complications of nutritional deficiencies can result in significant morbidity and mortality in individuals with the severe phenotype. Prolonged malabsorption of fat-soluble vitamins may lead to easy bruising or bleeding (caused by vitamin K deficiency), rickets (caused by vitamin D deficiency), and neurologic abnormalities (caused by vitamin E deficiency). In contrast, vitamin A levels – when measured – are often normal or elevated; supplementation is rarely required [Morris et al 2015, Squires et al 2017].

Poor growth becomes evident in early childhood. While this may be secondary to nutritional complications of cholestasis (which typically result in weight loss out of proportion to the decreased rate of linear growth), children with severe ATP8B1 deficiency typically manifest failure to thrive and poor growth beyond that expected in persons with cholestasis alone [Pawlikowska et al 2010].

Diarrhea. The profound diarrhea that can accompany ATP8B1 deficiency may also contribute to poor growth. Mechanisms are complex and may involve both pancreatic insufficiency and the extrahepatic (dys)function of ATP8B1 in the terminal ileum. Importantly, the diarrhea may persist or even worsen following liver transplantation [Davit-Spraul et al 2010, Pawlikowska et al 2010, Verhulst et al 2010, Folvik et al 2012, Bull et al 2018, Henkel et al 2021].

Chronic liver disease including (but not limited to) those resulting from complications of portal hypertension may develop. Cirrhosis and its attendant complications, including hepatic failure and death, typically ensue in the absence of surgical intervention such as partial biliary diversion or liver transplantation (see Management).

Post-transplantation steatohepatitis may also occur, and may evolve into cirrhosis [Lykavieris et al 2003, Miyagawa-Hayashino et al 2009, Davit-Spraul et al 2010, Hori et al 2011, Henkel et al 2021].

Extrahepatic disease manifestations are attributed to the widespread tissue distribution of ATP8B1. Some individuals with ATP8B1 deficiency have:

- **Sensorineural hearing loss**, most pronounced at higher frequencies and often detected in late adolescence and early adulthood, which can progress with time. Hearing loss is attributed to defects in the composition of membranes of inner ear cilia [Stapelbroek et al 2009, Pawlikowska et al 2010].
- **Pancreatitis or pancreatic exocrine insufficiency** [Tygstrup et al 1999, Davit-Spraul et al 2010, Pawlikowska et al 2010, Folvik et al 2012, Bull et al 2018]

Rare extrahepatic findings can include the following:

- Resistance to parathyroid hormone [Nagasaka et al 2004]
- Kidney stones or acute renal failure [Tygstrup et al 1999, Folvik et al 2012]
- Delayed puberty [Bull et al 2018]
- Epistaxis in the absence of a coagulopathy or thrombocytopenia
- Nail dystrophy [Bourke et al 1996, Klomp et al 2004]

Manifesting Heterozygotes

Intrahepatic cholestasis of pregnancy (ICP) manifests during pregnancy with pruritus, hepatic impairment, and cholestasis which usually resolves completely after delivery. While usually benign for the mother, adverse perinatal outcomes, such as fetal distress, premature birth, and stillbirth, can occur. ICP affects about 0.5%-4% of pregnancies, depending on the population.

Obligate heterozygotes for an *ATP8B1* pathogenic variant associated with ATP8B1 deficiency have developed ICP [Clayton et al 1969, de Pagter et al 1976, Bull et al 1998, Dixon et al 2017].

Transient neonatal cholestasis. A case report suggests that *ATP8B1* heterozygotes may be at increased risk for transient neonatal cholestasis [Jacquemin et al 2010].

Genotype-Phenotype Correlations

Disease severity generally correlates with variant type:

- Pathogenic variants likely to severely impair ATP8B1 structure and/or function (e.g., nonsense and frameshift variants and large deletions) are more often found in individuals with severe disease.
- Missense variants, which may have a lesser effect on ATP8B1 structure/function, are found more commonly in individuals with mild disease [Klomp et al 2004]. Of note, in individuals with a severe phenotype, the number of predicted protein-truncating variants (i.e., 0, 1, or 2) does not predict survival with native (i.e., non-transplanted) liver [van Wessel et al 2021].
- The p.Gly308Val pathogenic variant (frequently associated with the Old Amish kindred in which the disease was initially described) and the p.Asp554Asn variant (seen with Greenland familial cholestasis, typically present in early childhood) are associated with disease progression often necessitating surgical intervention (see Management) [Klomp et al 2000, Morris et al 2015, Squires et al 2017].
- The p.Ile661Thr pathogenic variant, which is frequently detected in persons of European descent with mild disease, appears occasionally to be non-penetrant, but is also occasionally found in compound heterozygous form in persons with severe disease [Klomp et al 2004].

Nomenclature

In this review, the term "ATP8B1 deficiency" is used to encompass the full phenotypic spectrum ranging from severe ATP8B1 deficiency to intermediate to mild ATP8B1 deficiency.

Other terms used to refer to severe ATP8B1 deficiency

- Phenotype-based nomenclature: progressive familial intrahepatic cholestasis (PFIC)

- Phenotype and locus-based nomenclature: progressive familial intrahepatic cholestasis type 1 (PFIC1) or severe familial intrahepatic cholestasis 1 (FIC1) deficiency
- Ethnicity-based nomenclature: Byler disease (refers to severe ATP8B1 deficiency in individuals of Amish ancestry [Clayton et al 1969]) and Greenland childhood cholestasis or Greenland familial cholestasis (refers to severe ATP8B1 deficiency in individuals of Inuit ancestry [Nielsen et al 1986, Ornvold et al 1989, Eiberg & Nielsen 1993])

Other terms used to refer to mild ATP8B1 deficiency. Phenotype and locus-based nomenclature: benign recurrent intrahepatic cholestasis type 1 (BRIC1) or mild FIC1 deficiency

Prevalence

Collectively, the estimated prevalence for all progressive familial intrahepatic cholestasis (PFIC) disorders accompanied by high serum gamma-glutamyltranspeptidase (γ-GT) levels and, in individuals with biallelic *ABCB4* pathogenic variants (PFIC3) is estimated at 1:50,000 to 1:100,000 births [Srivastava 2014]. The exact prevalence of ATP8B1 deficiency remains unknown. Although it has been considered rare, misdiagnosis or imprecise diagnosis may have contributed to underestimation of prevalence.

First described as Byler disease in children of Amish descent [Clayton et al 1969], it has now been reported in individuals of all races and many ethnicities. Except for certain populations (e.g., the Amish and Inuit) with increased consanguinity and founder variants (see Table 8), no other populations are known to be at a higher risk for ATP8B1 deficiency.

Carrier frequencies for ATP8B1 deficiency are unknown, except in the Greenland Inuit in whom the carrier frequency of the pathogenic variant p.Asp554Asn varies regionally. In East Greenland, the high carrier frequencies – which reach 0.16 in Ittoqqortoormiit and 0.23 in Kuummiut – warrant routine screening [Eiberg & Nielsen 1993, Eiberg et al 2004, Nielsen & Eiberg 2004, Andersen et al 2006].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ATP8B1*.

Differential Diagnosis

Table 4 summarizes other inherited disorders with cholestatic liver disease typically characterized by low or normal serum gamma-glutamyltranspeptidase (γ-GT) levels that need to be distinguished from the much more common cholestatic disorders characterized by elevated serum γ-GT level (including childhood-onset progressive familial intrahepatic cholestasis caused by biallelic *ABCB4* pathogenic variants [PFIC3; OMIM 602347]).

Table 4. Autosomal Recessive Pediatric Cholestatic Liver Disorders with Low or Normal Serum γ-GT Levels in the Differential Diagnosis of ATP8B1 Deficiency

Gene	Disorder	Typical Clinical Characteristics at Diagnosis	Characteristic Histology at Diagnosis	Other Serum Studies at Diagnosis
ATP8B1	**ATP8B1 deficiency** (topic of this *GeneReview*; incl for reference)	Multisystem disease	- Bland canalicular cholestasis - Coarsely granular canalicular bile	- Cholesterol concentrations usually not ↑ - Often marked ↑ of total bile acids [1, 2] - Modest ↑ of transaminases

Table 4. continued from previous page.

Gene	Disorder	Typical Clinical Characteristics at Diagnosis	Characteristic Histology at Diagnosis	Other Serum Studies at Diagnosis
ABCB11	ABCB11 deficiency (severe PFIC2; OMIM 601847)	• Primary manifestations are limited to the liver. [3] • Hepatobiliary malignancy (HCC & cholangiocarcinoma) in childhood [4, 5] • High incidence of gallstones	• Giant cell transformation & necrosis of hepatocytes • Bile pigment accumulation in hepatocytes & in lumina of bile canaliculi • Ultrastructural study of canalicular bile does not identify coarse granularity. [6] • Expression of ectoenzymes (e.g., γ-GT) along canalicular walls • ABCB11 expression is often deficient. [7]	• Transaminase activity values are higher in ABCB11 deficiency (than in ATP8B1 deficiency). [1, 2] • Albumin, bile acid, & AFP concentrations tend to be higher in severe ABCB11 deficiency. [1, 2]
MYO5B	MYO5B deficiency	Variable degree of intestinal involvement	• Giant cell change • Hepatocellular & canalicular cholestasis • Poor expression of γ-GT along bile canaliculi [8]	
NR1H4	PFIC5 (OMIM 617049)	Early-onset coagulopathy	• Intralobular cholestasis • Ductular reaction • Giant cell transformation	Markedly ↑ AFP
TJP2	PFIC4 (OMIM 615878)	Some extrahepatic features	Bland cholestasis	

Table 4. continued from previous page.

Gene	Disorder	Typical Clinical Characteristics at Diagnosis	Characteristic Histology at Diagnosis	Other Serum Studies at Diagnosis
USP53 [9]	USP53	Some extrahepatic features incl deafness	- Intralobular cholestasis - Giant cell transformation - Fibrotic changes - Ductular reaction - Ultrastructural changes may incl elongated hepatocyte-hepatocyte tight junctions	

Adapted from Table 1 in Bull & Thompson [2018]

AFP = alphafetoprotein; HCC = hepatocellular carcinoma; PFIC = progressive familial intrahepatic cholestasis; γ-GT = gamma-glutamyltranspeptidase

1. Davit-Spraul et al [2010]
2. Pawlikowska et al [2010]
3. Extrahepatic disease manifestations are less common in ABCB11 deficiency than in ATP8B1 deficiency. For example, while gallstone disease is more common in children with severe ABCB11 deficiency than in those with severe ATP8B1 deficiency, children with ATP8B1 deficiency appear more likely to manifest hearing loss, pancreatic disease, diarrhea, rickets, and poor growth [Davit-Spraul et al 2010, Pawlikowska et al 2010]. In contrast to ATP8B1 deficiency, after liver transplantation in ABCB11 deficiency, diarrhea, pancreatitis, and steatosis of the allograft are not described.
4. Knisely et al [2006], Scheimann et al [2007], Strautnieks et al [2008]
5. Malignancy is not a reported feature of ATP8B1 deficiency.
6. Bull et al [1997]
7. ABCB11 is usually well expressed along bile canaliculi in ATP8B1 deficiency.
8. Peters et al [2001], Gonzales et al [2017], Qiu et al [2017]
9. Maddirevula et al [2019], Zhang et al [2020], Alhebbi et al [2021], Bull et al [2021]

Locus heterogeneity for low γ-GT PFIC and benign recurrent intrahepatic cholestasis (BRIC). Evidence indicates the existence of an additional disease locus (or loci) for low γ-GT PFIC and BRIC beyond those presented in Table 4. Some individuals diagnosed on clinical and histopathologic evidence as having PFIC or BRIC in the past have not had variants in currently known genes; novel cholestasis genes continue to be identified.

Inborn errors of bile acid biosynthesis. Synthesis of cholic and chenodeoxycholic acids (the principal human bile acids) from cholesterol comprises several steps, involving cytoplasmic, mitochondrial, and peroxisomal sites [Bove et al 2000]. Variants in single genes that encode individual pathway enzymes thus may cause disease [Setchell et al 1998, Honda et al 1999, Bove et al 2000, Clayton et al 2002, Grange et al 2002, Setchell et al 2003]. Precursor bile acids are likely poor substrates for ABCB11 and thus accumulate in hepatocyte cytoplasm where they cause damage; cholestasis ensues. Although lack of primary bile salts in bile (see Table 4, ABCB11 deficiency) precludes elevations in serum γ-GT activity, γ-GT is well expressed along canalicular walls in the livers of such individuals. For disorders of bile-acid conjugation, see **Familial hypercholanemia** (following).

Familial hypercholanemia (FHC) is characterized by fluctuating but often extremely elevated serum concentrations of bile acids. Affected individuals often manifest pruritus, malabsorption of fat-soluble vitamins, and failure to thrive. Most do not become jaundiced. Causative pathogenic variants in four genes – *BAAT*, *EPHX1*, *SLC27A5*, and *TJP2* – have been identified [Carlton et al 2003, Zhu et al 2003, Chong et al 2012, Setchell et al 2013]. *BAAT* and *SLC27A5* encode enzymes involved in bile acid conjugation. Nonconjugated bile acids are poor substrates for ABCB11; they also can traverse cell membranes more readily than can conjugated bile acids. Thus, failure of serum γ-GT to rise in BAAT deficiency and SLC27A5 deficiency likely results from lack of detergent activity in canalicular bile. TJP2 is a scaffold protein in tight junctions, and the reported pathogenic

variant is proposed to increase the permeability of tight junctions with regard to bile acids; biallelic pathogenic variants in *TJP2* that have more severe effects can result in severe cholestasis (see Table 4). EPHX1 is implicated in hepatocyte uptake of bile acids from plasma.

Smith-Lemli-Opitz syndrome (SLOS) can secondarily lead to low γ-GT cholestasis [Grange et al 2002] via decreased synthesis of bile acid precursors.

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is characterized by Fanconi-type aminoaciduria, degeneration of anterior horn cells (i.e., lower motor neurons), conjugated hyperbilirubinemia without elevated serum γ-GT, and ichthyosis [Eastham et al 2001]. Inheritance is autosomal recessive; biallelic pathogenic variants in either *VPS33B* (OMIM 208085) or *VIPAS39* (OMIM 613404) are causative [Gissen et al 2004, Cullinane et al 2010]. In general, the extrahepatic findings strongly suggest the diagnosis [Bull et al 2006].

Management

Clinical practice guidelines for ATP8B1 deficiency have not been published.

Evaluations at Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ATP8B1 deficiency, all possible manifestations of this disorder (if not addressed as part of the evaluation that led to the diagnosis) should be included in the initial evaluation. See Table 5.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with ATP8B1 Deficiency

System/Concern	Evaluation	Comment
Constitutional	Comprehensive medical history & physical exam	
Cholestasis	Assessment by hepatologist	- Standard biochemical assays of hepatocellular function & hepatobiliary injury - Liver imaging - Liver biopsy if indicated by imaging studies &/or biochemical assays - Assess for portal hypertension.
Chronic liver disease		Same as cholestasis; also assess for other complications of end-stage liver disease
Pruritus		- Consider use of clinical tools to quantify itch. [1] - Consider serum bile acid quantification.
Poor growth		- Specific focus on diarrhea - Review of growth parameters - Consider measurements of mid-arm circumference.
Nutritional deficiencies (incl vitamins A, D, E, K)		Assessment for evidence of vitamin deficiencies
Sensorineural hearing loss	By audiologist	In all persons whether symptomatic or not
Resistance to parathyroid hormone	By endocrinologist	When serum levels of calcium are low & phosphorus levels are ↑
Pancreatitis or pancreatic exocrineinsufficiency	By hepatologist	If serum amylase & lipase levels are high, & fecal fat content is excessive, consider dedicated pancreatic imaging.
Genetic counseling	By genetics professionals [2]	To inform patients & families re nature, MOI, & implications of ATP8B1 deficiency to facilitate medical & personal decision making

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources		Assess: • Use of community resources & support/advocacy organizations (e.g., Parent to Parent); • Need for social work involvement for parental support.

MOI = mode of inheritance
1. Kamath et al [2018]
2. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with ATP8B1 Deficiency

Manifestation/Concern		Treatment	Considerations/Other
Cholestasis	**Severe ATP8B1 deficiency**	Pharmacotherapy	Ineffective
		Surgical interruption of enterohepatic circulation [1, 2]	• Can incl partial/total external diversion, partial/total internal diversion, or ileal exclusion • Primary surgical therapy; can ↓ pruritus & slow or reverse progression to hepatic fibrosis • Consider LTX if cirrhosis is present.
		LTX considered when liver disease progresses to decompensated cirrhosis	• In some LTX constitutes definitive therapy; in others secretory diarrhea in absence of steatorrhea continues or worsens after LTX • Consideration of diversion at time of transplantation to mitigate post-transplant diarrhea & steatohepatitis [3]
	Mild-to-moderate ATP8B1 deficiency	Nasobiliary drainage [4] & extracorporeal liver support [5]	May hasten end of episode of cholestasis
		Surgical interruption of enterohepatic circulation	Benefit is unknown
		LTX	Difficult to justify
Pruritus	**Severe ATP8B1 deficiency**	Choleretic agents (e.g., phenobarbital & UDCA, cholestyramine, rifampin, antihistamines, carbamazepine, sertraline, naltrexone, UVB light therapy, plasmapheresis)	• Relatively ineffective & do not alter progression to end-stage liver disease. • Future efforts focusing on real-world experience w/recently FDA-approved IBAT inhibitors are needed. [6]
	Mild-to-moderate ATP8B1 deficiency	Rifampicin, UDCA, sertraline, [7] naltrexone, [8] & bile acid binding resin	May be efficacious [9]
Secretory diarrhea		May require IV fluids	• Bile acid chelators [10] may ameliorate diarrhea after LTX, as they may divert bile produced by allograft away from the native gut. [11] • Clonidine has palliated diarrhea after LTX in some persons. [12] • Consider diversion at time of transplantation to mitigate post-transplant diarrhea & steatohepatitis. [3]

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Poor growth	Medium-chain triglyceride-based formulas	• May prevent &/or treat growth failure • Nasogastric tube feeding has been helpful in some. • May not be responsive to LTX
Nutritional deficiencies (incl vitamins A, D, E, K)	Fat-soluble vitamin supplementation to alleviate malabsorption of fat-soluble vitamins	• Preparations of vitamin E (e.g., tocopheryl polyethylene glycol-1000 succinate) are useful in severe cholestasis. • Vitamin K administration in newborn period (1st 28 days of life) is essential.
Sensorineural hearing loss	Habituation per treating audiologist	
Pancreatitis or pancreatic exocrine insufficiency	• Supportive care for acute pancreatitis episodes • Replacement therapy for insufficiency if documented	

IBAT = ileal bile acid transporter; LTX = liver transplantation; UDCA = ursodeoxycholic acid
1. In partial external biliary diversion the gallbladder apex is anastomosed to one end of a segment of bowel while the other end is used to create a cutaneous stoma from which bile is then drained and discarded, thus, interrupting the enterohepatic circulation of bile acids and reducing pruritus.
2. Squires et al [2017], Wang et al [2017], Bull et al [2018], Lemoine & Superina [2020], Verkade et al [2020], van Wessel et al [2021]
3. Mali et al [2016], Alrabadi et al [2018]
4. Stapelbroek et al [2006], Toros et al [2012]
5. Huster et al [2001], Saich et al [2005], Walensi et al [2012]
6. Kamath et al [2020]
7. Thébaut et al [2017]
8. Zellos et al [2010]
9. Uegaki et al [2008], Folvik et al [2012], Mizuochi et al [2012]
10. Egawa et al [2002]
11. Usui et al [2009], Nicastro et al [2012]
12. Kocoshis et al [2005]

Surveillance

Table 7. Recommended Surveillance for Individuals with ATP8B1 Deficiency

System/Concern	Evaluation	Frequency
Constitutional	Comprehensive medical history & physical exam	At least annually; frequency may depend on severity of disease.
Cholestasis	• Standard biochemical assays of hepatocellular function & of hepatobiliary injury • Liver imaging • Liver biopsy if indicated by imaging studies &/or biochemical assays • Assess for portal hypertension.	
Development of chronic liver disease	Same as cholestasis; also assess for other complications of end-stage liver disease.	
Pruritus	• Consider use of clinical tools to quantify itching. [1] • Consider serum bile acid quantification.	
Poor growth	• Specific focus on diarrhea • Review of growth parameters • Consider measurements of mid-arm circumference.	
Nutritional deficiencies (incl vitamins A, D, E, K)	Assessment for evidence of deficiency of these vitamins	

Table 7. continued from previous page.

System/Concern		Evaluation	Frequency
Pancreatitis or pancreatic exocrine insufficiency		• Standard biochemical assays • Consider dedicated pancreatic imaging if concern.	
SNHL	**For those w/known HL**	Per treating audiologist	
	For those w/o known HL	Screening audiogram	Every 5 yrs

SNHL = sensorineural hearing loss
1. Kamath et al [2018]

Note: Monitoring for hepatobiliary malignancy has not been shown to be necessary in ATP8B1 deficiency.

Agents/Circumstances to Avoid

Susceptibility to sensorineural hearing loss in ATP8B1 deficiency may argue against use of aminoglycoside antibiotics or other potentially ototoxic agents.

Oral contraceptive therapy can induce and/or exacerbate episodes of cholestasis.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment, surveillance, and awareness of agents and circumstances to avoid.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Cystic fibrosis transmembrane conductance regulator corrector compounds improved trafficking of mutated ATP8B1 protein in cell culture studies [van der Woerd et al 2016], providing support for the concept that these compounds may be suitable to be included in future therapeutic regimens for ATP8B1 deficiency.

Ileal bile acid transporter inhibitors have shown reduction in bile acid levels and reduced pruritus in children; various clinical trials are underway [Kamath et al 2020]. Recent FDA approval should prompt future real-world experience reports that are needed to better appreciate the true effectiveness of this therapy.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

ATP8B1 deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *ATP8B1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ATP8B1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Intrahepatic cholestasis of pregnancy has been reported occasionally in mothers of individuals with ATP8B1 deficiency [Clayton et al 1969, de Pagter et al 1976, Bull et al 1998] (see Clinical Description).

Sibs of a proband

- If both parents are known to be heterozygous for an *ATP8B1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of inheriting one pathogenic variant and being a heterozygote (carrier), and a 25% chance of inheriting both normal alleles.
- Although disease severity generally correlates with variant type, sibs with the same biallelic *ATP8B1* pathogenic variants do not always have disease of the same clinical severity (see Clinical Description). In addition, clinical severity can change over time.
- *ATP8B1* heterozygotes may be at increased risk for transient neonatal cholestasis and intrahepatic cholestasis of pregnancy (see Clinical Description, Manifesting Heterozygotes).

Offspring of a proband

- Unless the reproductive partner of an affected individual also has ATP8B1 deficiency or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ATP8B1*.

- The carrier frequencies of *ATP8B1* pathogenic variants are unknown; however, given that ATP8B1 deficiency is uncommon, the likelihood that an individual with ATP8B1 deficiency would have children with a carrier is low. Exceptions include populations in which a founder variant is present, such as the Amish or Greenland Inuit populations.* Offspring of an affected individual and a carrier have a 50% chance of being affected and a 50% chance of being carriers.

  * See Table 8 for information on founder variants in these populations.

- *ATP8B1* heterozygotes (carriers) may be at increased risk for transient neonatal cholestasis and intrahepatic cholestasis of pregnancy (see Clinical Description, Manifesting Heterozygotes).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ATP8B1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ATP8B1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and of reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ATP8B1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Liver Foundation**
  Phone: 800-465-4837 (HelpLine)
  www.liverfoundation.org

- **Canadian Liver Foundation**
  Canada
  Phone: 800-563-5483
  Email: clf@liver.ca
  www.liver.ca

- **Childhood Liver Disease Research Network (ChiLDReN)**
  Phone: 720-777-2598
  Email: joan.hines@childrenscolorado.org
  www.childrennetwork.org

- **Children's Liver Disease Foundation**
  United Kingdom
  Phone: +44 (0) 121 212 3839
  Email: info@childliverdisease.org
  childliverdisease.org

- **PFIC Advocacy and Resource Network, Inc.**

Email: emily@pfic.org

www.pfic.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. ATP8B1 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATP8B1	18q21.31	Phospholipid-transporting ATPase IC	CCHMC - Human Genetics Mutation Database (ATP8B1)	ATP8B1	ATP8B1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for ATP8B1 Deficiency (View All in OMIM)

211600	CHOLESTASIS, PROGRESSIVE FAMILIAL INTRAHEPATIC, 1; PFIC1
243300	CHOLESTASIS, BENIGN RECURRENT INTRAHEPATIC, 1; BRIC1
602397	ATPase, CLASS I, TYPE 8B, MEMBER 1; ATP8B1

Molecular Pathogenesis

ATP8B1 encodes ATP8B1, a member of the P4 subfamily of P-type ATPases; these proteins function as phospholipid "flippases," translocating phospholipids from the outer to the inner leaflet of plasma membranes [Andersen et al 2016], helping to maintain the normal asymmetric distribution of lipids between the two membrane leaflets. Although early studies suggested that ATP8B1 translocates phosphatidylserine, more recent work suggests phosphatidylcholine is the preferred substrate of ATP8B1 [Paulusma et al 2006, Paulusma et al 2008, Takatsu et al 2014]. Lack of ATP8B1 function may result in abnormal lipid composition of the membrane bilayer, increasing membrane vulnerability to damage by canalicular bile acids, impairing function of membrane proteins (including the bile salt export pump), and potentially impairing vesicular transport and membrane trafficking [Paulusma et al 2009, Andersen et al 2016]. ATP8B1 may also play a role in FXR signaling; however, findings differ between studies. ATP8B1 may be involved in the innate immune response [van der Mark et al 2017].

ATP8B1 is widely expressed, including in the liver, small intestine, colon, pancreas, stomach, bladder, heart, lung, kidney, and gallbladder. ATP8B1 is present in the canalicular membrane of hepatocytes and in the apical membrane of cholangiocytes within the liver, as well as at the apices of enteric epithelia [Bull et al 1998, Eppens et al 2001, Ujhazy et al 2001, van Mil et al 2004b, Demeilliers et al 2006]. The broad expression pattern of *ATP8B1* may explain the finding of some extrahepatic disease features in ATP8B1 deficiency.

For a broader review of this discussion, see Bull & Thompson [2018].

Mechanism of disease causation. Loss of function

Table 8. Notable *ATP8B1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_005603.5 NP_005594.1	c.625C>A	p.Pro209Thr	2 variants commonly found *in cis* in eastern China; which of the 2 causes disease is unknown [Liu et al 2010].
NM_005603.5	c.627+5G>T (IVS6+5G>T)		
NM_005603.5 NP_005594.1	c.923G>T	p.Gly308Val	Founder variant in Amish population [Bull et al 1998]
	c.1660G>A	p.Asp554Asn	Variant common in persons of Inuit ancestry from eastern Nunavut (Canadian Arctic), in both western & eastern Greenland, & in 1 kindred w/Athabascan & Norwegian ancestry [Klomp et al 2000, Klomp et al 2004]
	c.1982T>C	p.Ile661Thr	At least 1 copy of this variant is found in most persons of European descent [Bull et al 1998, Tygstrup et al 1999, Klomp et al 2004].
	c.1993G>T	p.Glu665Ter	Variant found in Dominican population [Klomp et al 2004]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

James E Squires, MD, MS joined the faculty at the Children's Hospital of Pittsburgh in 2015, where he is an associate professor in pediatrics, director of the pediatric advanced/transplant hepatology fellowship, and associate medical director of Hepatology. Dr Squires remains active in both clinical and research pursuits. He is a co-investigator in the Children Liver Disease Research Network (ChiLDReN), an NIH-funded consortium working to improve the lives of children with rare cholestatic liver diseases. He is also a member of the Society of Pediatric LIver Transplant (SPLIT), a multifaceted organization focused on improving outcomes for children receiving liver transplantation. He is the Clinical Lead for the Starzl Network for Excellence in Liver Transplantation, a novel learning health network of leading pediatric transplant institutions committed to continuous improvement until every child can achieve a long and healthy life, and has received funding from the Patient-Centered Outcomes Research Institute (PCORI) to advance this work. Other current interests include metabolic liver disease, acute liver failure, and liver transplant. Website: www.pediatrics.pitt.edu

Author History

Laura N Bull, PhD (2001-present)
AS Knisely, MD; King's College Hospital (2001-2021)
Raffaella Morotti, MD (2021-present)
Benjamin L Shneider, MD; Children's Hospital of Pittsburgh (2006-2021)
James E Squires, MD, MS (2021-present)
Kelly A Taylor, MS, CGC; Vanderbilt University (2001-2006)

Revision History

- 9 September 2021 (bp) Comprehensive update posted live
- 20 March 2014 (me) Comprehensive update posted live
- 13 August 2008 (cd) Revision: prenatal testing available for *ABCB11*

- 26 May 2006 (cd) Revision: prenatal testing available for 1660G>A (D554N) mutation in *ATP8B1*
- 15 February 2006 (me) Comprehensive update posted live
- 15 July 2003 (me) Comprehensive update posted live
- 15 October 2001 (me) Review posted live
- 24 April 2001 (kt) Original submission

References

Literature Cited

Alhebbi H, Peer-Zada AA, Al-Hussaini AA, Algubaisi S, Albassami A, AlMasri N, Alrusayni Y, Alruzug IM, Alharby E, Samman MA, Ayoub SZ, Maddirevula S, Peake RWA, Alkuraya FS, Wali S, Almontashiri NAM. New paradigms of USP53 disease: normal GGT cholestasis, BRIC, cholangiopathy, and responsiveness to rifampicin. J Hum Genet. 2021;66:151–9. PubMed PMID: 32759993.

Alrabadi LS, Morotti RA, Valentino PL, Rodriguez-Davalos MI, Ekong UD, Emre SH. Biliary drainage as treatment for allograft steatosis following liver transplantation for PFIC-1 disease: a single-center experience. Pediatr Transplant. 2018;22:e13184. PubMed PMID: 29654655.

Andersen S, Okkels H, Krarup H, Laurberg P. Geographical clustering and maintained health in individuals harbouring the mutation for Greenland familial cholestasis: A population-based study. Scand J Gastroenterol. 2006;41:445–50. PubMed PMID: 16635913.

Andersen JP, Vestergaard AL, Mikkelsen SA, Mogensen LS, Chalat M, Molday RS. P4-ATPases as phospholipid flippases- structure, function, and enigmas. Front Physiol. 2016;7:275. PubMed PMID: 27458383.

Bourke B, Goggin N, Walsh D, Kennedy S, Setchell KD, Drumm B. Byler-like familial cholestasis in an extended kindred. Arch Dis Child. 1996;75:223–7. PubMed PMID: 8976662.

Bove KE, Daugherty CC, Tyson W, Mierau G, Heubi JE, Balistreri WF, Setchell KD. Bile acid synthetic defects and liver disease. Pediatr Dev Pathol. 2000;3:1–16. PubMed PMID: 10594127.

Bull LN, Carlton VE, Stricker NL, Baharloo S, DeYoung JA, Freimer NB, Magid MS, Kahn E, Markowitz J, DiCarlo FJ, McLoughlin L, Boyle JT, Dahms BB, Faught PR, Fitzgerald JF, Piccoli DA, Witzleben CL, Connell O, Setchell NC, Agostini KD, Jr RM, Kocoshis SA, Reyes J, Knisely AS. Genetic and morphological findings in progressive familial intrahepatic cholestasis (Byler disease [PFIC-1] and Byler syndrome): evidence for heterogeneity. Hepatology. 1997;26:155–64. PubMed PMID: 9214465.

Bull LN, Ellmers R, Foskett P, Strautnieks S, Sambrotta M, Czubkowski P, Jankowska I, Wagner B, Deheragoda M, Thompson RJ. Cholestasis due to USP53 deficiency. J Pediatr Gastroenterol Nutr. 2021;72:667–73. PubMed PMID: 33075013.

Bull LN, Juijn JA, Liao M, van Eijk MJ, Sinke RJ, Stricker NL, DeYoung JA, Carlton VE, Baharloo S, Klomp LW, Abukawa D, Barton DE, Bass NM, Bourke B, Drumm B, Jankowska I, Lovisetto P, McQuaid S, Pawlowska J, Tazawa Y, Villa E, Tygstrup N, Berger R, Knisely AS, Freimer NB. Fine-resolution mapping by haplotype evaluation: the examples of PFIC1 and BRIC. Hum Genet. 1999;104:241–8. PubMed PMID: 10323248.

Bull LN, Mahmoodi V, Baker AJ, Jones R, Strautnieks SS, Thompson RJ, Knisely AS. VPS33B mutation with ichthyosis, cholestasis, and renal dysfunction but without arthrogryposis: incomplete ARC syndrome phenotype. J Pediatr. 2006;148:269–71. PubMed PMID: 16492441.

Bull LN, Thompson RJ. Progressive familial intrahepatic cholestasis. Clin Liver Dis. 2018;22:657–69. PubMed PMID: 30266155.

Bull LN, van Eijk MJ, Pawlikowska L, DeYoung JA, Juijn JA, Liao M, Klomp LW, Lomri N, Berger R, Scharschmidt BF, Knisely AS, Houwen RH, Freimer NB. A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. Nat Genet. 1998;18:219–24. PubMed PMID: 9500542.

Bull LN, Pawlikowska L, Strautnieks S, Jankowska I, Czubkowski P, Dodge JL, Emerick K, Wanty C, Wali S, Blanchard S, Lacaille F, Byrne JA, van Eerde AM, Kolho KL, Houwen R, Lobritto S, Hupertz V, McClean P, Mieli-Vergani G, Sokal E, Rosenthal P, Whitington PF, Pawlowska J, Thompson RJ. Outcomes of surgical management of familial intrahepatic cholestasis 1 and bile salt export protein deficiencies. Hepatol Commun. 2018;2:515–28. PubMed PMID: 29761168.

Carlton VE, Harris BZ, Puffenberger EG, Batta AK, Knisely AS, Robinson DL, Strauss KA, Shneider BL, Lim WA, Salen G, Morton DH, Bull LN. Complex inheritance of familial hypercholanemia with associated mutations in TJP2 and BAAT. Nat Genet. 2003;34:91–6. PubMed PMID: 12704386.

Chong CP, Mills PB, McClean P, Gissen P, Bruce C, Stahlschmidt J, Knisely AS, Clayton PT. Bile acid-CoA ligase deficiency--a new inborn error of bile acid metabolism. J Inherit Metab Dis. 2012;35:521–30. PubMed PMID: 22089923.

Clayton PT, Verrips A, Sistermans E, Mann A, Mieli-Vergani G, Wevers R. Mutations in the sterol 27-hydoxylase gene (CYP27A) cause hepatitis of infancy as well as cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2002;25:501–13. PubMed PMID: 12555943.

Clayton RJ, Iber FL, Ruebner BH, McKusick VA. Byler disease. Fatal familial intrahepatic cholestasis in an Amish kindred. Am J Dis Child. 1969;117:112–24. PubMed PMID: 5762004.

Cullinane AR, Straatman-Iwanowska A, Zaucker A, Wakabayashi Y, Bruce CK, Luo G, Rahman F, Gürakan F, Utine E, Ozkan TB, Denecke J, Vukovic J, Di Rocco M, Mandel H, Cangul H, Matthews RP, Thomas SG, Rappoport JZ, Arias IM, Wolburg H, Knisely AS, Kelly DA, Müller F, Maher ER, Gissen P. Mutations in VIPAR cause an arthrogryposis, renal dysfunction and cholestasis syndrome phenotype with defects in epithelial polarization. Nat Genet. 2010;42:303–12. PubMed PMID: 20190753.

Davit-Spraul A, Fabre M, Branchereau S, Baussan C, Gonzales E, Stieger B, Bernard O, Jacquemin E. ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. Hepatology. 2010;51:1645–55. PubMed PMID: 20232290.

de Pagter AGF, van Berge Henegouwen GP, Huinink TB, Brandt KH. Familial benign recurrent intrahepatic cholestasis. Gastroenterology. 1976;71:202–7. PubMed PMID: 939378.

Demeilliers C, Jacquemin E, Barbu V, Mergey M, Paye F, Fouassier L, Chignard N, Housset C, Lomri NE. Altered hepatobiliary gene expressions in PFIC1: ATP8B1 gene defect is associated with CFTR downregulation. Hepatology. 2006;43:1125–34. PubMed PMID: 16628629.

Dixon PH, Sambrotta M, Chambers J, Taylor-Harris P, Syngelaki A, Nicolaides K, Knisely AS, Thompson RJ, Williamson C. An expanded role for heterozygous mutations of ABCB4, ABCB11, ATP8B1, ABCC2 and TJP2 in intrahepatic cholestasis of pregnancy. Sci Rep. 2017;7:11823. PubMed PMID: 28924228.

Dröge C, Bonus M, Baumann U, Klindt C, Lainka E, Kathemann S, Brinkert F, Grabhorn E, Pfister ED, Wenning D, Fichtner A, Gotthardt DN, Weiss KH, McKiernan P, Puri RD, Verma IC, Kluge S, Gohlke H, Schmitt L, Kubitz R, Häussinger D, Keitel V. Sequencing of FIC1, BSEP and MDR3 in a large cohort of patients with cholestasis revealed a high number of different genetic variants. J Hepatol. 2017;67:1253–64. PubMed PMID: 28733223.

Eastham KM, McKiernan PJ, Milford DV, Ramani P, Wyllie J, van't Hoff W, Lynch SA, Morris AA. ARC syndrome: an expanding range of phenotypes. Arch Dis Child. 2001;85:415–20. PubMed PMID: 11668108.

Egawa H, Yorifuji T, Sumazaki R, Kimura A, Hasegawa M, Tanaka K. Intractable diarrhea after liver transplantation for Byler's disease: successful treatment with bile adsorptive resin. Liver Transpl. 2002;8:714–6. PubMed PMID: 12149765.

Eiberg H, Nielsen IM. Linkage studies of cholestasis familiaris groenlandica/Byler-like disease with polymorphic protein and blood group markers. Hum Hered. 1993;43:250–6. PubMed PMID: 8344670.

Eiberg H, Norgaard-Pedersen B, Nielsen IM. Cholestasis Familiaris Groenlandica/Byler-like disease in Greenland--a population study. Int J Circumpolar Health. 2004;63 Suppl 2:189–91. PubMed PMID: 15736649.

Eppens EF, van Mil SW, de Vree JM, Mok KS, Juijn JA, Oude Elferink RP, Berger R, Houwen RH, Klomp LW. FIC1, the protein affected in two forms of hereditary cholestasis, is localized in the cholangiocyte and the canalicular membrane of the hepatocyte. J Hepatol. 2001;35:436–43. PubMed PMID: 11682026.

Folvik G, Hilde O, Helge GO. Benign recurrent intrahepatic cholestasis: review and long-term follow-up of five cases. Scand J Gastroenterol. 2012;47:482–8. PubMed PMID: 22229830.

Gissen P, Johnson CA, Morgan NV, Stapelbroek JM, Forshew T, Cooper WN, McKiernan PJ, Klomp LW, Morris AA, Wraith JE, McClean P, Lynch SA, Thompson RJ, Lo B, Quarrell OW, Di Rocco M, Trembath RC, Mandel H, Wali S, Karet FE, Knisely AS, Houwen RH, Kelly DA, Maher ER. Mutations in VPS33B, encoding a regulator of SNARE-dependent membrane fusion, cause arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome. Nat Genet. 2004;36:400–4. PubMed PMID: 15052268.

Gonzales E, Taylor SA, Davit-Spraul A, Thébaut A, Thomassin N, Guettier C, Whitington PF, Jacquemin E. MYO5B mutations cause cholestasis with normal serum gamma-glutamyl transferase activity in children without microvillous inclusion disease. Hepatology. 2017;65:164–73. PubMed PMID: 27532546.

Grange DK, deMello DE, Hart MH, Kelley RI, Knisely AS, Nwokoro NA, Sotelo-Avila C. Cholestatic liver disease in Smith-Lemli-Opitz syndrome. Proc Greenwood Genet Center. 2002;21:48–9.

Henkel SAF, Salgado CM, Reyes-Mugica M, Soltys KA, Strauss K, Mazariegos GV, Squires RH, McKiernan PJ, Zhang X, Squires JE. Long-term liver transplant outcomes for progressive familial intrahepatic cholestasis type 1: The Pittsburgh experience. Pediatr Transplant. 2021;25:e14108. PubMed PMID: 34339082.

Honda A, Salen G, Shefer S, Batta AK, Honda M, Xu G, Tint GS, Matsuzaki Y, Shoda J, Tanaka N. Bile acid synthesis in the Smith-Lemli-Opitz syndrome: effects of dehydrocholesterols on cholesterol 7alpha-hydroxylase and 27-hydroxylase activities in rat liver. J Lipid Res. 1999;40:1520–8. PubMed PMID: 10428990.

Hori T, Egawa H, Takada Y, Ueda M, Oike F, Ogura Y, Sakamoto S, Kasahara M, Ogawa K, Miyagawa-Hayashino A, Yonekawa Y, Yorifuji T, Watanabe K, Doi H, Nguyen JH, Chen F, Baine AM, Gardner LB, Uemoto S. Progressive familial intrahepatic cholestasis: a single-center experience of living-donor liver transplantation during two decades in Japan. Clin Transplant. 2011;25:776–85. PubMed PMID: 21158920.

Huster D, Schubert C, Achenbach H, Caca K, Mössner J, Berr F. Successful clinical application of extracorporal albumin dialysis in a patient with benign recurrent intrahepatic cholestasis (BRIC). Z Gastroenterol. 2001;39 Suppl 2:13–4. PubMed PMID: 16215886.

Jacquemin E, Malan V, Rio M, Davit-Spraul A, Cohen J, Landrieu P, Bernard O. Heterozygous FIC1 deficiency: a new genetic predisposition to transient neonatal cholestasis. J Pediatr Gastroenterol Nutr. 2010;50:447–9. PubMed PMID: 20216097.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Kamath BM, Abetz-Webb L, Kennedy C, Hepburn B, Gauthier M, Johnson N, Medendorp S, Dorenbaum A, Todorova L, Shneider BL. Development of a novel tool to assess the impact of itching in pediatric cholestasis. Patient. 2018;11:69–82. PubMed PMID: 28710680.

Kamath BM, Stein P, Houwen RHJ, Verkade HJ. Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. Liver Int. 2020;40:1812–22. PubMed PMID: 32492754.

Klomp LW, Bull LN, Knisely AS, van Der Doelen MA, Juijn JA, Berger R, Forget S, Nielsen IM, Eiberg H, Houwen RH. A missense mutation in FIC1 is associated with greenland familial cholestasis. Hepatology. 2000;32:1337–41. PubMed PMID: 11093741.

Klomp LW, Vargas JC, van Mil SW, Pawlikowska L, Strautnieks SS, van Eijk MJ, Juijn JA, Pabon-Pena C, Smith LB, DeYoung JA, Byrne JA, Gombert J, van der Brugge G, Berger R, Jankowska I, Pawlowska J, Villa E, Knisely AS, Thompson RJ, Freimer NB, Houwen RH, Bull LN. Characterization of mutations in ATP8B1 associated with hereditary cholestasis. Hepatology. 2004;40:27–38. PubMed PMID: 15239083.

Knisely AS, Strautnieks SS, Meier Y, Stieger B, Byrne JA, Portmann BC, Bull LN, Pawlikowska L, Bilezikçi B, Ozçay F, László A, Tiszlavicz L, Moore L, Raftos J, Arnell H, Fischler B, Németh A, Papadogiannakis N, Cielecka-Kuszyk J, Jankowska I, Pawłowska J, Melín-Aldana H, Emerick KM, Whitington PF, Mieli-Vergani G, Thompson RJ. Hepatocellular carcinoma in ten children under five years of age with bile salt export pump deficiency. Hepatology. 2006;44:478–86. PubMed PMID: 16871584.

Kocoshis SA, Van Damme-Lombaerts R, Roskams T, Hupertz VF, Mazariegos GV, Squires RF Jr, Bull LN, Knisely AS. Clonidine administration ameliorates diarrhea after liver transplantation in severe FIC1 / ATP8B1 disease (progressive familial intrahepatic cholestasis, type 1). Hepatology. 2005;42:474A–5A.

Lemoine C, Superina R. Surgical diversion of enterohepatic circulation in pediatric cholestasis. Semin Pediatr Surg. 2020;29:150946. PubMed PMID: 32861450.

Liu LY, Wang XH, Wang ZL, Zhu QR, Wang JS. Characterization of ATP8B1 gene mutations and a hot-linked mutation found in Chinese children with progressive intrahepatic cholestasis and low GGT. J Pediatr Gastroenterol Nutr. 2010;50:179–83. PubMed PMID: 20038848.

Lykavieris P, van Mil S, Cresteil D, Fabre M, Hadchouel M, Klomp L, Bernard O, Jacquemin E. Progressive familial intrahepatic cholestasis type 1 and extrahepatic features: no catch-up of stature growth, exacerbation of diarrhea, and appearance of liver steatosis after liver transplantation. J Hepatol. 2003;39:447–52. PubMed PMID: 12927934.

Maddirevula S, Alhebbi H, Alqahtani A, Algoufi T, Alsaif HS, Ibrahim N, Abdulwahab F, Barr M, Alzaidan H, Almehaideb A, AlSasi O, Alhashem A, Hussaini HA, Wali S, Alkuraya FS. Identification of novel loci for pediatric cholestatic liver disease defined by KIF12, PPM1F, USP53, LSR, and WDR83OS pathogenic variants. Genet Med. 2019;21:1164–72. PubMed PMID: 30250217.

Mali VP, Fukuda A, Shigeta T, Uchida H, Hirata Y, Rahayatri TH, Kanazawa H, Sasaki K, de Ville de Goyet J, Kasahara M. Total internal biliary diversion during liver transplantation for type 1 progressive familial intrahepatic cholestasis: a novel approach. Pediatr Transplant. 2016;20:981–6. PubMed PMID: 27534385.

Miyagawa-Hayashino A, Egawa H, Yorifuji T, Hasegawa M, Haga H, Tsuruyama T, Wen MC, Sumazaki R, Manabe T, Uemoto S. Allograft steatohepatitis in progressive familial intrahepatic cholestasis type 1 after living donor liver transplantation. Liver Transpl. 2009;15:610–18. PubMed PMID: 19479804.

Mizuochi T, Kimura A, Tanaka A, Muto A, Nittono H, Seki Y, Takahashi T, Kurosawa T, Kage M, Takikawa H, Matsuishi T. Characterization of urinary bile acids in a pediatric BRIC-1 patient: effect of rifampicin treatment. Clin Chim Acta. 2012;413:1301–4. PubMed PMID: 22525741.

Morris AL, Bukauskas K, Sada RE, Shneider BL. Byler disease: early natural history. J Pediatr Gastroenterol Nutr. 2015;60:460–6. PubMed PMID: 25825852.

Nagasaka H, Chiba H, Hui SP, Takikawa H, Miida T, Takayanagi M, Yorifuji T, Hasegawa M, Ota A, Hirano K, Kikuchi H, Tsukahara H, Kobayashi K. Depletion of high-density lipoprotein and appearance of triglyceride-rich low-density lipoprotein in a Japanese patient with FIC1 deficiency manifesting benign recurrent intrahepatic cholestasis. J Pediatr Gastroenterol Nutr. 2007;45:96–105. PubMed PMID: 17592371.

Nagasaka H, Yorifuji T, Egawa H, Yanai H, Fujisawa T, Kosugiyama K, Matsui A, Hasegawa M, Okada T, Takayanagi M, Chiba H, Kobayashi K. Evaluation of risk for atherosclerosis in Alagille syndrome and progressive familial intrahepatic cholestasis: two congenital cholestatic diseases with different lipoprotein metabolisms. J Pediatr. 2005;146:329–35. PubMed PMID: 15756213.

Nagasaka H, Yorifuji T, Hirano K, Ota A, Toyama-Nakagawa Y, Takatani T, Tsukahara H, Kobayashi K, Takayanagi M, Inomata Y, Uemoto S, Miida T. Effects of bezafibrate on dyslipidemia with cholestasis in children with familial intrahepatic cholestasis-1 deficiency manifesting progressive familial intrahepatic cholestasis. Metabolism. 2009;58:48–54. PubMed PMID: 19059530.

Nagasaka H, Yorifuji T, Kosugiyama K, Egawa H, Kawai M, Murayama K, Hasegawa M, Sumazaki R, Tsubaki J, Kikuta H, Matsui A, Tanaka K, Matsuura N, Kobayashi K. Resistance to parathyroid hormone in two patients with familial intrahepatic cholestasis: possible involvement of the ATP8B1 gene in calcium regulation via parathyroid hormone. J Pediatr Gastroenterol Nutr. 2004;39:404–9. PubMed PMID: 15448432.

Nicastro E, Stephenne X, Smets F, Fusaro F, de Magnée C, Reding R, Sokal EM. Recovery of graft steatosis and protein-losing enteropathy after biliary diversion in a PFIC 1 liver transplanted child. Pediatr Transplant. 2012;16:E177–82. PubMed PMID: 21672103.

Nielsen IM, Eiberg H. Cholestasis Familiaris Groenlandica: an epidemiological, clinical and genetic study. Int J Circumpolar Health. 2004;63 Suppl 2:192–4. PubMed PMID: 15736650.

Nielsen IM, Ornvold K, Jacobsen BB, Ranek L. Fatal familial cholestatic syndrome in Greenland Eskimo children. Acta Paediatr Scand. 1986;75:1010–6. PubMed PMID: 3564958.

Ornvold K, Nielsen IM, Poulsen H. Fatal familial cholestatic syndrome in Greenland Eskimo children. A histomorphological analysis of 16 cases. Virchows Arch A Pathol Anat Histopathol. 1989;415:275–81. PubMed PMID: 2503928.

Paulusma CC, Groen A, Kunne C, Ho-Mok KS, Spijkerboer AL, Rudi de Waart D, Hoek FJ, Vreeling H, Hoeben KA, van Marle J, Pawlikowska L, Bull LN, Hofmann AF, Knisely AS, Oude Elferink RP. Atp8b1 deficiency in mice reduces resistance of the canalicular membrane to hydrophobic bile salts and impairs bile salt transport. Hepatology. 2006;44:195–204. PubMed PMID: 16799980.

Paulusma CC, Folmer DE, Ho-Mok KS, de Waart DR, Hilarius PM, Verhoeven AJ, Oude Elferink RP. ATP8B1 requires an accessory protein for endoplasmic reticulum exit and plasma membrane lipid flippase activity. Hepatology. 2008;47:268–78. PubMed PMID: 17948906.

Paulusma CC, de Waart DR, Kunne C, Mok KS, Elferink RP. Activity of the bile salt export pump (ABCB11) is critically dependent on canalicular membrane cholesterol content. J Biol Chem. 2009;284:9947–54. PubMed PMID: 19228692.

Pawlikowska L, Strautnieks S, Jankowska I, Czubkowski P, Emerick K, Antoniou A, Wanty C, Fischler B, Jacquemin E, Wali S, Blanchard S, Nielsen IM, Bourke B, McQuaid S, Lacaille F, Byrne JA, van Eerde AM, Kolho KL, Klomp L, Houwen R, Bacchetti P, Lobritto S, Hupertz V, McClean P, Mieli-Vergani G, Shneider B, Nemeth A, Sokal E, Freimer NB, Knisely AS, Rosenthal P, Whitington PF, Pawlowska J, Thompson RJ, Bull LN. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. J Hepatol. 2010;53:170–8. PubMed PMID: 20447715.

Peters J, Lacaille F, Horslen S, Thompson RJ, Jaffe R, Brousse N, Wisecarver J, Knisely AS. Microvillus inclusion disease treated by small bowel transplantation: Development of progressive intrahepatic cholestasis with low serum concentrations of g-glutamyl transpeptidase activity. Hepatology. 2001;34:213A.

Qiu YL, Gong JY, Feng JY, Wang RX, Han J, Liu T, Lu Y, Li LT, Zhang MH, Sheps JA, Wang NL, Yan YY, Li JQ, Chen L, Borchers CH, Sipos B, Knisely AS, Ling V, Xing QH, Wang JS. Defects in myosin VB are associated with a spectrum of previously undiagnosed low γ-glutamyltransferase cholestasis. Hepatology. 2017;65:1655–69. PubMed PMID: 28027573.

Saich R, Collins P, Ala A, Standish R, Hodgson H. Benign recurrent intrahepatic cholestasis with secondary renal impairment treated with extracorporeal albumin dialysis. Eur J Gastroenterol Hepatol. 2005;17:585–8. PubMed PMID: 15827452.

Scheimann AO, Strautnieks SS, Knisely AS, Byrne JA, Thompson RJ, Finegold MJ. Mutations in bile salt export pump (ABCB11) in two children with progressive familial intrahepatic cholestasis and cholangiocarcinoma. J Pediatr. 2007;150:556–9. PubMed PMID: 17452236.

Setchell KD, Heubi JE, Bove KE, O'Connell NC, Brewsaugh T, Steinberg SJ, Moser A, Squires RH Jr. Liver disease caused by failure to racemize trihydroxycholestanoic acid: gene mutation and effect of bile acid therapy. Gastroenterology. 2003;124:217–32. PubMed PMID: 12512044.

Setchell KD, Schwarz M, O'Connell NC, Lund EG, Davis DL, Lathe R, Thompson HR, Weslie Tyson R, Sokol RJ, Russell DW. Identification of a new inborn error in bile acid synthesis: mutation of the oxysterol 7alpha-hydroxylase gene causes severe neonatal liver disease. J Clin Invest. 1998;102:1690–703. PubMed PMID: 9802883.

Setchell KD, Heubi JE, Shah S, Lavine JE, Suskind D, Al-Edreesi M, Potter C, Russell DW, O'Connell NC, Wolfe B, Jha P, Zhang W, Bove KE, Knisely AS, Hofmann AF, Rosenthal P, Bull LN. Genetic defects in bile Acid conjugation cause fat-soluble vitamin deficiency. Gastroenterology. 2013;144:945–55.e6. PubMed PMID: 23415802.

Squires JE, Celik N, Morris A, Soltys K, Mazariegos G, Shneider B, Squires RH. Clinical variability after partial external biliary diversion in familial intrahepatic cholestasis 1 deficiency. J Pediatr Gastroenterol Nutr. 2017;64:425–30. PubMed PMID: 28045770.

Srivastava A. Progressive familial intrahepatic cholestasis. J Clin Exp Hepatol. 2014;4:25–36. PubMed PMID: 25755532.

Stapelbroek JM, Peters TA, van Beurden DH, Curfs JH, Joosten A, Beynon AJ, van Leeuwen BM, van der Velden LM, Bull L, Oude Elferink RP, van Zanten BA, Klomp LW, Houwen RH. ATP8B1 is essential for maintaining normal hearing. PNAS. 2009;106:9709–14. PubMed PMID: 19478059.

Stapelbroek JM, van Erpecum KJ, Klomp LW, Venneman NG, Schwartz TP, van Berge Henegouwen GP, Devlin J, van Nieuwkerk CM, Knisely AS, Houwen RH. Nasobiliary drainage induces long-lasting remission in benign recurrent intrahepatic cholestasis. Hepatology. 2006;43:51–3. PubMed PMID: 16374853.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Strautnieks SS, Byrne JA, Pawlikowska L, Cebecauerová D, Rayner A, Dutton L, Meier Y, Antoniou A, Stieger B, Arnell H, Ozçay F, Al-Hussaini HF, Bassas AF, Verkade HJ, Fischler B, Németh A, Kotalová R, Shneider BL, Cielecka-Kuszyk J, McClean P, Whitington PF, Sokal E, Jirsa M, Wali SH, Jankowska I, Pawłowska J, Mieli-Vergani G, Knisely AS, Bull LN, Thompson RJ. Severe bile salt export pump deficiency: 82 different ABCB11 mutations in 109 families. Gastroenterology. 2008;134:1203–14. PubMed PMID: 18395098.

Takatsu H, Tanaka G, Segawa K, Suzuki J, Nagata S, Nakayama K, Shin HW. Phospholipid flippase activities and substrate specificities of human type IV P-type ATPases localized to the plasma membrane. J Biol Chem. 2014;289:33543–56. PubMed PMID: 25315773.

Thébaut A, Habes D, Gottrand F, Rivet C, Cohen J, Debray D, Jacquemin E, Gonzales E. Sertraline as an additional treatment for cholestatic pruritus in children. J Pediatr Gastroenterol Nutr. 2017;64:431–5. PubMed PMID: 27557426.

Toros AB, Ozerdenen F, Bektaş H, Sari ND. A case report: nasobiliary drainage inducing remission in benign recurrent intrahepatic cholestasis. Turk J Gastroenterol. 2012;23:75–8. PubMed PMID: 22505385.

Tygstrup N, Steig BA, Juijn JA, Bull LN, Houwen RH. Recurrent familial intrahepatic cholestasis in the Faeroe Islands. Phenotypic heterogeneity but genetic homogeneity. Hepatology. 1999;29:506–8. PubMed PMID: 9918928.

Uegaki S, Tanaka A, Mori Y, Kodama H, Fukusato T, Takikawa H. Successful treatment with colestimide for a bout of cholestasis in a Japanese patient with benign recurrent intrahepatic cholestasis caused by ATP8B1 mutation. Intern Med. 2008;47:599–602. PubMed PMID: 18379143.

Ujhazy P, Ortiz D, Misra S, Li S, Moseley J, Jones H, Arias IM. Familial intrahepatic cholestasis 1: studies of localization and function. Hepatology. 2001;34:768–75. PubMed PMID: 11584374.

Usui M, Isaji S, Das BC, Kobayashi M, Osawa I, Iida T, Sakurai H, Tabata M, Yorifuji T, Egawa H, Uemoto S. Liver retransplantation with external biliary diversion for progressive familial intrahepatic cholestasis type 1: a case report. Pediatr Transplant. 2009;13:611–4. PubMed PMID: 18785905.

van der Mark VA, Ghiboub M, Marsman C, Zhao J, van Dijk R, Hiralall JK, Ho-Mok KS, Castricum Z, de Jonge WJ, Oude Elferink RP, Paulusma CC. Phospholipid flippases attenuate LPS-induced TLR4 signaling by mediating endocytic retrieval of Toll-like receptor 4. Cell Mol Life Sci. 2017;74:715–30. PubMed PMID: 27628304.

van der Woerd WL, Wichers CG, Vestergaard AL, Andersen JP, Paulusma CC, Houwen RH, van de Graaf SF. Rescue of defective ATP8B1 trafficking by CFTR correctors as a therapeutic strategy for familial intrahepatic cholestasis. J Hepatol. 2016;64:1339–47. PubMed PMID: 26879107.

van Mil SW, van der Woerd WL, van der Brugge G, Sturm E, Jansen PL, Bull LN, van den Berg IE, Berger R, Houwen RH, Klomp LW. Benign recurrent intrahepatic cholestasis type 2 is caused by mutations in ABCB11. Gastroenterology. 2004a;127:379–84. PubMed PMID: 15300568.

van Mil SW, van Oort MM, van den Berg IE, Berger R, Houwen RH, Klomp LW. Fic1 is expressed at apical membranes of different epithelial cells in the digestive tract and is induced in the small intestine during postnatal development of mice. Pediatr Res. 2004b;56:981–7. PubMed PMID: 15496606.

van Ooteghem NA, Klomp LW, van Berge-Henegouwen GP, Houwen RH. Benign recurrent intrahepatic cholestasis progressing to progressive familial intrahepatic cholestasis: low GGT cholestasis is a clinical continuum. J Hepatol. 2002;36:439–43. PubMed PMID: 11867191.

van Wessel DBE, Thompson RJ, Gonzales E, Jankowska I, Shneider BL, Sokal E, Grammatikopoulos T, Kadaristiana A, Jacquemin E, Spraul A, Lipiński P, Czubkowski P, Rock N, Shagrani M, Broering D, Algoufi T, Mazhar N, Nicastro E, Kelly D, Nebbia G, Arnell H, Fischler B, Hulscher JBF, Serranti D, Arikan C, Debray D, Lacaille F, Goncalves C, Hierro L, Muñoz Bartolo G, Mozer-Glassberg Y, Azaz A, Brecelj J, Dezsőfi A, Luigi Calvo P, Krebs-Schmitt D, Hartleif S, van der Woerd WL, Wang JS, Li LT, Durmaz Ö, Kerkar N, Hørby Jørgensen M, Fischer R, Jimenez-Rivera C, Alam S, Cananzi M, Laverdure N, Targa Ferreira C, Ordonez F, Wang H, Sency V, Mo Kim K, Chen HL, Carvalho E, Fabre A, Quintero Bernabeu J, Alonso EM, Sokol RJ, Suchy FJ, Loomes KM, McKiernan PJ, Rosenthal P, Turmelle Y, Rao GS, Horslen S, Kamath BM, Rogalidou M, Karnsakul WW, Hansen B, Verkade HJ, et al. Impact of genotype, serum bile acids, and surgical biliary diversion on native liver survival in FIC1 deficiency. Hepatology. 2021;74:892–906. PubMed PMID: 33666275.

Verhulst PM, van der Velden LM, Oorschot V, van Faassen EE, Klumperman J, Houwen RH, Pomorski TG, Holthuis JC, Klomp LW. A flippase-independent function of ATP8B1, the protein affected in familial intrahepatic cholestasis type 1, is required for apical protein expression and microvillus formation in polarized epithelial cells. Hepatology. 2010;51:2049–60. PubMed PMID: 20512993.

Verkade HJ, Thompson RJ, Arnell H, Fischler B, Gillberg PG, Mattsson JP, Torfgård K, Lindström E. Systematic review and meta-analysis: partial external biliary diversion in progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr. 2020;71:176–83. PubMed PMID: 32433433.

Vitale G, Gitto S, Raimondi F, Mattiaccio A, Mantovani V, Vukotic R, D'Errico A, Seri M, Russell RB, Andreone P. Cryptogenic cholestasis in young and adults: ATP8B1, ABCB11, ABCB4, and TJP2 gene variants analysis by high-throughput sequencing. J Gastroenterol. 2018;53:945–58. PubMed PMID: 29238877.

Walensi M, Canbay A, Witzke O, Gerken G, Kahraman A. Long-term therapy of a patient with summerskill-walshe-tygstrup syndrome by applying prometheus® liver dialysis: a case report. Case Rep Gastroenterol. 2012;6:550–6. PubMed PMID: 22949896.

Wang KS, Tiao G, Bass LM, Hertel PM, Mogul D, Kerkar N, Clifton M, Azen C, Bull L, Rosenthal P, Stewart D, Superina R, Arnon R, Bozic M, Brandt ML, Dillon PA, Fecteau A, Iyer K, Kamath B, Karpen S, Karrer F, Loomes KM, Mack C, Mattei P, Miethke A, Soltys K, Turmelle YP, West K, Zagory J, Goodhue C, Shneider BL, et al. Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis. Hepatology. 2017;65:1645–54. PubMed PMID: 28027587.

Wang NL, Li LT, Wu BB, Gong JY, Abuduxikuer K, Li G, Wang JS. The features of GGT in patients with ATP8B1 or ABCB11 deficiency improve the diagnostic efficiency. PLoS One. 2016;11:e0153114. PubMed PMID: 27050426.

Zellos A, Roy A, Schwarz KB. Use of oral naltrexone for severe pruritus due to cholestatic liver disease in children. J Pediatr Gastroenterol Nutr. 2010;51:787–9. PubMed PMID: 20948447.

Zhang J, Yang Y, Gong JY, Li LT, Li JQ, Zhang MH, Lu Y, Xie XB, Hong YR, Yu Z, Knisely AS, Wang JS. Low-GGT intrahepatic cholestasis associated with biallelic USP53 variants: Clinical, histological and ultrastructural characterization. Liver Int. 2020;40:1142–50. PubMed PMID: 32124521.

Zhu QS, Xing W, Qian B, von Dippe P, Shneider BL, Fox VL, Levy D. Inhibition of human m-epoxide hydrolase gene expression in a case of hypercholanemia. Biochim Biophys Acta. 2003;1638:208–16. PubMed PMID: 12878321.

License