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Pediatric Genetic Cholestatic Liver Disease Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding pediatric genetic cholestatic liver diseases, including their clinical characteristics and recommended approaches to diagnosis, management, and genetic counseling. The following are the goals of this overview.

Goal 1

Briefly describe the common clinical characteristics of inherited cholestatic liver diseases in which cholestasis is a primary manifestation of the underlying causative pathology. Note: Disorders in which cholestasis is a secondary manifestation of the underlying causative pathology are outside the scope of this chapter.

Goal 2

Review the genetic causes of primary cholestatic liver disease.

Goal 3

Provide an evaluation strategy to identify the genetic cause of primary cholestatic liver disease in a proband (when possible).

Goal 4

Inform genetic counseling of family members of an individual with primary genetic cholestatic liver disease.

Goal 5

Review high-level dietary, medical, and surgical management of primary genetic cholestatic liver disease.

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1. Clinical Characteristics of Genetic Cholestatic Liver Disease

For the purposes of this chapter, the term "primary cholestatic liver disease" is used to designate those inherited disorders in which cholestasis is a primary manifestation of the underlying causative pathology (such as transport of bile acids and phospholipids, bile acid synthesis, and bile acid metabolism or transport). Disorders in which cholestasis is a secondary manifestation of the underlying causative pathology are outside the scope of this chapter.

Cholestasis is absent or reduced bile flow associated with a pathologic condition. Cholestasis is suspected in the presence of the following clinical manifestations and is defined by the following laboratory findings.

Clinical manifestations of cholestasis

- Jaundice (yellowing of the skin and/or mucous membranes and/or peripheral sclera of the eye – i.e., scleral icterus)
- Pruritus or itching (commonly related to the relative elevation of serum bile acids)
- Malabsorption of fat-soluble vitamins (i.e., vitamins A, D, E, and K), resulting in:
  - Poor weight gain
  - Easy bleeding or bruising (secondary to coagulopathy from vitamin K deficiency)
- Hepatosplenomegaly
- Discolored and/or pale stools (i.e., acholic stools)

The first episode of cholestasis may occur in infancy in any of the pediatric genetic disorders discussed in this overview, regardless of the natural history of the disorder.

The natural history of many genetic cholestatic disorders is progression to fibrosis (i.e., general scarring of the liver secondary to injury) that can be graded 1-4. Cirrhosis, the most severe form of fibrosis, is generally accompanied by other complications such as portal hypertension, synthetic liver dysfunction, and increased risk for hepatocellular carcinoma.

Laboratory findings of cholestasis

- Conjugated or direct hyperbilirubinemia

  Note: (1) While consensus guidelines recommend evaluation of cholestatic disease for conjugated or direct bilirubin concentrations above 1.0 mg/dL (17 µmol/L) [Fawaz et al 2017], others have proposed a more conservative approach, suggesting investigations in individuals with conjugated or direct bilirubin measurements of 0.3 mg/dL (5 µmol/L) [Harpavat et al 2016, Feldman & Sokol 2019]. (2) Conjugated or direct bilirubin levels may not be an accurate marker of cholestasis.

- Gamma-glutamyl transpeptidase (GGTP; also referred to as gamma-glutamyl transferase [GGT]) levels are integral to identifying different causes of cholestatic liver disease, including:
  - Low-normal GGTP levels in most disorders known as progressive familial intrahepatic cholestasis (see Table 1);
  - Elevated GGTP levels in disorders with abnormal biliary duct morphology or cholangiociliopathies/ciliary development (see Table 3).

- Elevated serum bile acids
  - While the majority of cholestatic conditions have elevated primary serum bile acids (cholic and chenodeoxycholic acids), the family of bile acid synthetic defect disorders may be defined by the absence of primary bile acids and the presence of atypical bile acids specific to each primary defect (see Table 2).

- Elevated alkaline phosphatase is used infrequently to assess children with cholestasis, as it often reflects alternative processes such as bone injury or growth.

Liver and abdominal ultrasound imaging findings in individuals with pediatric genetic cholestatic liver disease may be nonspecific.

Liver ultrasound findings may include [Squires & McKiernan 2018]:

- Coarseness, nodularity, or increased echogenicity
- Hepatomegaly
- Antegrade portal blood flow on Doppler assessment
- Bile duct abnormalities including:
  - Dilatation with mechanical obstruction
  - Diminutive extrahepatic ducts and gall bladder abnormalities

Abdominal ultrasound may include:

- Splenomegaly
- Ascites

Extrahepatic clinical manifestations may be observed in certain metabolic or developmental disorders (see Table 3).

2. Causes of Genetic Cholestatic Liver Disease

Note: Pathologic cholestasis occurs in one in 2,500 newborns in North America, 40% of which is attributed to biliary atresia, an inflammatory cholangiopathy that requires immediate diagnosis (suggested by liver ultrasound examination and liver biopsy and confirmed with intraoperative cholangiogram) and life-saving surgical intervention [Karpen 2020].

The subject of this overview is the estimated 25%-50% of pediatric primary genetic cholestasis NOT related to biliary atresia that has an identifiable genetic etiology [Feldman & Sokol 2019].

The genetic disorders discussed in Tables 1, 2, and 3 of this overview are organized by the mechanism of disease causation and presence of extrahepatic findings:

- Disorders of transport of bile acids or phospholipids (Table 1)
- Disorders of bile acid synthesis (Table 2)
- Disorders with extrahepatic metabolic or developmental findings (Table 3)

Disorders of Transport of Bile Acids or Phospholipids

Table 1 summarizes primary cholestatic liver disease caused by defects that impair bile acid transport and result in progressive cholestasis. These disorders, many of which have overlapping clinical findings, are historically referred to as progressive familial intrahepatic cholestasis (PFIC) and are generally associated with onset in early infancy or childhood. However, it is increasingly apparent that pathogenic variants in PFIC-associated genes can also contribute to the adult-onset diseases benign recurrent intrahepatic cholestasis (BRIC) – intermittent episodes of cholestasis of varying severity – and intrahepatic cholestasis of pregnancy (ICP) – cholestasis, pruritus, and hepatic impairment that manifests with pregnancy and usually resolves completely after delivery. See Table 1 for the range of phenotypes observed in association with each PFIC-related gene.

Note: (1) Although some investigators have proposed the use of gene-based nomenclature (e.g., ATP8B1 deficiency) rather than phenotype-based nomenclature (e.g., PFIC1) to enable gene-specific clinical care and facilitate scientific discovery [Biesecker et al 2021, Squires & Monga 2021], this chapter primarily relies on

historical phenotype-based nomenclature and classification for consistency with their use in most contemporary medical literature. (2) Table 1 does not include provisionally identified genes for which data available to date are not sufficient to associate variants with a specific phenotype or an underlying disease mechanism.

Table 1. Pediatric Genetic Cholestatic Liver Diseases: Genes and Clinical Features of Defects in Transport of Bile Acids or Phospholipids

Gene [1]	Disorder Designation(s)	Laboratory Findings	PFIC Clinical Features / Comments	Adult-Onset Phenotypes	
				BRIC	ICP
ABCB4 [2]	PFIC3; MDR3 deficiency (OMIM 602347)	↑ AST/ALT; ↑↑↑ GGTP	↑ risk for HCC & CCA; ↑ risk for intrahepatic stone formation; typically AR inheritance but can be AD		+
ABCB11 [2]	PFIC2; BSEP deficiency (OMIM 601847)	↑ AST/ALT; ↓ or normal GGTP	Jaundice, pruritus, & portal HTN; poor growth & malabsorption; rapid progression in 1st 5 yrs; early-onset cirrhosis; ≤15% rate of malignancy (HCC & CCA) in children as young as 13 mos	+	+
ATP8B1 [2]	FIC1 deficiency; ATP8B1 deficiency (incl PFIC1 & BRIC1)	↑ AST/ALT & bilirubin; ↓ or normal GGTP; ↑ electrolytes on sweat chloride test	May have profound diarrhea, poor growth, short stature, pancreatic insufficiency, & hearing loss; [3] carrier frequencies relatively high in Inuit populations of Greenland & northern Canada & Amish kindreds [4, 5]	+	+
KIF12 [6]	KIF12 deficiency (OMIM 619662)	↑ GGTP	Rapid progression to liver fibrosis & portal HTN; progressive sclerosing cholangitis w/age		
LSR [7]	LSR deficiency	↑ AST/ALT, bile acids, & bilirubin; ↓ or normal GGTP	Intractable itching		
MYO5B [2, 8]	PFIC6	↑ AST/ALT & bilirubin; ↓ or normal GGTP	Microvillus inclusion disease; liver disease can be transient, progressive, or recurrent.		
NR1H4 [2]	PFIC5 (OMIM 617049)	↑ AST/ALT & bilirubin; ↓ or normal GGTP; ↑↑ AFP; coagulopathy	Rapid progression to ESLD		
TJP2 [9]	PFIC4	↑ AST/ALT & bilirubin; ↓ or normal GGTP	Severe cholestasis & pruritus; rapid progression; ↑ risk for HCC; neurologic or respiratory deficits; high carrier frequency for *TJP2*-related genetic cholestatic liver disease among Lancaster County Old Order Amish [10]		+

Table 1. continued from previous page.

Gene [1]	Disorder Designation(s)	Laboratory Findings	PFIC Clinical Features / Comments	Adult-Onset Phenotypes	
				BRIC	ICP
USP53 [9]	USP53 deficiency (OMIM 619658)	↑ AST/ALT; normal GGTP	Intractable pruritus & hypocalcemia; w/or w/o progressive hearing loss		

Adapted from Tables 1-6 in Squires & McKiernan [2018]
AD = autosomal dominant; AFP = alpha-fetoprotein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AR = autosomal recessive; AST = aspartate aminotransferase; BSEP = bile salt export pump; BRIC = benign recurrent intrahepatic cholestasis; CCA = cholangiocarcinoma; ESLD = end-stage liver disease; GGTP = gamma-glutamyl transpeptidase; HCC = hepatocellular carcinoma; HTN = hypertension; ICP = intrahepatic cholestasis of pregnancy; PFIC = progressive familial intrahepatic cholestasis
1. Genes are listed alphabetically.
2. Goldberg & Mack [2020]
3. Henkel et al [2019]
4. Clayton et al [1969], Klomp et al [2000]
5. "Byler disease" refers to severe ATP8B1 deficiency in individuals of Amish ancestry; "Greenland childhood cholestasis" or "Greenland familial cholestasis" refers to severe ATP8B1 deficiency in individuals of Inuit ancestry.
6. Maddirevula et al [2019]
7. Maddirevula et al [2019], Uehara et al [2020]
8. Gonzales et al [2017]
9. Maddirevula et al [2019], Zhang et al [2020], Alhebbi et al [2021], Bull et al [2021]
10. Carlton et al [2003]

Disorders of Bile Acid Synthesis

Table 2 summarizes primary cholestatic liver disease caused by disorders of bile acid synthesis. These disorders, generally associated with onset in early infancy or childhood, are characterized by fat-soluble vitamin deficiency with growth deficiency.

There are two main mechanisms by which bile acid synthesis defects can damage the liver:

- Defective bile acids affect bile-induced bile flow, resulting in cholestasis.
- Buildup of intermediates/metabolites from the process of bile acid synthesis are toxic to hepatocytes.

Note: Table 2 does not include provisionally identified genes for which data available to date are not sufficient to associate variants with a specific phenotype or an underlying disease mechanism.

Table 2. Pediatric Genetic Cholestatic Liver Diseases: Genes and Clinical Features of Disorders of Bile Acid Synthesis

Gene [1, 2]	Disorder	Laboratory Findings	Clinical Features / Comments
AKR1D1 [3]	CBAS2 (OMIM 235555)	↑ AST/ALT; ↑ GGTP	No pruritus; HSM
AMACR [3]	CBAS4 (OMIM 214950)	↓ serum bile acids	Motor neuropathy in adult-onset phenotype
BAAT [4]	Bile acid conjugation defect 1 (OMIM 619232)	↑ or normal AST/ALT	Possible ESLD; high carrier frequency of *BAAT*-related genetic cholestatic liver disease in Lancaster County Old Order Amish community [5]
CYP7B1 [3]	CBAS3 (OMIM 613812)	↑ AST/ALT; ↓ or normal GGTP	HSM, synthetic dysfunction
CYP27A1 [6]	Cerebrotendinous xanthomatosis	Cholestasis w/↓ or normal bile acids	Neonatal onset; neurologic findings & diarrhea

Table 2. continued from previous page.

Gene [1, 2]	Disorder	Laboratory Findings	Clinical Features / Comments
HSD3B7 [3]	CBAS1 (OMIM 607765)	↑ AST/ALT; ↓ or normal GGTP; ↓ serum bile acids	Most common defect; similar clinically to PFIC1 (see ATP8B1 deficiency in Table 1) but w/o pruritus or HSM

Adapted from Tables 1-6 in Squires & McKiernan [2018]
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBAS = congenital defect in bile acid synthesis; ESLD = end-stage liver disease; GGTP = gamma-glutamyl transpeptidase; HSM = hepatosplenomegaly; PFIC = progressive familial intrahepatic cholestasis
1. Genes are listed alphabetically.
2. Selected references included
3. Heubi et al [2007]
4. Setchell et al [2013]
5. Carlton et al [2003]
6. Gong et al [2017]

Disorders with Cholestatic Liver Disease and Extrahepatic Findings

Table 3 includes genetic disorders with extrahepatic metabolic or developmental findings in which cholestasis is the primary manifestation of underlying disease pathology that can be localized to the liver.

Note: Table 3 does not include provisionally identified genes for which data available to date are not sufficient to associate variants with a specific phenotype or an underlying disease mechanism.

Table 3. Pediatric Genetic Cholestatic Liver Diseases: Genes and Clinical Features of Disorders with Extrahepatic Metabolic or Developmental Findings

Gene(s) [1] (Disorder [2])	Age of Onset	Laboratory Findings	Clinical Features / Comments
CFTR [3] (cystic fibrosis)	Childhood/ adolescence	Diagnosis requires ≥2 of following findings: • ↑ AST/ALT & GGTP for >6 mos • HSM, confirmed on ultrasound • Coarseness, nodularity, ↑ echogenicity or portal HTN on ultrasound • Liver biopsy w/biliary or multilobular cirrhosis [4] Synthetic dysfunction is usually minimal.	Cystic fibrosis liver disease is diagnosed in 10%-15% of persons w/CF & is cause of mortality in 2%-3% of persons w/CF. [4] Cirrhosis & portal HTN are most clinically significant manifestations. Neonatal cholestasis is possible presenting feature.
CLDN1 [5] (neonatal ichthyosis-sclerosing cholangitis) (OMIM 607626)	Neonatal	↑ ALT & GGTP	Portal HTN; ichthyosis & alopecia
DCDC2 [6] (neonatal sclerosing cholangitis) (OMIM 617394)	Neonatal	↑ ALT & GGTP	Acholic stools, HSM, coagulopathy, ascites (variable presentation), renal disease

Table 3. continued from previous page.

Gene(s) [1] (Disorder [2])	Age of Onset	Laboratory Findings	Clinical Features / Comments
HNF1B [7] (HNF1B deficiency) (OMIM 137920)	Neonatal to adulthood	↑ AST/ALT; ↑ GGTP	Spectrum of hepatic involvement ranges from severe neonatal cholestasis to asymptomatic increase of transaminases in adulthood; clinical manifestations incl paucity of intralobular bile ducts sometimes assoc in newborns w/IUGR. HCC has been reported. Other findings can incl kidney involvement (CAKUT, tubulopathy, &/or interstitial kidney disease), MODY5, &/or pancreatic insufficiency.
JAG1; *NOTCH2* [8] (Alagille syndrome)	Infancy	↑↑↑ GGTP	Cholestasis, progressing to ESLD in some; butterfly vertebrae, xanthomas, CHD, posterior embryotoxon, vascular abnormalities
NPC1; *NPC2* (Niemann-Pick disease type C)	Neonatal to adulthood		Neonatal features incl cholestasis, HSM, & in some cases ALF; neurodegenerative findings in older groups
PEX genes (Zellweger spectrum disorder)	Neonatal	Abnormal VLCFA	Cholestasis + hepatomegaly; neurologic deficits
PKHD1 [9] (polycystic kidney disease, autosomal recessive)	Infancy to adulthood	Abnormal lab findings may be absent in newborns w/ARPKD.	Congenital hepatic fibrosis; variable dilatation of intrahepatic bile ducts (Caroli syndrome) & dilatation of common bile duct; nephromegaly, HTN, & varying degrees of renal dysfunction
SCYL1 [10] (cholestasis, acute liver failure, & neurodegeneration) (OMIM 616719)	Infancy	Low GGTP	Cholestasis, fibrosis, & recurrent ALF; DD, neuropathy, cerebellar atrophy, ataxia, chronic anemia, skeletal dysplasia
SERPINA1 (alpha-1 antitrypsin deficiency)	Infancy to adulthood	↑ AST/ALT & GGTP in 20%	Neonatal onset in severe phenotype w/ cholestasis & progressive liver disease. HCC possible; chronic obstructive lung disease, panniculitis, & vasculitis; rare in Asian populations
SLC25A13 (neonatal intrahepatic cholestasis caused by citrin deficiency) (See Citrin Deficiency.)	Age <1 yr	Hypoproteinemia, synthetic liver dysfunction; ↑ NH_3; ↓ glucose	↓ birth weight, growth restriction; transient cholestasis; resolves by age 1 yr in most
SLC51A [11] (SLC51A deficiency)	Neonatal	↑ AST/ALT/ALP	Diarrhea & malabsorption, poor weight gain & bleeding; early fibrosis & cirrhosis w/cholestasis
SLC51B [12] (primary bile acid malabsorption 2) (OMIM 619481)	Neonatal	↑ AST/ALT & GGTP; ↑ INR, normal albumin; ↓ fat-soluble vitamins	Congenital diarrhea; prolonged jaundice in neonatal period
TALDO1 [13] (transadolase 1 deficiency)	Neonatal	↑ AST/ALT/ALP; normal GGTP	Hepatomegaly, pancytopenia, renal defects, cardiac defects, fetal hydrops, & dysmorphic features; ↑ HCC risk

Table 3. continued from previous page.

Gene(s) [1] (Disorder [2])	Age of Onset	Laboratory Findings	Clinical Features / Comments
TTC26 [14] (biliary, renal, neurologic & skeletal syndrome) (OMIM 619534)	Neonatal	↑ liver enzymes; ↑ bilirubin; ↑ GGTP in some cases	Cardiac defects, renal abnormalities (small/echogenic kidneys, hydronephrosis), DD, pituitary stalk interruption syndrome
VIPAS39 (*VIPAR*); *VPS33B* (arthrogryposis, renal dysfunction, & cholestasis) (OMIM PS208085)	Neonatal	↑ AST/ALT & bilirubin; ↓ or normal GGTP	Arthrogryposis, renal tubular acidosis, & ichthyosis; poor growth; largely fatal in 1st yr of life
ZFYVE19 [15] (ciliopathy of bile duct epithelia) (OMIM 619849)	Neonatal	↑ GGTP & bile acids; hyperlipidemia	Fibrosis/cirrhosis w/o effect on synthetic function; HSM

Adapted from Tables 1-6 in Squires & McKiernan [2018]
ALF = acute liver failure; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARPKD = autosomal recessive polycystic kidney disease; AST = aspartate aminotransferase; CAKUT = congenital anomalies of the kidney and urinary tract; CHD = congenital heart disease; DD = developmental delay; ESLD = end-stage liver disease; GGTP = gamma-glutamyl transpeptidase; HCC = hepatocellular carcinoma; HSM = hepatosplenomegaly; HTN = hypertension; INR = international normalized ratio; IUGR = intrauterine growth restriction; MODY5 = maturity-onset diabetes of the young type 5; VLCFA = very long-chain fatty acids
1. Genes are listed alphabetically.
2. Link to *GeneReview* or OMIM entry
3. Kamal et al [2018]
4. Leung & Narkewicz [2017]
5. Grosse et al [2012]
6. Girard et al [2016]
7. Mandato et al [2019], Pinon et al [2019], Gambella et al [2023]
8. Saleh et al [2016]
9. Shneider & Magid [2005]
10. Lenz et al [2018]
11. Gao et al [2020]
12. Sultan et al [2018]
13. Grammatikopoulos et al [2022]
14. David et al [2020], Shaheen et al [2020], Alfadhel et al [2021]
15. Goldberg & Mack [2020], Luan et al [2021], Mandato et al [2021]

3. Evaluation Strategies to Identify the Cause of a Genetic Cholestatic Liver Disease in a Proband

Establishing a specific cause of pediatric genetic cholestatic liver disease:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Family history. A three-generation family history should be taken with attention to relatives with manifestations of a genetic cholestatic liver disease and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing. Because the vast majority of genetic cholestatic liver diseases are inherited in an autosomal recessive manner, the family history may show affected sibs and/or parental consanguinity. Absence of a known family history does not preclude the diagnosis.

Molecular genetic testing approaches can include gene-targeted testing (multigene panel) or comprehensive genomic testing (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **A cholestatic liver disease multigene panel** that includes some or all of the genes listed in Tables 1, 2, and 3 is 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*. Of note, given the rarity of some of the genes associated with genetic cholestatic liver disease, some panels may not include all the genes mentioned in this overview. (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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved and may be used if clinical suspicion for a genetic etiology remains high but more targeted investigations have not identified a genetic cause. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

4. 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

The vast majority of pediatric genetic primary cholestatic liver diseases are inherited in an autosomal recessive manner. Exceptions include autosomal dominant inheritance of liver disease associated with *JAG1* or *NOTCH2* pathogenic variants (i.e., Alagille syndrome), autosomal dominant inheritance (in some individuals) of *ABCB4*-related liver disease (i.e., PFIC3) [Stättermayer et al 2020], and autosomal codominant inheritance associated with pathogenic variants in *SERPINA1* (i.e., alpha-1 antitrypsin deficiency). Recurrence risk depends on the mode of inheritance associated with the condition.

Note: If a proband has a specific genetic disorder or syndrome associated with cholestatic liver disease (e.g., alpha-1 antitrypsin deficiency or Alagille syndrome [see Table 3]), genetic counseling for that condition is indicated.

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for one of the pathogenic variants identified in the proband.
- Once a molecular diagnosis is established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and

parental identity testing has confirmed biological maternity and paternity, 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.
- The heterozygous parents of a proband are typically asymptomatic but may rarely manifest related features. Intrahepatic cholestasis of pregnancy has been reported occasionally in mothers of individuals with progressive familial intrahepatic cholestasis (PFIC).

Sibs of a proband

- If both parents are known to be heterozygous for a 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, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygous sibs may be at increased risk for transient neonatal cholestasis. Female sibs who are heterozygous for a PFIC-associated pathogenic variant may be at risk for intrahepatic cholestasis of pregnancy.

Offspring of a proband

- Unless an affected individual's reproductive partner also has autosomal recessive cholestatic liver disease or is a carrier, offspring will be obligate heterozygotes for a pathogenic variant.
- Offspring of an affected individual and a carrier have a 50% chance of being affected and a 50% chance of being carriers. Higher carrier frequencies have been reported in some populations.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a cholestatic liver disease-related pathogenic variant.

Carrier Detection

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

Related Genetic Counseling Issues

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 PFIC-causing 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.

- **Alagille Syndrome Alliance**
  Phone: 901-286-8869
  Email: alagille@alagille.org
  www.alagille.org
- **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
  www.childliverdisease.org
- **PFIC Advocacy and Resource Network, Inc.**
  Email: emily@pfic.org
  www.pfic.org

5. Management

The interventions discussed here focus on symptomatic treatment of clinical manifestations, surveillance issues, and disease-specific treatments/surveillance.

Symptomatic Treatment of Clinical Manifestations

Nutritional Supplements

Standard nutritional approaches for malabsorption of fat and fat-soluble vitamins that benefit growth and development:

- Supplementation of the fat-soluble vitamins A, D, E, and K
- Use of dietary medium-chain triglycerides (MCTs), as they are absorbed independent of bile acids. MCTs can be provided either as infant formula (e.g., Alimentum®, Pregestimil®) or as MCT oil.

Pruritus – Medical Management

Synthetic bile acids

- **Oral ursodeoxycholic acid** (UDCA), a hydrophilic bile acid, can both replace circulating toxic hydrophobic bile salts and stimulate hepatobiliary secretion of bile salts to improve bile flow. UDCA, which is FDA approved, may be prescribed by physicians for an "off-label" indication in pediatric cholestatic liver disease (see Table 4).
- **Oral cholic acid**, available as Cholbam®, an FDA-approved bile acid, is specifically used in inborn errors of bile acid synthesis (see Table 5).
- **Glycocholic acid** is a bile acid approved as an investigational drug by the FDA for conjugation defects (see Table 5).

Antipruritic agents

- Cholestyramine binds bile acids in the gut and enhances fecal bile acid secretion
- Rifaximin is an antibiotic that induces enzymes of drug metabolism to modify and increase excretion of bile salts. Because rifaximin can cause drug-induced hepatitis, its use must be closely monitored [Kriegermeier & Green 2020].
- Ileal bile acid transporter inhibitors (IBAT), such as odevixibat or maralixibat, reduce enterohepatic circulation of bile acids by decreasing their reabsorption in the ileum, thus increasing their excretion. Studies have shown that these agents are as effective in treating pruritus and normalizing bile acid levels in certain cholestatic liver diseases, including PFIC and Alagille syndrome [Slavetinsky & Ekkehard 2020].
- Naloxone, hydroxyzine, and sertraline (which have less well-understood mechanisms of action) may lessen pruritus in some affected individuals [Thébaut et al 2017, Squires & McKiernan 2018].

Pruritis – Surgical Management

Surgical management by either **partial external biliary diversion** (PEBD) or **partial ileal exclusion** improves pruritus by interrupting the enterohepatic circulation of bile and decreasing bile reabsorption. Both surgical interventions are generally well tolerated and improve pruritus, normalize serum markers of liver disease, and prevent progression of liver disease (by unknown mechanisms). Of note, cirrhosis at the time of surgical intervention is associated with poorer outcomes [Squires et al 2017].

Although no studies have demonstrated superiority of either of these surgical interventions, the response to PEBD may be longer lasting than the response to ileal exclusion.

Partial external biliary diversion (PEBD), the most common procedure, uses a segment of intestine to form a conduit between the gallbladder and an opening (ostomy) in the abdominal wall. With this approach, the 30%-50% of bile excreted by the liver drains through the ostomy and can be discarded.

Initially described for children with low-GGTP forms of PFIC, PEBD is associated with an excellent long-term outcome when serum bile acid levels normalize within one year.

Some data suggest that PEBD is effective in PFIC1 (ATP8B1 deficiency) and mild-to-moderate PFIC2 (BSEP deficiency) in which some enzyme function is retained [Henkel et al 2019]; however, it may not be effective in severe PFIC2 (see Table 4). PEBD may also be effective for other forms of cholestasis – namely, Alagille syndrome (see Table 6).

Partial ileal exclusion, a less utilized approach, uses a loop of small intestine to bypass the terminal ileum, the site of most bile acid reabsorption. Complications of bypassing a portion of the small intestine can include severe malabsorption (particularly of vitamin B_{12}) and diarrhea.

Liver Transplantation

When the medical and surgical interventions discussed above fail to provide relief from severe pruritus or prevent progression to end-stage liver disease with cirrhosis, liver transplantation often provides a good outcome.

Note that liver transplantation fails to prevent the extrahepatic complications for any of the disorders described in Tables 1, 2, and 3.

Surveillance Issues

Monitoring for complications of chronic liver disease including fibrosis and cirrhosis can be done by abdominal ultrasound examination as a first step. The presence of hepatomegaly and thrombocytopenia has been used to define clinically evident portal hypertension [Bass et al 2019].

Screening for hepatocellular carcinoma (HCC). While HCC can occur in any individual in whom cirrhosis develops, persons with BSEP deficiency (see Table 1) and alpha-1 antitrypsin deficiency are at the highest risk. In those with significant fibrosis or cirrhosis, lifelong screening is warranted with a serum AFP concentration and abdominal ultrasound examination every six to 12 months.

Screening for cholangiocarcinoma. No guidelines have been established.

Disease-Specific Treatment of Manifestations

Disorders of Transport of Bile Acids or Phospholipids

Nutritional supplements are often required for disorders of transport of bile acids or phospholipids (see Table 1).

UDCA (see Pruritus -- Medical Management) is also used as a synthetic hydrophilic bile acid replacement in all these disorders.

The two indications for liver transplantation in these conditions are disease refractory to medical/surgical supportive treatments and progression to end-stage liver disease [Henkel et al 2019].

Additional treatment is summarized in Table 4.

Table 4. Pediatric Genetic Cholestatic Liver Diseases: Treatment of Manifestations and Surveillance Issues for Disorders of Transport of Bile Acids or Phospholipids

Gene [1]	Disorder	Pruritus Management		Liver Transplantation	Surveillance
		Rx	Biliary diversion [2, 3]		
ABCB4	PFIC3; MDR3 deficiency	Rifaximin, cholestyramine, naltrexone, sertraline, odevixibat (IBAT)	+	+	For HCC
ABCB11	PFIC2; BSEP deficiency		+ but less helpful in severe PFIC2	Anti-BSEP antibodies can occur afterward & cause recurrent disease.	
ATP8B1	ATP8B1 deficiency; PFIC1; Byler syndrome		+	Transplant possible, but worsening diarrhea & allograft steatohepatitis are post-transplant complications.	

Table 4. continued from previous page.

Gene [1]	Disorder	Pruritus Management		Liver Transplantation	Surveillance
		Rx	Biliary diversion [2, 3]		
KIF12	KIF12 deficiency	Rifaximin, cholestyramine, naltrexone, sertraline	Unknown	Case reports [Maddirevula et al 2019, Stalke et al 2022]	
MYOB5	Myosin VB deficiency		+	+ when pruritus is refractory	
NR1H4	PFIC5		Not used due to rapid progression to ESLD [4]	+	
TJP2	PFIC4		+	Transplantation possible at younger age due to severity of neonatal disease [4]	For HCC
USP53	USP53 deficiency	Rifaximin more effective than UDCA [5]	Unknown	Unknown	

BSEP = bile salt export pump; ESLD = end-stage liver disease; HCC = hepatocellular carcinoma; PFIC = progressive familial intrahepatic cholestasis; UDCA = ursodeoxycholic acid

1. Genes are listed alphabetically.

2. The surgical treatment for pruritus used in most cases is a partial external biliary diversion (PEBD). A partial internal biliary diversion (PIBD) and ileal exclusion have been documented as other methods of surgical treatment of pruritus.

3. PEBD is associated with an excellent long-term outcome when serum bile acid levels normalize within one year.

4. Henkel et al [2019]

5. Maddirevula et al [2019]

Disorders of Bile Acid Synthesis

Nutritional supplements are often required for disorders of bile acid synthesis, since fat-soluble vitamin deficiency is a hallmark of their disease. Additional treatment is summarized in Table 5.

Table 5. Pediatric Genetic Cholestatic Liver Diseases: Treatment of Manifestations and Surveillance Issues for Disorders of Bile Acid Synthesis

Gene [1]	Disorder	Treatment (synthetic bile acids)
AKR1D1	CBAS2	Cholic acid
AMACR	CBAS4	
BAAT	Bile acid conjugation defect 1	Glycocholic acid
CYP7B1	CBAS3	Chenodeoxycholic acid may be effective.
CYP27A1	Cerebrotendinous xanthomatosis	Cholic acid
HSD3B7	CBAS1	

CBAS = congenital defect in bile acid synthesis

1. Genes are listed alphabetically

Disorders with Cholestatic Liver Disease and Extrahepatic Findings

Management of extrahepatic metabolic or developmental manifestations, which typically persist despite treatment of hepatic manifestations, is outside the scope of this overview.

Nutritional supplements are required. In addition to these supplements, children with cystic fibrosis may benefit from pancreatic enzymes to assist with pancreatic exocrine insufficiency, if present.

Table 6. Pediatric Genetic Cholestatic Liver Diseases: Treatment of Manifestations and Surveillance Issues for Disorders with Extrahepatic Metabolic or Developmental Findings

Gene(s) [1]	Disorder	Synthetic Bile Acids	Pruritus Management		Liver Transplantation
			Rx	Biliary diversion	
CFTR	Cystic fibrosis	UDCA, but efficacy uncertain			Severe loss of hepatic synthetic function or complications of portal HTN
CLDN1	Neonatal ichthyosis-sclerosing cholangitis	Usually UDCA			For severe progressive liver disease
DCDC2	Neonatal sclerosing cholangitis		Antipruritic agents		For severe, progressive liver disease
JAG1; *NOTCH2*	Alagille syndrome	UDCA	Maralixibat (IBAT)	+	Severe loss of hepatic synthetic function, uncontrolled pruritus, or complications of portal HTN [2]
NPC1; *NPC2*; *SMPD*	Niemann-Pick disease type C				
PEX genes	Zellweger spectrum disorder	Cholic acid			–
PKHD1	Polycystic kidney disease, autosomal recessive	UDCA used when intrahepatic ductal dilatation is present (i.e., Caroli syndrome).			Severe cases: liver transplant or combined renal-hepatic transplant
SCYL1	Cholestasis, acute liver failure, and neurodegeneration				
SERPINA1	Alpha-1 antitrypsin deficiency				For progressive liver dysfunction / liver failure [3]
SLC25A13	Neonatal intrahepatic cholestasis caused by citrin deficiency (See Citrin Deficiency.)				Liver findings typically resolve spontaneously by age 1 yr; liver transplant for severe progressive liver disease
SLC51A	SLC51A deficiency		Antipruritic agents		
SLC51B	Primary bile acid malabsorption 2		Antipruritic agents		
TALDO1	Transadolase 1 deficiency				Liver transplant in early, severe cases; higher risk for early-onset HCC
TTC26	Biliary, renal, neurologic, & skeletal syndrome				Liver transplant in severe cases w/fibrosis & cirrhosis

Table 6. continued from previous page.

Gene(s) [1]	Disorder	Synthetic Bile Acids	Pruritus Management		Liver Transplantation
			Rx	Biliary diversion	
VIPAS39 (*VIPAR*); *VPS33B*	Arthrogryposis, renal dysfunction, & cholestasis [4]				
ZFYVE19	Ciliopathy of bile duct epithelia		Antipruritic agents		

HCC = hepatocellular carcinoma; HTN = hypertension; UDCA = ursodeoxycholic acid

1. Genes are listed alphabetically.

2. For more detailed information about the clinical manifestations of the liver disease in Alagille syndrome and its management, see Childhood Liver Disease Research Network, Alagille Syndrome (pdf).

3. For more detailed information about the clinical manifestations of the liver disease in alpha-1 antitrypsin deficiency and its management, see Childhood Liver Disease Research Network, Alpha-1 Antitrypsin Deficiency (pdf).

4. No specific treatment or management of cholestatic liver disease in arthrogryposis, renal dysfunction, and cholestasis has been recommended.

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 Childhood 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, with 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.

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- 25 May 2023 (aa) Revision: *HNF1B* added to Table 3
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