

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Inherited Disorders of Bile Acid Transport or Synthesis

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**G&H** How common are the genetic defects that can lead to disorders of bile acid transport?

**WB** There are at least 20 recognized inborn errors of bile acid synthesis or defects in transport proteins that can lead to altered bile formation. These disorders, which present as intrahepatic cholestasis (IHC), are designated by eponyms or, preferably, by specific gene location (Table 1). Each of these disorders has been described in the past 20 years. Currently, there are only a few centers that are capable of making a precise molecular diagnosis, so it is very difficult to provide statistics in terms of their frequency and incidence. However, in our practice, these defects account for 25–30% of the cases of IHC presenting in infants and children.

**G&H** How were these genetic defects first detected?

**WB** Our initial investigations into this problem began in children with what was called “idiopathic neonatal hepatitis.” This term is a default misnomer, as these patients do not have hepatitis; they have IHC. In searching for the underlying mechanisms, it became clear that these “experiments of nature” actually represent inborn errors in the fundamental process of bile formation. From that broad category of idiopathic neonatal hepatitis, it is now possible to define each of the genetic disorders listed in Table 1 and apply them to some adult patients as well, thus significantly shrinking the category of idiopathic hepatic disease.

**G&H** Could you describe how these defects affect liver function?

**WB** There are multiple steps in the hepatic excretory processes required to form bile. Therefore, any step that fails to function will cause a similar end result—impaired bile formation. Specific genetic defects will affect either the synthesis of bile acids (the main motive force driving bile formation) from cholesterol or impede the transport of bile acids into the bile canaliculus. The resultant impairment in bile formation is typically manifested as jaundice, elevated conjugated bilirubin levels, and chronic cholestasis.

**G&H** Do these genetic defects ever manifest later in life?

**WB** There is a notion that these are extraordinarily rare disorders that are only detected in newborns. However, this idea acknowledges only the tip of the iceberg, the obvious, very ill patients who present in the newborn period because they have the most severe forms of these disorders. What we are learning is that a significant proportion of individuals carry one copy of these gene mutations and that as heterozygotes they are not only susceptible to IHC but they may also be predisposed to more severe hepatobiliary injury due to other disorders. The broader implication is that the platform of underlying genetic defects in bile formation may contribute to common forms of liver disease such as nonalcoholic steatohepatitis or alpha-1 antitrypsin deficiency. Internists are now assessing women with IHC of pregnancy and patients with idiosyncratic drug toxicities and documenting these patients as heterozygous for one of the transport defects. Presumably, in these two examples, the combination of hormonal changes or drug-induced injury and the genetic susceptibility due to the defect leads to more significant disease. These serve as proofs of principle that these gene defects predispose subjects to more severe liver disease of any form. I believe that as time goes by, this scenario will continue to be played out and that genetic defects may partially explain the disease course in a wide variety of

**Table 1.** Molecular Defects in Bile Acid Transport or Synthesis that Manifest as Inherited Forms of Intrahepatic Cholestasis

Gene	Protein	Function, Substrate	Disorder
<i>ABCB11</i>	BSEP	Canalicular protein with ATP binding cassette (ABC family of proteins); works as a pump transporting bile acids through the canalicular domain	PFIC Type 2, BRIC Type 2
<i>ABCB4</i>	MDR3	Canalicular protein with ATP binding cassette (ABC family of proteins); works as a phospholipid flippase in canalicular membrane	PFIC Type 3, ICP, cholelithiasis
<i>CFTR</i>	CFTR	Chloride channel with ATP binding cassette (ABC family of proteins); regulates chloride transport	Cystic fibrosis
<i>ATP8B1</i>	FIC1	P-type ATPase; aminophospholipid translocase that flips phosphatidylserine and phosphatidylethanolamine from the outer to the inner layer of the canalicular membrane	PFIC Type 1 (Byler's disease), BRIC Type 1, GFC
<i>CLDN1</i>	Claudin 1	Tight junction protein	NISCH
<i>VPS33B</i>	Vascular protein sorting 33	Regulates fusion of proteins to cellular membrane	ARC syndrome
<i>AKR1D1</i>	5 $\beta$ -reductase	3-oxo-4-steroid 5 $\beta$ -reductase gene; regulates bile acid synthesis; chromosome 7q32-33	BAS: neonatal cholestasis with giant cell hepatitis
<i>HSD3B7</i>	C27-3 $\beta$ -HSD	3 $\beta$ -hydroxy-5-C27-steroid oxido-reductase (C27-3 $\beta$ -HSD) gene; regulates bile acid synthesis; chromosome 16p11.2-12	BAS: chronic intrahepatic cholestasis
<i>CYP7B1</i>	CYP7B1	Oxysterol 7 $\alpha$ -hydroxylase; regulates the acidic pathway of bile acid synthesis; chromosome 8q21.3	BAS: neonatal cholestasis with giant cell hepatitis
<i>TJP2 (ZO-2)</i>	Tight junction protein	Belongs to the family of membrane-associated guanylate kinase homologs that are involved in the organization of epithelial and endothelial intercellular junction; regulates paracellular permeability	FHC
<i>BAAT</i>	BAAT	Enzyme that transfers the bile acid moiety from the acyl-CoA thioester to either glycine or taurine	FHC
<i>EPHX1</i>	Epoxide hydrolase	Microsomal epoxide hydrolase regulates the activation and detoxification of exogenous chemicals	FHC
<i>JAG1</i>	JAG1	Transmembrane, cell-surface proteins that interact with Notch receptors to regulate cell fate during embryogenesis	Alagille syndrome
<i>PKHD1</i>	Fibrocystin	Protein involved in ciliary function and tubulogenesis	ARPKD
<i>PRKCSH</i>	Hepatocystin	Assembles with glucosidase II alpha subunit in endoplasmic reticulum	ADPLD
<i>ABCC2</i>	MRP2	Canalicular protein with ATP binding cassette (ABC family of proteins); regulates canalicular transport of GSH conjugates and arsenic	Dubin-Johnson syndrome
<i>CIRH1A</i>	Cirhin	Cell signaling?	NAIC

ADPLD=autosomal dominant polycystic liver disease; ARC=arthrogryposis-renal dysfunction-cholestasis syndrome (low g-glutamyltransferase); ARPKD=autosomal recessive polycystic kidney disease; BAS=bile acid synthetic defect; BRIC=benign recurrent intrahepatic cholestasis (low g-glutamyltransferase, BRIC Type 1 and 2); BSEP=bile salt export pump; CFTR=cystic fibrosis transmembrane conductance regulator; FHC=familial hypercholelanemia; GFC=Greenland familial cholestasis; ICP=intrahepatic cholestasis of pregnancy; NAIC=North American Indian childhood cirrhosis; NISCH=neonatal sclerosing cholangitis with ichthyosis, leukocyte vacuoles, and alopecia; PFIC=progressive familial intrahepatic cholestasis (low g-glutamyltransferase, PFIC Type 1 and 2).

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hepatobiliary disorders. Ultimately, defects in bile formation may play a primary or exacerbating role in almost all adult cholestatic diseases.

**G&H** Is there a greater prevalence in any single subpopulation?

**WB** There is no specific difference in the incidence of these disorders between genders or among ethnic groups.

**G&H** How do you confirm these genetic disorders in patients presenting with various hepatic diseases?

**WB** The best studied group is affected infants, but the principles learned here seem to apply to all age groups. The first step is to recognize that the infant has cholestasis. Many physicians ascribe jaundice in a newborn to breastfeeding or physiologic jaundice, which is actually associated with unconjugated hyperbilirubinemia. Once cholestasis has been recognized, the goal is to exclude some of the more common disorders (biliary atresia, for example), which can be done through specific serologic tests and liver biopsy. Once those disorders are excluded, inborn errors of bile acid synthesis or bile acid transport must be considered. The serum level of gamma glutamyl transpeptidase (GGT) is a helpful clue. In some forms of these disorders, GGT levels, which would be expected to be markedly elevated in correlation with elevated conjugated bilirubin levels, are normal. This is certainly a red flag for an inherited disorder. Liver biopsy can also provide a clue as to which disorder is present: Some of these genetic disorders exhibit a unique histologic picture; others are more generic. Ultimately, a molecular diagnosis is required.

**G&H** Is there a noninvasive serologic test that will detect any of the inherited disorders of bile transport?

**WB** Not yet, although progress is being made. In the past few months, Dr. Bezerra of our group has described

a method (the “Jaundice Chip”) that incorporates five of the more common mutations in one screening test on a single sample of blood. In the coming years, this type of technology will likely become more common, more inclusive, and widely available.

**G&H** What steps can be taken in treating these inherited disorders once a diagnosis has been made?

**WB** The first discovered defect, which was described in 1988 at our institution, occurred in a set of identical twins who had one of the less common inherited defects of bile acid synthesis. Their brother had died 3 years previously of the same disease. We developed an oral therapy that could be administered as a replacement for the missing natural bile acids. When they were treated with bile acids, these boys responded with normalization of liver function. They are now thriving as teenagers. These cases set the stage for the treatment of bile acid synthesis defects with replacement therapy.

For other defects, there may not be a specific therapy; thus, we utilize ursodeoxycholic acid to stimulate the preserved pathways or to enhance bile flow. However, in some cases, liver transplantation must be considered. Future treatment research will need to focus on gene therapy and modification of the transporter function.

**Suggested Reading**

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