Progressive Familial Intrahepatic Cholestasis

Laura N. Bull, PhD[a,*], Richard J. Thompson, MD, PhD[b]

KEYWORDS

• Cholestasis • Genetics • Bile acids • Pediatrics • PFIC

KEY POINTS

- Progressive familial intrahepatic cholestasis (PFIC) is an umbrella term and describes the severest form of a number of genetically discrete diseases.
- Mechanisms of cholestasis include defects of canalicular transport, tight junction integrity, nuclear signaling, vesicular trafficking, and membrane maintenance.
- Human bile acids are highly detergent and most cellular and organ damage in PFIC is mediated through a failure of bile acid and lipid homeostasis.
- Genetic technology has helped reveal disease mechanisms, and can now be incorporated in new diagnostic algorithms.

INTRODUCTION

Bile was recognized by the ancient Greeks as 1 of the 4 humors; its importance is still recognized in twenty-first century medicine, although maybe only by hepatologists. Bile formation is essential for normal liver and gastrointestinal functions. Jaundice is the most frequent manifestation of liver disease, and exemplifies the importance of bile in the disposal of a major waste product, bilirubin. Bile is in truth a complex liquid. It is an alkali solution, rich in a variety of lipids, containing numerous organic anions. Many of the latter are metabolites of drugs and other xenobiotics that have been conjugated and excreted by the liver. The lipids are largely composed of bile acids, which are themselves amphipaths with powerful detergent properties. Human bile acids are particularly powerful detergents. The biliary tree, like every other epithelium, is composed of cells, themselves defined by the lipid plasma membrane. The normal lipid composition of the canalicular and cholangiocyte apical membrane renders the cells more resistant to detergent damage than most epithelia. Furthermore, the

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[a] Department of Medicine and Institute for Human Genetics, University of California San Francisco, UCSF Liver Center Laboratory, Zuckerberg San Francisco General, 1001 Potrero Avenue, Building 40, Room 4102, San Francisco, CA 94110, USA; [b] Institute of Liver Studies, King's College London, King's College Hospital, Denmark Hill, London SE5 9RS, UK
* Corresponding author.
E-mail address: Laura.Bull@ucsf.edu

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detergent effect of bile acids is significantly moderated through packaging into mixed micelles, the other major component of which is phosphatidylcholine (PC).

The diseases described in this article are collectively known as progressive familial intrahepatic cholestasis, or PFIC. This term predates our understanding of the different disease mechanisms. It also fails to acknowledge that nearly all the genetic deficiencies that we describe occur in spectra, ranging from infrequent symptoms, often precipitated by exogenous factors, through to severe early-onset disease. For most diseases described, those with the most severe disease manifest autosomal recessive inheritance and could be labeled as having PFIC. The diseases described represent defects in major processes involved in bile acid handling (bile acid synthesis defects are described elsewhere). Bile salt transport out of the liver is mediated by the bile salt export pump (BSEP) located in the canalicular membrane; BSEP expression is regulated by farnesoid X receptor (FXR). Correct localization of apical membrane transporters, such as BSEP, is dependent on intracellular trafficking processes, mediated in part by myosin 5B (MYO5B). Inclusion of PC into bile is dependent on MDR3. Familial intrahepatic cholestasis 1 (FIC1) is important for distribution of lipids between the 2 leaflets of the apical membrane. The canaliculi themselves are sealed by tight junctions, themselves dependent on intracellular anchors, including TJP2. The major genes underlying the different types of PFIC, and typical phenotypes, are summarized in **Table 1**.

Table 1
Summary of the typical features of progressive familial intrahepatic cholestasis associated with different genetic etiologies

Deficiency	Mutated Gene	Typical Clinical Characteristics	Characteristic Histology at Diagnosis	Typical Clinical Outcomes
FIC1	*ATP8B1*	Multisystem disease Normal γGT Only modest elevation of transaminases	Bland canalicular cholestasis Coarsely granular canalicular bile	Moderate rate of progression Posttransplant hepatic steatosis and diarrhea
BSEP	*ABCB11*	Normal γGT High risk of HCC High incidence of gallstones	Giant cell transformation	Moderate to rapid progression Allo-antibody formation after transplantation in some
MDR3	*ABCB4*	Progressive cholangiopathy Elevated γGT	Cholangiolytic changes	Highly variable rate of progression
TJP2	*TJP2*	Some extrahepatic features Near-normal γGT	Bland cholestasis	Rapid progression
FXR	*NR1H4*	Early-onset coagulopathy Normal γGT Markedly elevated AFP	Intralobular cholestasis Ductular reaction Giant cell transformation	Very rapid progression Posttransplant hepatic steatosis
MYO5B	*MYO5B*	Normal γGT Variable degree of intestinal involvement	Giant cell change Hepatocellular and canalicular cholestasis	Slow progression

Abbreviations: γGT, γ-glutamyltranspeptidase; AFP, α-fetoprotein; HCC, hepatocellular carcinoma.