A Case of Neonatal Cholestasis Presenting With Neurologic Symptoms in an Adolescent

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Disclosures

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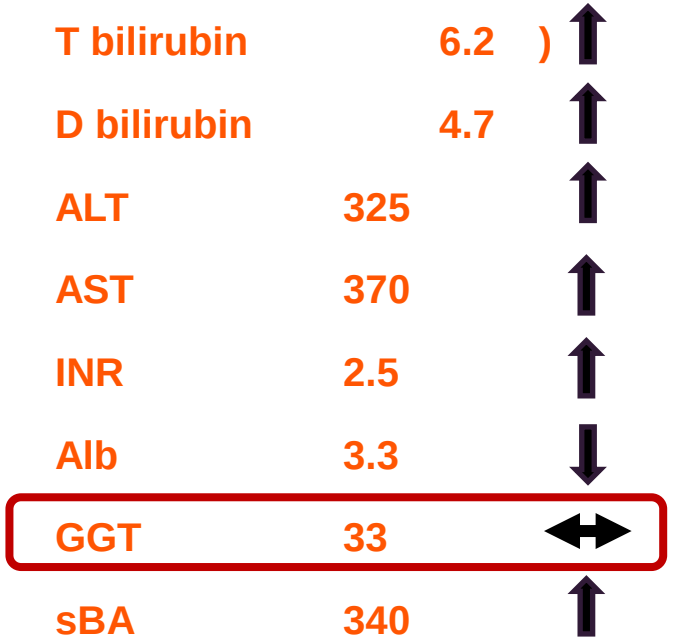
- Editorial Board Involvement: Expert Opinion on InvesTgaTonal Drugs

Objectives

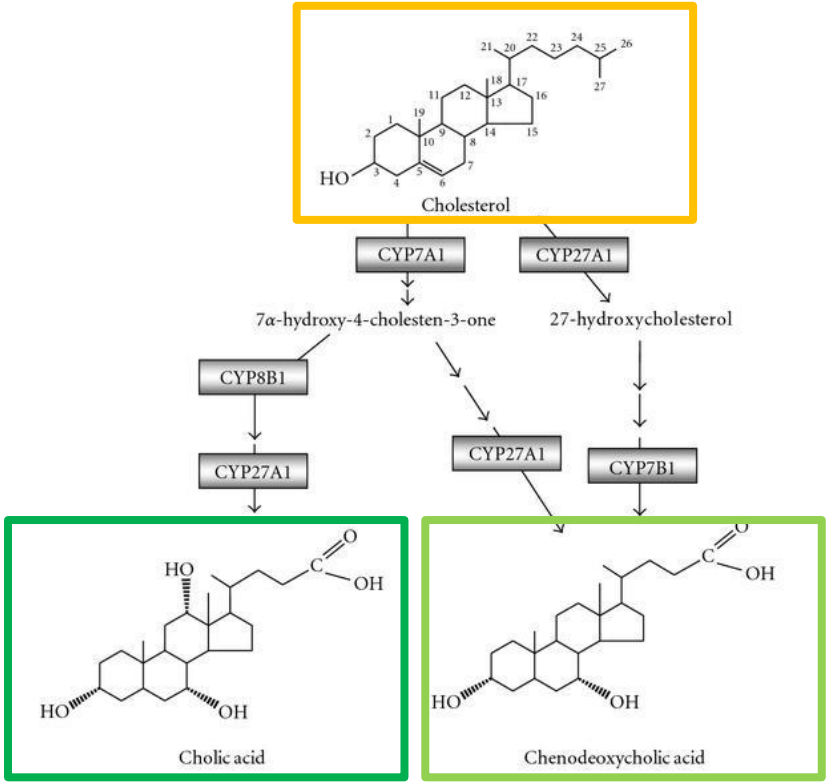
- Briefly describe the differential diagnosis of neonatal cholestasis.
- Discuss the extrahepatic manifestations of cholestasis.
- @AlkhouriNaim
- @azliver

Case Presentation

- A 13-year-old boy from Mexico who presented with a diagnosis of “idiopathic cholestasis”.
- He was observed to have cholestatic liver disease at age 1 with **<u>normal GGT.</u>**

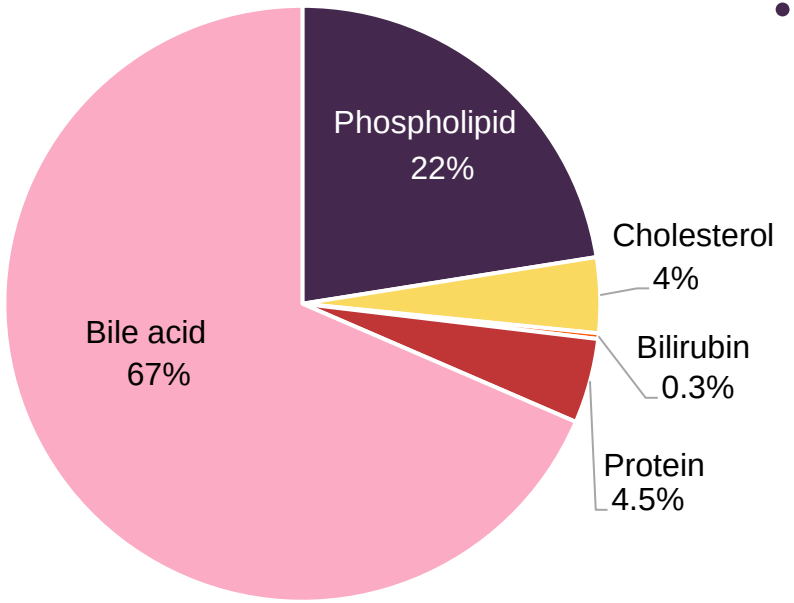


Bile Acid Synthesis from Cholesterol

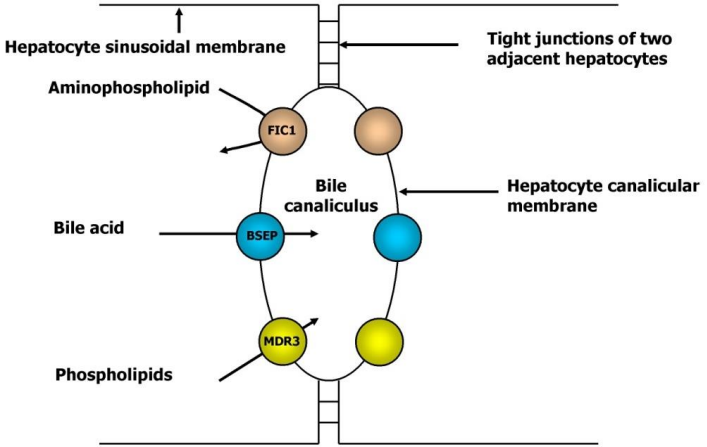


- Bile Acid Synthesis Defects (BASD):
  - Low serum BAs + low GGT cholestasis

Bile and Canalicular Transporters



- **Progressive Familial Intrahepatic Cholestasis (PFICs)**
  - High serum BAs + low GGT cholestasis

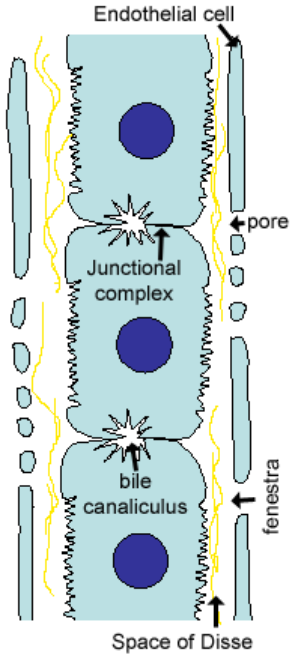


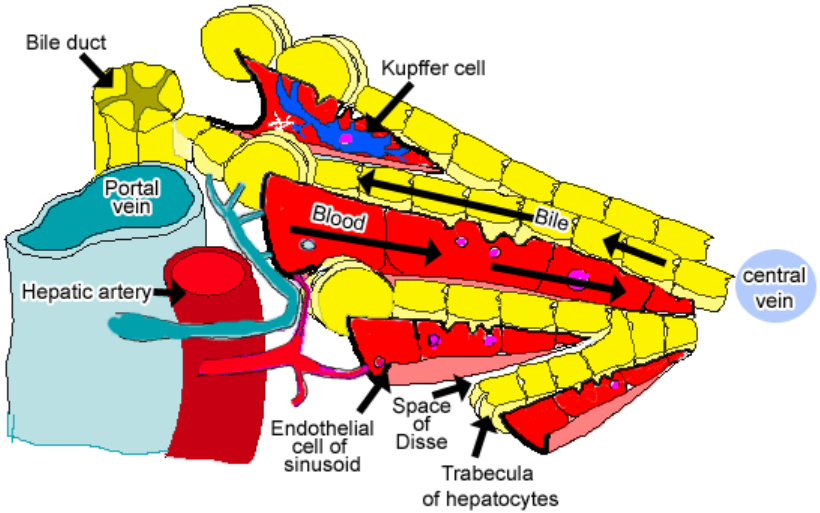
Key Clinical Features

	PFIC1	PFIC2	PFIC3
Feature	**ATP8B1**	**ABCB11**	**ABCB4**
Direct hyper bilirubinemia	Birth – 6m	Birth – 6m	Birth – adulthood
GGT	**LOW**	**LOW**	**HIGH**
Earliest time to cirrhosis	Late childhood and adolescence	Early infancy	Any age
Extrahepatic Sx	**Diarrhea**, Hearing Loss, Pancreatitis, Pneumonia	NO	NO
Pruritus	**YES**	**YES**	YES/NO
Cholelithiasis	NO	YES	YES (**Intrahepatic**)
Cancer	?	**HCC**	**HCC & CCA (teens +)**

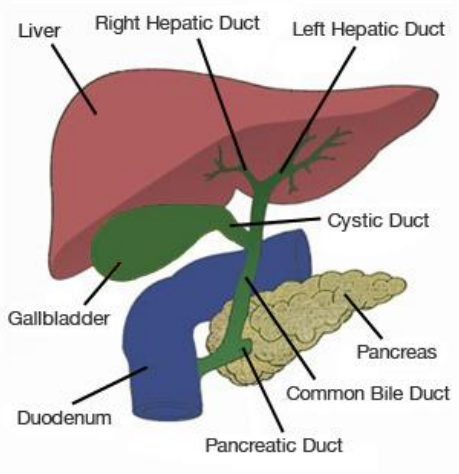
Adapted from: Morotti RA, Suchy FJ, Magid MS, et al. Progressive familial intrahepatic cholestasis (PFIC) type 1, 2, and 3: a review of the liver pathology findings. *Semin Liver Dis*. 2011 Feb;31(1):3–10.

Paucity of the Intrahepatic Bild Ducts



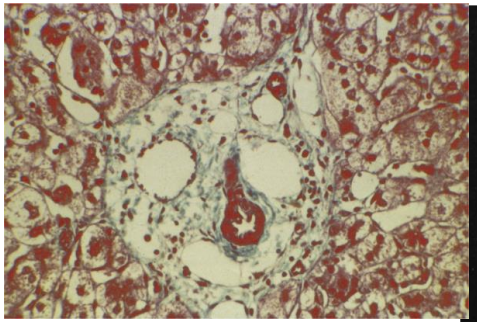


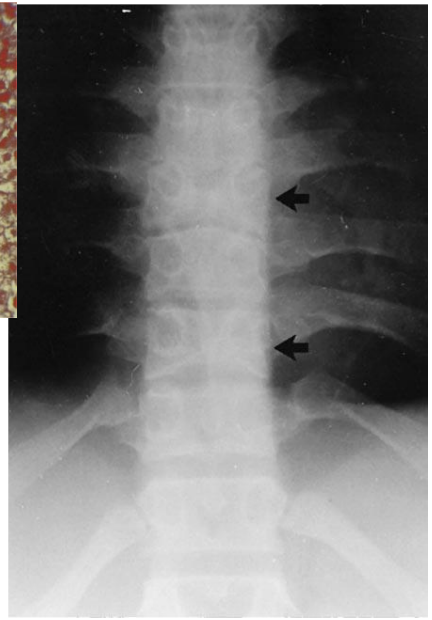
- **Alagille Syndrome**
  - JAG1 mutation >> NOTCH 2 mutation
  - Very high GGT



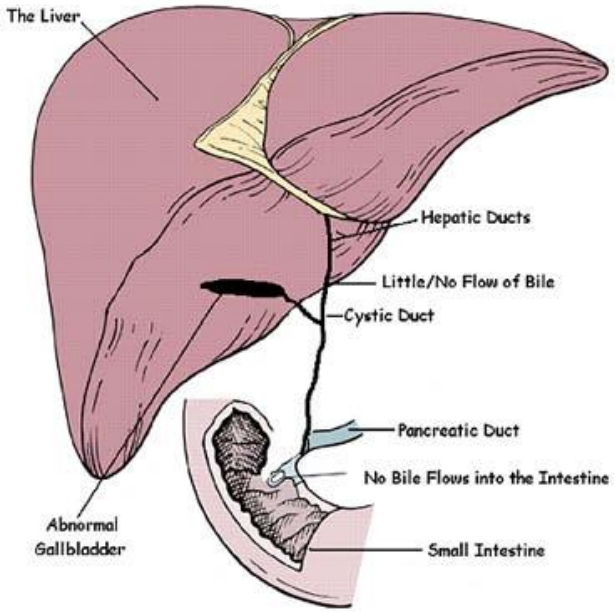
Alagille Syndrome

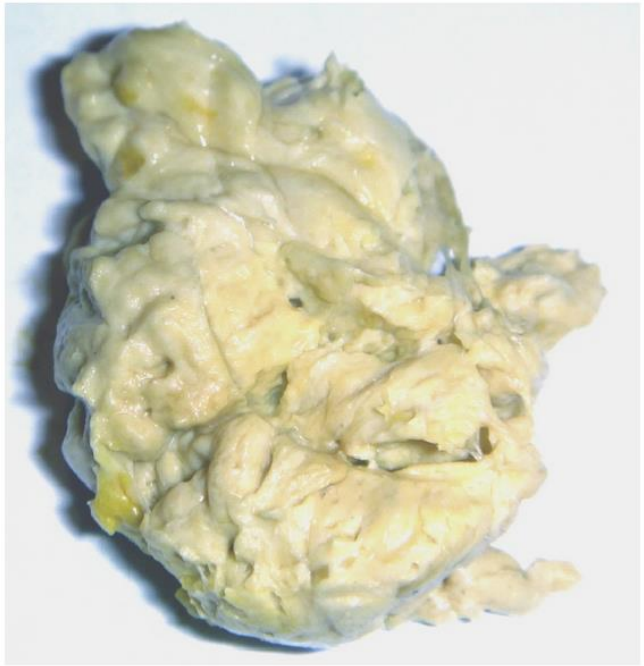
- Pulmonic stenosis/ TOF
- Aneurysms/ Vascular malformations → Brain MRI/ MRA
- Horseshoe kidneys

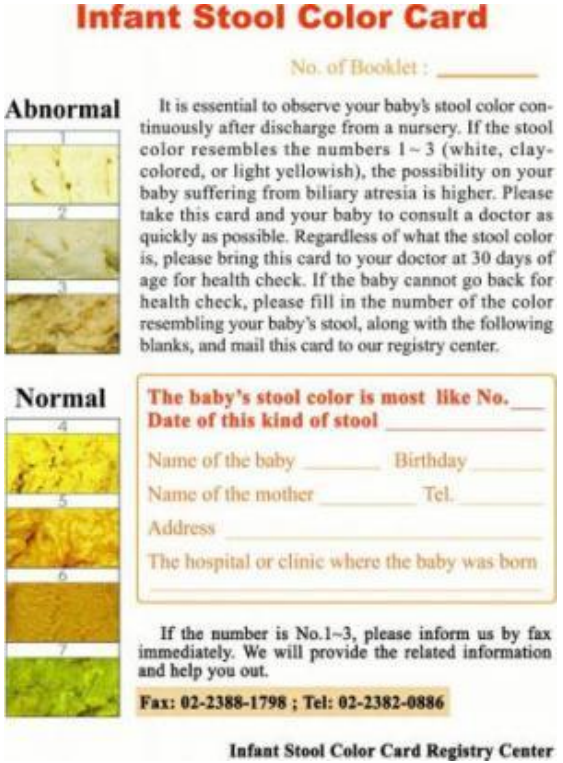




Extrahepatic Biliary Atresia

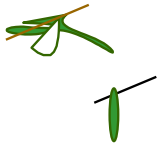






Neonatal Cholestasis

Extrahepatic Bile Duct



Biliary atresia

Choledochal cyst

Bile duct hypoplasia

Bile duct duplication

Agenesis of the extrahep. ducts

Choledocholithiasis

Inspissated bile syndrome

Miscellaneous:

Endocrine: panhypopituitarism, hypothyroidism

Gestational Alloimmune Liver Disease (GALD)

PN associated cholestasis

Sepsis

Intrahepatic Bile Duct

Bile duct paucity:

Alagille Syndrome

Non-syndromic

Ductal Plate Malformation:

Congenital Hepatic Fibrosis

Caroli disease

ARPKD

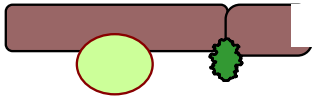
ADPKD

von Meyenburg complexes

Cystic Fibrosis

Neonatal sclerosing cholangitis

Hepatocytes



Indeterminant (“Neonatal Hepatitis”)

Viral Infection:

CMV, HSV

Rubella, Parvovirus B19

HAV, HBV, Adenovirus, Enterovirus

Bacterial/Parasitic Infection:

Gram negative sepsis

Syphillis, TB, Listeria

Transporter genes:

PFIC1 (FIC1/ATPB1)

PFIC2 (BSEP/ABCB11)

PFIC3 (MDR3/ABCB4)

Metabolic/Storage diseases:

Lipid metabolism — Niemann-Pick

Tyrosinemia

Galactosemia

Bile acid synthesis defect

Peroxisomal — Zellweger's

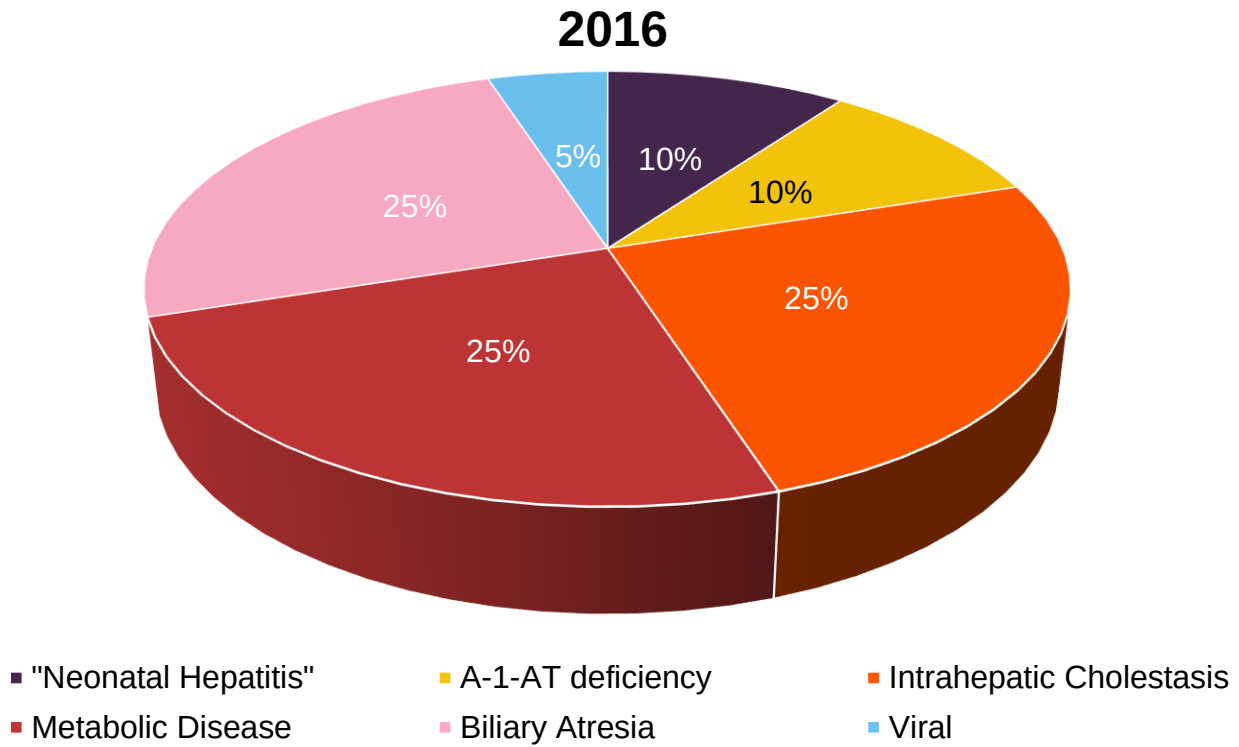
Mitochondrial disorders

a_1-antitrypsin deficiency

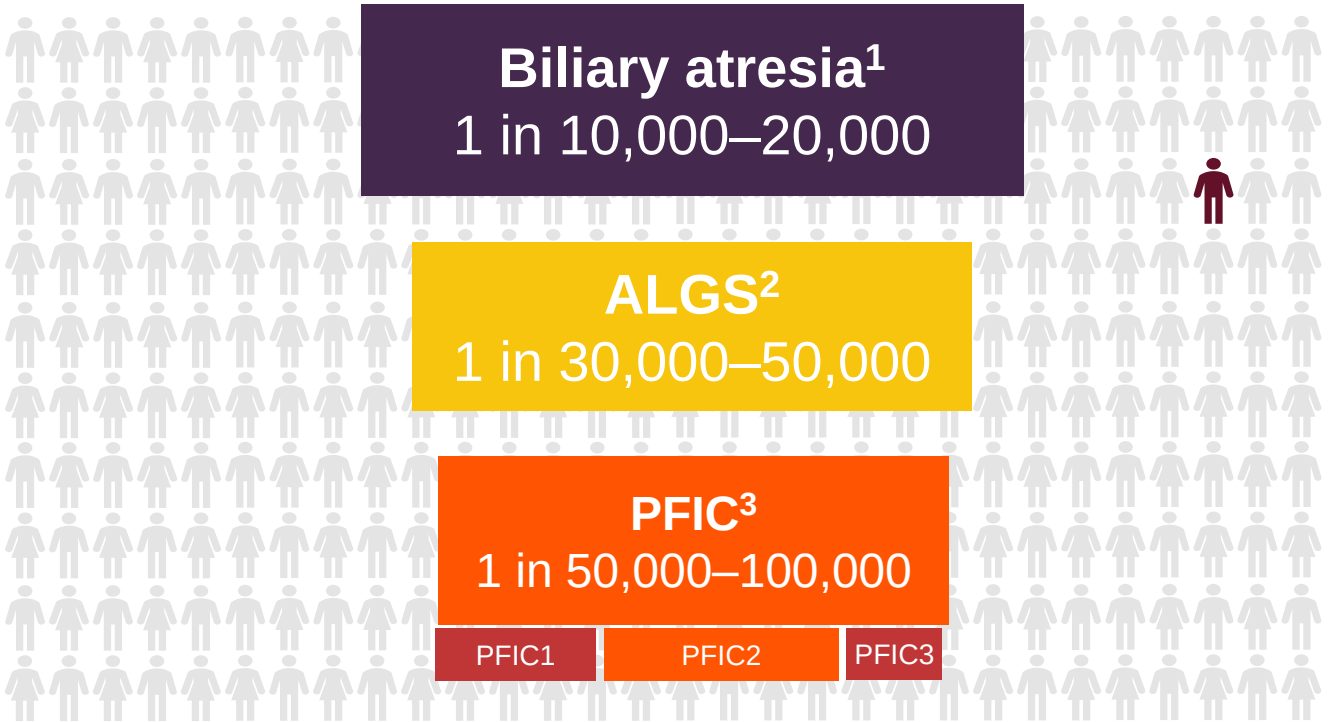
Lysosomal acid lipase deficiency

Drug toxicity

Differential – Neonatal Cholestasis



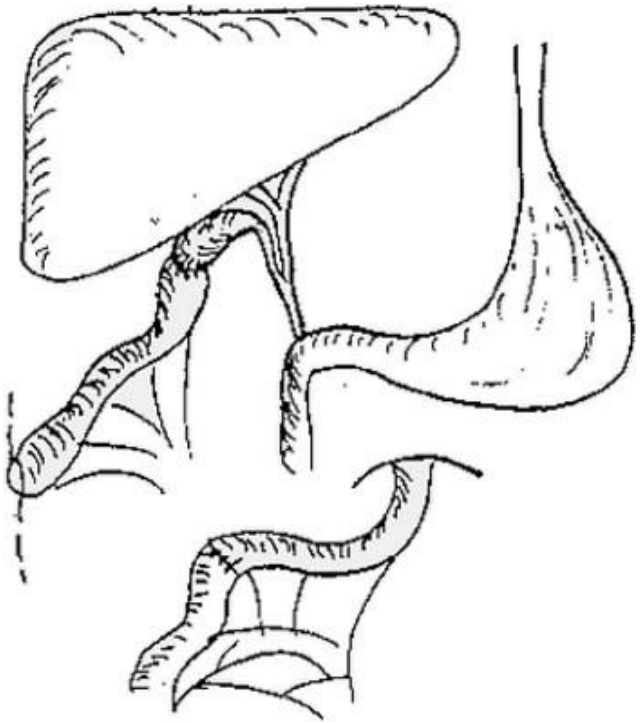
Incidence: ALGS, PFIC, and Biliary Atresia Are Rare Diseases



1. Childhood Liver Disease Research Network (childrennetwork.org; Accessed October 2020); 2. Kamath BM, et al. *J Pediatr Gastroenterol Nutr.* 2018; **67**:148–156; 3. Jacquemin E. *Clin Res Hepatol Gastro.* 2012; **36**:526–535.

Case Presentation (Continued)

- Had worsening pruritus that was unresponsive to ursodiol and rifampin until age 3.5 → PFIC type 1 diagnosis was made based on clinical history.
- He underwent Roux-en-Y partial biliary diversion at age 3.5, which resolved his pruritus.



PREVENTION GENETICS

TRAVERE THERAPEUTICS

CHOLESTASIS GENETIC PANEL:
77-GENE TESTING PANEL TO HELP IDENTIFY GENETIC CAUSES OF CHOLESTASIS

Travere Therapeutics (formerly Retrophin) has partnered with PreventionGenetics to offer a 77-gene cholestasis panel.* ***This resource is provided at no cost to patients, physicians, or payers.**** It is easy to use and detects an array of potential causes of cholestasis or jaundice, many of which may be life threatening.

**The 66-gene cholestasis panel that was performed through EGL Genetics is now being run through PreventionGenetics as a 77-gene panel. This test is still available at no-cost to qualifying patients.*

HOW TO ORDER THE CHOLESTASIS GENETIC PANEL

Create your profile (US physicians Only) | Order your collection kit (see options below) | The kit will be delivered within 48 hours | Send completed kit back to PreventionGenetics | Receive results within 2–4 weeks

2 COLLECTION KIT OPTIONS

SALIVA COLLECTION KIT

BLOOD COLLECTION KIT

LOG IN TO ORDER KIT

Username:

Password:

Next time log me in automatically.

LOG IN

Forgot your password?

CREATE NEW ACCOUNT

(US physicians Only)

Username:

Password:

Confirm password:

CREATE ACCOUNT

***Log in for more information on eligibility for waiving the cost of testing.*
Program may be canceled or changed at any time.

www.testcholestasis.com

Case Presentation (Continued)

- The patient maintained appropriate growth and development until age 12 → Acute onset of neurologic symptoms:
  - Regression of speech, loss of fine and gross motor milestones, cerebellar ataxia, severe dysarthria, slow speech, and concern for vision loss.
- Magnetic resonance imaging of his brain and 24-hour video electroencephalogram were normal.

Neurologic findings were all attributed to severe vitamin E deficiency, as levels were undetectable

Case Presentation (Continued)

- Genetic testing → compound heterozygote for two missense mutations (c.3457C>T and c.499G>A) in the ABCB11 gene → confirming the diagnosis of **PFIC 2.**
- Given significant neurologic morbidity, the patient was listed for LTx with MELD score of 6.
- He received an anonymous orthotopic left lateral segment living donor liver transplant 18 days after listing.
- POD# 8, vitamin E alpha levels were undetectable. Vitamin E supplementation was started → Level on POD# 39 was 7.8 mg/L.
- The patient is now 16 years old, ambulates independently, can speak in full sentences, and has markedly improved coordination.