Cincinnati Children's

Division of Human Genetics

Progressive Familial Intrahepatic Cholestasis

Genes Tested: *ATP8B1, ABCB11, ABCB4*

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Additional information and test requisitions are available at:
www.cincinnatichildrens.org/molecular-genetics

Helping you fit the pieces together

Shipping Instructions

Please enclose test requisition with sample. All information must be completed before sample can be processed.

Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

Ship to:
Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of rare, autosomal recessive disorders resulting from defects that lead to abnormal bile formation. Patients with PFIC typically present in infancy or childhood with hepatomegaly, coagulopathy, cholestasis and pruritis and may progress to end-stage liver disease before adulthood.

ATP8B1 (PFIC1 and BRIC1):

Three genes have been specifically associated with PFIC. PFIC1 is caused by mutations in the *ATP8B1* gene which maps to 18q21. *ATP8B1* encodes a 1251 amino acid protein known as familial intrahepatic cholestasis 1 (FIC1) which plays an unspecified role in bile acid transport. The *ATP8B1* gene consists of 28 exons, and mutations have been described throughout the gene. Clinically, patients with PFIC1 present with hepatomegaly, coagulopathy, cholestasis and pruritis. They may also develop severe diarrhea, failure to thrive and pancreatic insufficiency. Laboratory findings include elevated serum bile acids and normal to low GGT. Liver biopsy may show granular bile in canaliculi by electron microscopy. Treatment consists of supplementation of fat-soluble vitamins, the use of choleretic agents, nutritional supplementation, and diagnosis and treatment of complications from end-stage liver disease. Liver transplantation is used for end-stage cirrhosis.

ABCB11 (PFIC2 and BRIC2):

PFIC2 is caused by mutations in the *ABCB11* gene which maps to2q31.1. *ABCB11* consists of 28 exons and encodes for a 1321 amino acid residue protein called BSEP which is the primary bile salt export pump in humans. Clinically, patients with PFIC2 present with hepatomegaly, coagulopathy, cholestasis and pruritis. Some of the patients may progress rapidly to end-stage cirrhosis. Patients with mutations in *ABCB11* also have an increased risk of developing hepatocellular carcinoma early in life. In contrast to patients with PFIC1, extrahepatic symptoms are usually not seen in patients with PFIC2. Laboratory findings include elevated serum bile acids and normal to low GGT. Liver biopsy may show giant cell hepatitis and amorphous bile in the canaliculi by electron microscopy. Treatment is similar to that of PFIC1.

ABCB4 (PFIC3 and BRIC3):

PFIC3 is caused by mutations in the *ABCB4* gene which maps to 7q21.1. *ABCB4* consists of 28 exons and encodes for a 446 amino acid class III multidrug resistance P-glycoprotein (MDR3). Clinically, patients with PFIC3 present with hepatomegaly, coagulopathy, cholestasis and pruritis. As with the other two types of PFIC, the disease may progress to end-stage cirrhosis. In contrast to patients with PFIC1, extrahepatic symptoms are usually not seen in patients with PFIC3. Laboratory findings include elevated serum bile acids and high GGT. Liver biopsy may show giant cell hepatitis, bile duct proliferation, and portal inflammation. Treatment is similar for that of PFIC1, but some patients may be very responsive to ursodeoxycholic acid. Genetic defects in *ABCB4* have been associated with low phospholipid-associated cholelithiasis.

Mutations in *ATP8B1*, *ABCB11* and *ABCB4* also result in allelic conditions known as benign recurrent intrahepatic cholestasis (BRIC1, BRIC2); a more benign form may also exist for mutations in *ABCB4*. Symptoms of BRIC include intermittent bouts of cholestasis, pruritis and diarrhea. Homozygous, compound heterozygous and heterozygous individuals may all be affected. A common mutation, I661T, is identified in about 40% of patients with BRIC1. Of importance, this mutation is also seen in children with PFIC1. In general, missense mutations are more likely to be associated with BRIC, while mutations that affect protein expression (frameshifts, nonsense mutations and gross deletions) are more often associated with PFIC1, 2 or 3. In addition, female carriers of *ABCB4* mutations may experience intrahepatic cholestasis of pregnancy.

INDICATIONS:

- Confirmation of mutation in a symptomatic individual
- Presymptomatic testing of at-risk siblings
- Carrier identification in individuals with a family history of PFIC
- Prenatal diagnosis of an at-risk fetus, after confirmation of biallelic mutations in the parents (by prior arrangement only)

SPECIMEN:

At least 2 mL whole blood in purple top (EDTA) tube. Label tube with patient's name, birth date, and date of collection.

METHODOLOGY:

Testing is performed by PCR-based sequencing of the entire coding regions and intron/exon boundaries of the *ATP8B1*, *ABCB11* or *ABCB4* genes.

Our JaundiceChip resequencing array detects mutations in *JAG1* and *SERPINA1*, as well as in *ATP8B1*, *ABCB11* and *ABCB4* . Please see website for details.

ANALYTICAL SENSITIVITY:

The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions, and insertions in the regions analyzed. Analytical sensitivity may be compromised by rare primer site mutations. Mutations in regulatory regions or other untranslated regions are not detected by this test. Multiple exon deletions, large insertions and genetic recombinational events may not be identified using these methods. If the patient has received a liver transplant or recent blood transfusion, donor DNA may be present in the blood along with patient DNA (chimerism). In this case, additional testing may be required to rule out chimerism.

TURN-AROUND TIME:

3-4 weeks

COST:

Please call 1-866-450-4198 for pricing or with any billing questions.

CPT CODES:

- *ATP8B1* 81479
- *ABCB11* 81479
- *ABCB4* 81479

- Family specific mutation analysis 81403

Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

Updated 12/2011