

Progressive Familial Intrahepatic Cholestasis

Genes Tested: *ATP8B1*, *ABCB11*, *ABCB4*, *BAAT*, *TJP2*

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of rare, autosomal recessive disorders resulting from defects in the *ATP8B1* (PFIC1), *ABCB11* (PFIC2), *ABCB4* (PFIC3), or *TJP2* (PFIC4) genes that lead to abnormal bile formation and elevated serum bile acids. Patients with variable levels of PFIC typically present in infancy or childhood with hepatomegaly, coagulopathy, cholestasis and pruritis. Patients may progress to end-stage liver disease before adulthood. Patients with PFIC1 may develop severe diarrhea, failure to thrive and pancreatic insufficiency. In contrast to patients with PFIC1 and PFIC4, extrahepatic symptoms are usually not seen in patients with PFIC2, PFIC3, or PFIC4. In patients with PFIC1, PFIC2, or PFIC4, GGT levels are normal to low and in patients with PFIC3, GGT levels are typically elevated. Treatment consists of supplementation of fat-soluble vitamins, the use of choleric agents, nutritional supplementation, and diagnosis and treatment of complications of end-stage liver disease. Liver transplantation is used for end-stage cirrhosis. Patients with *ABCB4* mutations may be very responsive to ursodeoxycholic acid. New therapies are also in development to improve pruritus associated with these disorders, such as inhibitors of the ileal sodium-dependent bile acid transporter and molecular chaperones.

Mutations in *ATP8B1* and *ABCB11* also result in allelic conditions known as benign recurrent intrahepatic cholestasis (BRIC1 and BRIC2 respectively). 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. 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 PFIC.

In addition, female carriers of *ABCB4* mutations may experience intrahepatic cholestasis of pregnancy. Genetic defects in *ABCB4* have been associated with low phospholipid-associated cholelithiasis.

Familial Hypercholanemia is an autosomal recessive condition caused by mutations in the *BAAT* gene. Oligogenic inheritance has also been proposed for this condition. Familial Hypercholanemia is primarily seen in patients of Amish descent and is characterized by elevated serum bile acids, pruritis, and fat malabsorption. Patients can develop failure to thrive, vitamin K dependent coagulopathy, and rickets. Laboratory findings include normal or mildly increased GGT levels. Mutations in the *TJP2* gene were reported in children with low-GGT cholestasis. They share clinical features similar to PFIC1 and 2, and may also have pulmonary symptoms.

Turn-Around Times:

- 28 days

Costs:

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

CPT Codes:

- ***ATP8B1***: 81479
- ***ABCB11***: 81479
- ***ABCB4***: 81479
- ***BAAT***: 81479
- ***TJP2***: 81479
- **Family specific mutation analysis**: 81479

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:

TruSeq Custom Amplicon enrichment followed by next-generation sequencing with > 20 fold coverage at every target base and Sanger confirmation of all variants OR PCR-based sequencing, of all exons and exon/intron boundaries of the genes.

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.

Results:

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.

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