Liver Diseases Genetic Testing Program

Description:

We offer comprehensive analysis of genes associated with inherited liver diseases. Our testing includes four liver panels by next-generation sequencing (NGS), single gene analysis for any gene on a panel, targeted variant analysis, and targeted deletion/duplication analysis.

Panels Offered:

- Liver Diseases Panel (71 genes)
- Jaundice Panel (5 genes)
- Bile Acid Synthesis Defects Panel (5 genes)
- Cystic Diseases of the Liver/Kidney Panel (9 genes)

Indications:

NGS Panels:

- Confirmation of genetic diagnosis in a patient with a clinical diagnosis of liver disease
- Carrier identification in individuals with a family history of liver disease of unknown genetic basis

Gene Specific Sequencing:

- Confirmation of genetic diagnosis in a patient with liver disease and in whom a specific genetic diagnosis is suspected

Deletion/Duplication Analysis:

- Completion of the diagnostic evaluation in a patient with a clinical diagnosis of inherited liver disease who has had a negative NGS panel or who is heterozygous for a variant in a gene associated with an autosomal recessive condition

Variant Specific Analysis:

- Carrier testing of parents and other relatives for recurrence risk assessment
- Presymptomatic testing of at-risk family members for medical management
- Prenatal diagnosis of an at-risk fetus, after confirmation of variant(s) in the parent(s) and by prior arrangement only

Liver Disease Panel by NGS:

This panel is designed to diagnose the most common genetic causes of hereditary liver disease. Inherited liver disease can present with clinical features including bile acid synthesis defects, cholestasis, and jaundice. Hereditary liver disease is caused by variants in many different genes, and may be inherited in an autosomal dominant or autosomal recessive manner.

ABCB11, ABCB4, ABCC2, ABCD3, ABCG5, ABCG8, AKR1D1, ALDOB, AMACR, ATP7B, ATP8B1, BAAT, CC2D2A, CFTR, CLDN1, CYP27A1, CYP7A1, CYP7B1, DCDC2, DGUOK, DHCR7, EHHADH, EPHX1, FAH, GPBAR1, HNF1A, HNF1B, HSD17B4, HSD3B7, INVS, JAG1, LIPA, MKS1, MPV17, MYO5B, NEUROG3, NOTCH2, NPC1, NPC2, NPHP1, NPHP3, NPHP4, NR1H4, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, POLG, SCP2, SERPINA1, SLC10A1, SLC10A2, SLC25A13, SLC27A5, SMPD1, TJP2, TMEM216, TRMU, UGT1A1, VIPAS39, VPS33B*

*excluding exons 1, 2, and 4 in *NOTCH2* due to high homologous regions

Jaundice Panel by NGS:

Inherited intrahepatic cholestasis is a heterogeneous group of disorders typically presenting as neonatal jaundice and leading to persistent liver dysfunction in children and adults. Although some of these conditions are associated with extrahepatic symptoms and varying laboratory and pathologic findings, there remains considerable clinical overlap between these disorders.

ABCB11, ABCB4, ATP8B1, JAG1, TJP2

Bile Acid Synthesis Defects Panel by NGS:

Congenital bile acid synthesis defects are a group of autosomal recessive conditions associated with neonatal onset liver disease. The impaired production and release of bile acids leads to cholestasis. Bile acid synthesis defects can progress to chronic liver disease, and if left untreated

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can lead to cirrhosis and death in childhood. Additional symptoms may include failure to thrive, jaundice, fat malabsorption, and rickets.

ABCD3, AKR1D1, AMACR, CYP7B1, HSD3B7

Cystic Diseases of the Liver/Kidney Panel by NGS:

Polycystic liver disease with or without kidney cysts is usually inherited as autosomal dominant condition and becomes apparent in adulthood. Symptoms can range from asymptomatic to obstructive issues and complications such as intracystic hemorrhage, portal infection or rupture of cysts. Only a subset of patients develop kidney cysts, which usually incidental and do not result in clinically significant renal disease.

Polycystic kidney disease with or without liver disease may be inherited as an autosomal dominant or recessive condition. Presentation varies depending on the causative gene, ranging from neonatal period to adulthood. End-stage renal disease (ESRD) is a common complication in most of these conditions.

ALG8, DNAJB11, DZIP1L, GANAB, LRP5, PKD2, PKHD1, PRKCSH, SEC63

Specimen:

At least 3 mLs whole blood in a lavender top (EDTA) tube or saliva in an Oragene saliva kit. Please call 513-636-4474 for a free saliva collection kit.

Note: If the patient has received a liver transplant or recent blood transfusion, donor DNA may be present in the blood along with the patient DNA (chimerism). In this case, additional testing may be required to rule out chimerism.

Testing Methodology:

NGS Panels: Our panels are performed by enrichment of the coding exons, flanking intronic and untranslated regions (5' and 3'), as well as known pathogenic variants (HGMD 2018.1) in the promoter and deep intronic regions of the genes specified above using oligonucleotide probe hybridization followed by next-generation sequencing with >50X coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing. Regions with <50X will be filled in by Sanger sequencing. A detailed non-coding variant list is available upon request.

Gene Specific Sequencing: PCR-based or NGS-based sequencing of entire coding region, intron/exon boundaries, as well as known pathogenic variants (HGMD 2018.1) in the promoter and deep intronic regions of the specified gene.

Deletion/Duplication Analysis: Copy number variant analysis of the gene by comparative genomic hybridization.

Variant Specific Analysis: Sanger sequencing following PCR amplification of the targeted variant(s) of the specified gene.

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. Exons 1, 2 and 4 of *NOTCH2* are not covered by this test due to high homologous regions.

Limitations: Variants in regulatory regions and non-reported variants in untranslated regions may not be detected by this test. Large deletions involving entire single exons or multiple exons, large insertions, and other complex genetic events will not be identified using NGS methodology. Rare primer site variants may lead to erroneous results.

Note: Single gene sequencing is available for all genes on the panel. Deletion/duplication analysis is available for all genes listed except *ABCC2, ABCD3, AKR1D1, AMACR, CLDN1, CYP27A1, CYP7A1, CYP7B1, DCDC2, DNAJB11, DZIP1L, EHHADH, EPHX1, GANAB, GPBAR1, HSD17B4, HSD3B7, MYO5B, NEUROG3, NOTCH2, NR1H4, PEX10, PEX11B, PEX13, PEX16, PEX19, PKHD1, SEC63, SCP2, SLC10A1, SLC10A2, VIPAS39,* and *VPS33B.*

For further details, visit:
www.cincinnatichildrens.org/deldup.

Turn-Around Time:

Liver Disease Panel, Jaundice Panel, Bile Acid Defects Panel, Cystic Disease of the Liver/Kidney Panel: 28 days

Single Gene Sequencing: 28 days

Deletion/Duplication Analysis by Targeted CGH: 28 days

CPT Codes:

- Liver Diseases 71 gene panel: 81405 x1, 81406 x1, 81479 x1
- Jaundice 5 gene panel: 81407 x1, 81479 x1
- Bile Acid Synthesis Defects 5 gene panel: 81407 x1, 81479 x1
- Cystic Diseases of the Liver/Kidney Panel 9 gene panel: 81407 x1, 81479 x1
- Single gene testing, targeted variant analysis, and deletion/duplication analysis: call for information

Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

Results:

Results will be reported to the referring physician or health care provider as specified on the 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 Saturday.

Ship to:

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

References:

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Van der Woerd, W.L., S.W.C. van Mil, et al. (2010) "Familial Cholestasis: Progressive Familial Intrahepatic Cholestasis, Benign Recurrent Intrahepatic Cholestasis and Intrahepatic Cholestasis of Pregnancy." Best Practice & Research. Clinical Gastroenterology 24(5): 541–53.

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Gene Name	Liver Disease Panel	Jaundice Panel	Bile Acid Defects	Cystic liver and kidney
ABCB11	x	x		
ABCB4	x	x		
ABCC2	x			
ABCD3	x		x	
ABCG5	x			
ABCG8	x			
AKR1D1	x		x	
ALDOB	x			
ALG8				x
AMACR	x		x	
ATP7B	x			
ATP8B1	x	x		
BAAT	x			
CC2D2A	x			
CFTR	x			
CLDN1	x			
CYP27A1	x			
CYP7A1	x			
CYP7B1	x		x	
DCDC2	x			
DGUOK	x			
DHCR7	x			
DNAJB11				x
DZIP1L				x
EHHADH	x			
EPHX1	x			
FAH	x			
GANAB				x
GPBAR1	x			
HNF1A	x			
HNF1B	x			
HSD17B4	x			
HSD3B7	x		x	
INVS	x			
JAG1	x	x		
LIPA	x			
LRP5				x
MKS1	x			
MPV17	x			
MYO5B	x			

Gene Name	Liver Disease Panel	Jaundice Panel	Bile Acid Defects	Cystic liver and kidney
NEUROG3	x			
NOTCH2	x			
NPC1	x			
NPC2	x			
NPHP1	x			
NPHP3	x			
NPHP4	x			
NR1H4	x			
PEX1	x			
PEX10	x			
PEX11B	x			
PEX12	x			
PEX13	x			
PEX14	x			
PEX16	x			
PEX19	x			
PEX2	x			
PEX26	x			
PEX3	x			
PEX5	x			
PEX6	x			
PEX7	x			
PKD2				x
PKHD1				x
POLG	x			
PRKCSH				x
SCP2	x			
SEC63				x
SERPINA1	x			
SLC10A1	x			
SLC10A2	x			
SLC25A13	x			
SLC27A5	x			
SMPD1	x			
TJP2	x	x		
TMEM216	x			
TRMU	x			
UGT1A1	x			
VIPAS39	x			
VPS33B	x			