Peroxisomal Disorders Panel, Sequencing

Peroxisomal disorders are a group of diseases caused by gene defects impairing the formation (peroxisome biogenesis disorders) or function of the peroxisomes, with symptoms that impact a wide range of body systems. Peroxisome biogenesis disorders include Zellweger spectrum disorders (ZSDs) and rhizomelic chondrodysplasia punctata (RCDP). Single enzyme defects include Refsum disease, peroxisomal acyl-CoA oxidase deficiency, peroxisomal bifunctional deficiency, defects of bile acid synthesis, and primary hyperoxaluria. Some single enzyme defects present with similar clinical features to ZSD (eg, ACOX1, HSD17B4) or RCDP (eg, AGPS, GNPAT), although these often can be distinguished by extensive biochemical testing.

Tests to Consider

Peroxisomal Disorder Panel, Sequencing 3002700

Method: Massively Parallel Sequencing

Use to confirm a suspected diagnosis of a peroxisomal disorder, including peroxisome biogenesis disorders such as ZSDs and RCDP type 1 or single enzyme disorders such as Refsum disease. This test will not detect ABCD1 defects associated with X-linked adrenoleukodystrophy/adrenomyeloneuropathy.

Screening Test

Very Long-Chain and Branched-Chain Fatty Acids Profile 2004250

Method: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

Initial test to screen for disorders of peroxisomal biogenesis and/or function

See Related Tests for more screening tests.

Disease Overview

Symptoms

Common features of peroxisomal disorders include:

- Hypotonia, seizures, peripheral neuropathy, and ataxia
- Abnormal brain magnetic resonance imaging (MRI) findings such as neuronal migration defects, leukodystrophy, or cerebellar atrophy
- Poor growth, feeding problems, and fat-soluble vitamin deficiency
- Hepatic dysfunction, hepatomegaly, and cholestasis
- Progressive adrenal insufficiency
- Renal cortical cysts or kidney stones
- Skeletal abnormalities such as stippling of the growth plates, chondrodysplasia punctata, or progressive loss of bone mineral density
- Deafness or progressive hearing loss
- Visual impairment due to cataracts, glaucoma, optic nerve hypoplasia, band keratopathy, or progressive retinal dystrophy
- Developmental delay and intellectual disability

Testing Strategy

When a peroxisomal disorder is suspected, the following screening tests may be considered:

- Very long-chain fatty acids in plasma
- C26-lysophosphatidylcholine (LPC) in whole blood or plasma
- Phytanic and pristanic acids in plasma
- Plasmalogens in erythrocytes
- Pipecolic acid in urine (neonates) and plasma (older children or adults)
- Bile acid intermediates in plasma and urine

These biochemical tests may not detect individuals with moderate or mild disease. Some assays are sensitive to age or diet and the complexity of biochemical profiles associated with different peroxisomal disorders requires expertise for optimal interpretation. Therefore, multigene panels are often used to confirm a diagnosis of a peroxisomal disorder.

See Related Tests.

Genetics

Etiology

Pathogenic variants in genes related to the structure and function of peroxisomes (see the Genes Tested table)

Incidence

At least 1 in 50,000 live births

Genes Tested

Gene	MIM #	Associated Disorder	Inheritance
ABCD3	170995	Congenital bile acid synthesis defect	AR
ACBD5	616618	Retinal dystrophy with leukodystrophy	AR
ACOX1	609751	Peroxisomal acyl-CoA oxidase deficiency	AR
		Mitchell Syndrome	AD
AGPS	603051	RCPD type 3	AR
AGXT	604285	Primary hyperoxaluria	AR
AMACR	604489	Alpha-methylacyl-CoA racemase deficiency	AR
DNM1L	603850	Encephalopathy, lethal, due to defective mitochondrial peroxisomal fission	AD, AR
		Optic atrophy	AR
FAR1	616107	Peroxisomal fatty acyl-CoA reductase (RCDP type 4)	AR
GNPAT	602744	RCDP type 2	AR
HSD17B4	601860	D-bifunctional protein deficiency, Perrault syndrome	AR
PEX1	602136	ZSD	AR
PEX10	602859	ZSD	AR
PEX11B	603867	ZSD	AR
PEX12	601758	ZSD	AR
PEX13	601789	ZSD	AR
PEX14	601791	ZSD	AR

Gene	MIM #	Associated Disorder	Inheritance
PEX16	603360	ZSD	AR
PEX19	600279	ZSD	AR
PEX2	170993	ZSD	AR
PEX26	608666	ZSD	AR
PEX3	603164	ZSD	AR
PEX5	600414	ZSD	AR
		RCDP type 5	AR
PEX6	601498	ZSD	AR, AD
PEX7	601757	RCDP type 1	AR
PHYH	602026	Refsum disease	AR
SCP2	184755	Leukoencephalopathy with dystonia and motor neuropathy	AR

Genotype-Phenotype Correlations

The majority of *PEX5* variants are associated with ZSD. One variant, c.722dupA in coding exon 7, has been associated with RCDP type 5.[1]

One *PEX6* complex variant, p.Arg860Trp with *442_445delTAAA in cis, has been associated with autosomal dominant ZSD. However, p.Arg860Trp with homozygosity for *442_445delTAAA has been reported in unaffected individuals.[2]

Loss-of-function variants in *ACOX1* are associated with peroxisomal acyl-CoA oxidase deficiency. One gain-of-function variant, p.Asn237Ser, is associated with Mitchell syndrome.[3]

Test Interpretation

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Significance
Positive	One or more pathogenic or likely pathogenic variants detected	Confirms a diagnosis of a heritable peroxisomal disorder or related disorder Specific diagnosis depends on the variant(s) detected
Inconclusive	One or more variants of uncertain significance detected	Unknown if the variant(s) are disease-causing or benign
Negative	No pathogenic variants detected	Diagnosis of a peroxisomal disorder or related disorder is less likely, though not excluded

Limitations

- A negative result does not exclude a heritable form of peroxisomal dysfunction.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - ACBD5(NM_001352568) exon(s) 6
    - ACBD5(NM_001352569) exon(s) 6
    - ACBD5(NM_001352570) exon(s) 13
    - ACBD5(NM_001352571) exon(s) 5
    - ACBD5(NM_001352573) exon(s) 6
    - ACBD5(NM_001352574) exon(s) 6
    - ACBD5(NM_001352575) exon(s) 6
    - ACBD5(NM_001352576) exon(s) 6
    - ACBD5(NM_001352581) exon(s) 6
    - ACBD5(NM_001352585) exon(s) 5
    - ACBD5(NM_001352586) exon(s) 5
    - ACBD5(NM_001352568) partial exon(s) 1(Chr10:27529638-27529648)
    - ACBD5(NM_001352572) partial exon(s) 1(Chr10:27529638-27529648)
    - SCP2(NM_001007098) exon(s) 11
    - SCP2(NM_001330587) exon(s) 12
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

References

1. Barøy T, Koster J, Strømme P, et al. A novel type of rhizomelic chondrodysplasia punctata, RCDP5, is caused by loss of the PEX5 long isoform. Hum Mol Genet. 2015;24(20):5845-5854.

2. Falkenberg KD, Braverman NE, Moser AB, et al. Allelic expression imbalance promoting a mutant PEX6 allele causes Zellweger spectrum disorder. Am J Hum Genet. 2017;101(6):965-976.

3. Chung HL, Wangler MF, Marcogliese PC, et al. Loss- or gain-of-function mutations in ACOX1 cause axonal loss via different mechanisms. Neuron. 2020;106(4):589-606.e6.

Additional Resources

Braverman NE, Raymond GV, Rizzo WB, et al. Peroxisome biogenesis disorders in the Zellweger spectrum: an overview of current diagnosis, clinical manifestations, and treatment guidelines. Mol Genet Metab. 2016;117(3):313-321.

Ebberink MS, Mooijer PA, Gootjes J, et al. Genetic classification and mutational spectrum of more than 600 patients with a Zellweger syndrome spectrum disorder. Hum Mutat. 2011;32(1):59-69.

Related Information

X-Linked Adrenoleukodystrophy
X-Linked Adrenoleukodystrophy Testing

Related Tests

Pipecolic Acid, Urine 2008131

Method: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

Pipecolic Acid, Serum or Plasma 2007406

Method: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

Pyridoxine-Dependent Epilepsy Panel, Urine 2013355

Method: Quantitative Liquid Chromatography-Tandem Mass Spectrometry

Pyridoxine-Dependent Epilepsy Panel, Serum or Plasma 2013352

Method: Quantitative Liquid Chromatography-Tandem Mass Spectrometry

Bile Acids, Fractionated and Total by LC-MS/MS 0092610

Method: Quantitative High Performance Liquid Chromatography-Tandem Mass Spectrometry

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