Very Long-Chain and Branched-Chain Fatty Acids Profile

FOR PATIENTS WITH A SUPSECTED PEROXISOMAL DISORDER

Disease Overview

Peroxisomes are organelles involved in several metabolic processes in the cell, including alpha and beta oxidation of very long-chain fatty acids, synthesis of plasmalogens, and oxidation of bile acids and cholesterol.

Peroxisomal disorders include disorders of peroxisome biogenesis as well as single-enzyme or transporter deficiencies. At least 17 peroxisomal disorders have been identified. The most severe are the peroxisome biogenesis disorders (PBDs), which include:

- **Zellweger syndrome spectrum (ZSS) disorders.** ZSS disorders include Zellweger syndrome (most severe), neonatal adrenoleukodystrophy (NALD), and infantile refsum disease (IRD, least severe). ZSS disorders are caused by mutations in the PEX genes, which code for peroxins, which are involved in transporting peroxisomal proteins into the peroxisome. Peroxins recognize and bind to a peroxisome targeting signal (PTS1 or PTS2) contained in the peroxisomal protein, which allows for proper transport of proteins and proper assembly of the peroxisome.
  - Clinical presentation of ZSS disorders may vary but can include hypotonia, seizures, poor feeding, intellectual and developmental disabilities, distinctive facies, episodes of hemorrhage, liver disease, retinopathy, and hearing loss before age 1 year. These conditions are often progressive.
  - Treatment for PBDs is typically targeted to individual symptoms, as there is no curative therapy at this time.
- **Rhizomelic chondrodysplasia punctata type 1 (RCDP1).** RCDP1 is a type of PBD caused by mutations in the *PEX7* gene. Peroxisomal proteins containing the PTS1 signal are transported normally, but proteins containing the PTS2 signal cannot enter the peroxisome.
  - Features of RCDP1 include skeletal anomalies (proximal shortening of long bones, stippling at epiphyses), dysmorphic features, cataracts, severe intellectual disability with spasticity, and often seizures.
  - As with other PBDs, treatment is targeted to symptoms.
- **X-linked adrenoleukodystrophy (X-ALD).** X-ALD is the most common single-enzyme defect of the peroxisomal disorders. Clinical presentation is extremely variable.
  - In the childhood cerebral form, symptoms begin in childhood with rapid progression of neurologic disturbances, including hyperactivity, ataxia, seizures, spasticity, paralysis, and loss of vision, hearing, and the ability to speak or swallow.
  - The adrenomyeloneuropathy (AMN) form presents with neurological disturbances over decades, often with impaired adrenocortical function.
  - The "Addison disease only" form presents with adrenocortical impairment, with onset ranging from childhood to adulthood. Adrenal steroid hormone therapy is important for patients with adrenal insufficiency.

Diagnosis of a peroxisomal disorder can be confirmed by the following testing:

- Very long-chain fatty acids (VLCFA) in plasma, plasmalogens in red blood cells, and pristanic/phytanic acids in plasma
- Enzyme assay or complementation studies in dermal fibroblasts
- DNA testing in whole blood

Epidemiology

- Incidence of a ZSS disorder is approximately 1/50,000.
- Incidence of RCDP1 is <1/100,000.
- Incidence of X-ALD is approximately 1/20,000.

Genetics

- Most peroxisomal disorders are autosomal recessive. X-ALD is X-linked.
  - Female carriers of X-ALD may develop AMN-like symptoms in middle age or later.
- ZSS disorders are caused by mutations in one of several *PEX* genes.
  - Mutations in the *PEX1* gene accounts for approximately 70% of cases.
  - Other *PEX* genes include *PXMP3 (PEX2), PEX3, PEX5, PEX6, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19,* and *PEX26*.
- RCDP1 is caused by mutations in the *PEX7* gene.
- X-ALD is caused by mutations in the *ABCD1* gene.

Indications for Ordering

First-line test for an individual with a suspected peroxisomal disorder.

Contraindications for Ordering

This test will not determine carrier status.

Methodology

- Liquid chromatography/tandem mass spectrometry
- Test measures concentration of very long-chain fatty acids (C22–C26), pristanic acid, and phytanic acid.

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Interpretation

	VLCFA	Phytanic Acid	Pristanic Acid
Zellweger syndrome spectrum	Elevated	Elevated*	Elevated*
RCDP1	Normal	Elevated*	Normal
X-ALD	Elevated	Normal	Normal

*Note: Newborns with a peroxisomal disorder may have normal levels of phytanic/pristanic acid due to limited dietary intake.

Limitations

This test cannot predict disease severity.

References

1. Braverman NE, Moser AB, Steinberg SJ. Rhizomelic chondrodysplasia punctata type 1. GeneReviews. http://www.ncbi.nlm.nih.gov/books/NBK1270/. Accessed July 22, 2011.
2. Steinberg SJ, et al. Peroxisome biogenesis disorders, Zellweger syndrome spectrum. GeneReviews. http://www.ncbi.nlm.nih.gov/books/NBK1448/. Accessed July 22, 2011.
3. Moser AB, Steinberg SJ, Raymond GV. X-linked adrenoleukodystrophy. GeneReviews.http://www.ncbi.nlm.nih.gov/books/NBK1315/. Accessed July 22, 2011.
4. Wanders RJA. Inborn errors of peroxisome biogenesis and function . In: Sarafoglou K, Hoffman GF, Roth KS, eds. *Pediatric Endocrinology and Inborn Errors of Metabolism*. 2009; New York, NY: McGraw-Hill; 2009:323–337.

Test Information

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

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.
For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

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