Very Long-Chain Acyl-CoA Dehydrogenase/VLCAD (*ACADVL*) Sequencing and Deletion/Duplication

DNA TESTING TO DIAGNOSE VLCAD DEFICIENCY

Disease Overview

- Very long-chain acyl-CoA dehydrogenase (VLCAD) is the initial enzyme involved in mitochondrial fatty acid beta-oxidation, fueling hepatic ketogenesis during periods of high energy demand after hepatic glycogen stores have been depleted. VLCAD deficiency leads to the accumulation of very long-chain fatty acids.
- Symptoms include hypoketotic hypoglycemia, hepatomegaly, hepatic failure, and fasting-induced coma. Affected individuals may present with acute disease in the newborn period, with milder disease in infancy or early childhood, or with adolescent or adult-onset muscle disease resembling carnitine palmitoyltransferase 2 (CPT2).
- Newborns may develop metabolic acidosis, arrhythmia, Reye-like symptoms, hypertrophic cardiomyopathy, and sudden infant death. Morbidity and mortality is high for patients with the acute newborn presentation.
- A milder form of VLCAD deficiency, with symptoms resembling medium-chain acyl-coA dehydrogenase (MCAD) deficiency, presents with fasting intolerance and Reye-like syndrome triggered by prolonged fasting or illness.
- A third form of VLCAD deficiency, with symptoms resembling CPT2 deficiency, presents with myopathy, exercise-induced rhabdomyolysis, and myoglobinuria.
- Prognosis is poor for individuals with acute newborn disease, but good for patients treated presymptomatically. Management by the avoidance of fasting, as well as a low-fat diet supplemented with medium-chain triglycerides and in some cases L-carnitine, can help prevent morbidity and mortality.
- Normal plasma acylcarnitine levels do not exclude a diagnosis of VLCAD deficiency, especially when the patient is healthy; genetic testing of the *ACADVL* gene and/or functional assays are needed for definitive diagnosis.

Epidemiology

Incidence is approximately one in 40,000 in the United States based on newborn screening data.

Genetics

- Autosomal recessive inheritance.
- *ACADVL* is the only gene associated with VLCAD deficiency.
- Mutations throughout the *ACADVL* gene are responsible for VLCAD deficiency. Some genotype-phenotype correlation may exist.

Indications for Ordering

- Abnormal newborn screen suggestive of VLCAD deficiency.
- Diagnostic testing for patients with clinical and/or biochemical evidence of VLCAD deficiency.
- Carrier testing for the reproductive partner of an individual that is affected with, or a carrier of, VLCAD deficiency.

Contraindication for Ordering

Prenatal testing.

Additional Ordering Notes

If there is a family history of VLCAD and the specific familial mutations have already been identified, testing can be performed on at-risk family members by contacting ARUP's genetic counselor and requesting a custom sequencing test for the familial mutation(s) only.

Interpretation

- The detection of two severe *ACADVL* gene mutations on opposite chromosomes predicts VLCAD deficiency.
- When one deleterious mutation is detected in a clinically unaffected individual, the patient is predicted to be at least a carrier of VLCAD deficiency. If the patient is clinically affected, an undetected mutation may be present on the opposite chromosome.
- When one or no deleterious mutations are detected in a clinically affected individual, medical management should rely on clinical findings.
- Lack of any detectable mutations by gene sequencing and deletion/duplication analysis reduces the chance that the patient is affected with, or a carrier of, VLCAD deficiency.
- *ACADVL* mutations of unknown clinical significance may be detected by this assay.

Methodology and Limitations

- Bidirectional sequencing of the entire coding region and intron/exon boundaries of the *ACADVL* gene.
- Multiplex ligation-dependent probe amplification (MLPA) to identify large deletions/duplications in the *ACADVL* gene.
- Clinical sensitivity may be as high as 95 percent for sequencing and deletion/duplication together, 90 percent by sequencing alone, and as high as 10 percent by deletion/duplication analysis.

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- Analytical sensitivity and specificity are 99 percent.
- Regulatory region mutations and deep intronic mutations will not be detected.
- Rare diagnostic errors may occur due to primer-site mutations.

Related Tests

- Acylcarnitine Quantitative Profile, Plasma (0040033)
- Carnitine Panel (0081110)

References

1. Schymik I. Pitfalls of neonatal screening for very-long-chain acyl-CoA dehydrogenase deficiency using tandem mass spectrometry. *J Pediatr* 2006;149(1):128–30.
2. Introduction to disorders of fatty acid oxidation. In *Atlas of Metabolic Diseases*, 2nd ed. WN Nyhan, BA Barshop, PT Ozand, eds. 2005; London:Hodder Education.
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4. Saudubray JM. Recognition and management of fatty acid oxidation defects: a series of 107 patients. *J Inherit Metab Dis* 1999;22(4):488–502.
5. Liebig M. Neonatal screening for very long-chain acyl-coA dehydrogenase deficiency: enzymatic and molecular evaluation of neonates with elevated C14:1-carnitine levels. *Pediatrics* 2006;118(3):1065–9.

Test Information

2004212	**Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (*ACADVL*) Sequencing and Deletion/Duplication**
2002001	**Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (*ACADVL*) Sequencing**
2004208	**Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (*ACADVL*) Deletion/Duplication**

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.