EGL Genetics | Eurofins Clinical Diagnostics
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Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD): *ACADVL* Gene Sequencing

Test Code: HK
Turnaround time: 4 weeks
CPT Codes: 81406 x1

Condition Description

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD) is an autosomal recessive disorder of mitochondrial fatty acid beta-oxidation [1]. Three heterogeneous phenotypes of the disorder have been described ranging from a severe onset with cardiac failure in infancy, an intermediate childhood form with hypoketotic hypoglycemia, to an adult onset myopathic form with exertional rhabdomyolysis, primarily affecting skeletal muscle. The severe neonatal form is the most common type [2] and presents with cardiomyopathy, hepatopathy, and skeletal myopathy. The intermediate form is mainly characterized by episodes of hypoketotic hypoglycemia in infancy and cardiomyopathy occurs very rarely in this type [3]. The adult form is characterized by isolated skeletal myopathy, usually triggered by exercise or fasting [4]. Biochemical analysis of VLCADD patients reveals impairment of palmitoyl-CoA oxidation, with reduced or deficient very long-chain acyl-CoA dehydrogenase (VLCAD) activity and VLCAD protein in fibroblasts [5]. The molecular analysis of the *ACADVL* gene (17p13) in these patients depicts a heterogeneous mutational spectrum, including missense mutations, single amino acid deletions, and splicing defects, with most patients being compound heterozygotes [6]. Few phenotype-genotype correlations are well understood [7]. Gene sequencing is available to test for mutations in the *ACADVL* gene (HK). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (HN).

References:
1. Roe and Ding. Mitochondrial Fatty Acid Oxidation Disorders, in: C.R. Scriver, A.L. Beaudet, W. Sly, D. Valle (Eds.), The Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill, New York, 2001, pp. 2305-2308.
2. Andresen B, Olpin S, Poorthuis BJ, Scholte HR, Vianey-Saban C, Wanders R, Ijlst L, Morris A, Pourfarzam M, Bartlett K, Baumgartner ER, deKlerk JB, Schroeder LD, Corydon TJ, Lund H, Winter V, Bross P, Bolund L, Gregersen N (1999) Clear correlation of genotype with disease phenotype in very-long-chain acyl-coA dehydrogenase deficiency. Am J Hum Genet 64:479-494.
3. Vianey-Saban C, Divry P, Brivet M, Nada M, Zabot MT, Mathieu M, Roe C (1998) Mitochondrial very-long-chain acyl-coenzyme A dehydrogenase deficiency: clinical characteristics and diagnostic considerations in 30 patients. Clin Chim Acta 269:43-62.
4. Ogilvie I, Poufarzam M, Jackson S, Stockdale C, Bartlett K, Turnbull DM (1994) Very-long-chain acyl-CoA dehydrogenase deficiency presenting with exercise-induced myoglobinuria. Neurology 44:467-473
5. Pons et al. Clinical and molecular heterogeneity in very-long-chain acyl-coenzyme A dehydrogenase deficiency. Pediatr Neurol 2000, 22(2):98-105.
6. Andresen et al. Cloning and characterization of human very-long-chain acyl-CoA dehydrogenase cDNA, identification in four patients of nine different mutations within the *VLCAD* gene. Hum Mol Genet 1996, 5:461-72.
7. Andresen et al. Clear correlation of genotype with disease phenotype in very-long-chain acyl-CoA dehydrogenase deficiency. Am J Hum Genet 1999, 64:479-94.
8. Liebig et al. 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.
9. Schulze et al. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. Pediatrics 2003, 111(6 Pt 1):1399-406.

Genes

ACADVL

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of VLCADD.
- Carrier testing in adults with a family history of VLCAD.

Methodology

PCR amplification of 20 exons contained in the *VLCAD* gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements. Large deletions are not detected by this analysis.

Detection

Full Gene Sequencing: >90%. The majority of patients with clinical and biochemical diagnosis of VLCADD will have an abnormal DNA test [7].

Analytical Sensitivity: ~99%

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

Type: DNA, Isolated

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Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old: 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Urine Organic Acids (OA) and Plasma Acylcarnitine Profile (AR) are used in the diagnosis of a patient with VLCADD.
- Custom Diagnostics Known Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD) Deletion/Duplication Assay (HN) is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.