Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD): ACADVL Gene Sequencing

**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:

**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
* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**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.