**ACADVL Gene Analysis in Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency**

**Mendelian Inheritance in Man Numbers:** 201475 – VLCAD Deficiency; 609575 – ACADVL gene

**Clinical features:**
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) is an autosomal recessive, rare disorder of fatty acid oxidation. Presentation is variable, and has been classified into three forms: a severe neonatal form with high mortality and hypertrophic cardiomyopathy, hepatomegaly and hypotonia, a milder childhood form with hypoketotic hypoglycemia, hepatomegaly and hypotonia, and an adult-onset form with isolated skeletal muscle involvement, leading to muscle pain, rhabdomyolysis or myoglobinuria. 1,2

**Inheritance pattern:** Autosomal Recessive

**Genetics and biochemical features:**
VLCAD deficiency is caused by mutations in the ACADVL gene on chromosome 17p13.1-p11.2, encoding a very long-chain acyl-CoA dehydrogenase, which is involved in the initial reaction of very long-chain fatty acid oxidation. Mutations in the ACADVL gene cause accumulation of very long-chain fatty acids and their metabolites. Infants with VLCAD deficiency may be identified through newborn screening programs, although some cases are not detected by screening. Follow-up testing for VLCAD deficiency is normally by analysis of plasma acylcarnitines. Confirmation can be done by molecular analysis of the ACADVL gene. The incidence of VLCAD deficiency is unknown but has been estimated to be as high as 1/40,000.

**Reasons for referral:**
1. Diagnostic confirmation
2. Carrier testing
3. Genetic counseling
4. Prenatal diagnosis in at risk pregnancies

**Test method:**
Mutation analysis of the ACADVL gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-20, and corresponding intron/exon boundaries. If sequencing identifies a mutation on only one allele of the ACADVL gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

**Test sensitivity:**
In clinically affected patients or individuals with deficient enzyme activity or a demonstrated fatty acid oxidation defect, with abnormal plasma acylcarnitine profiles or characteristic abnormalities of unsaturated fatty acid metabolism in urine and plasma or in cultured skin fibroblasts, mutation analysis identified more than 90% of mutant alleles. 1
Mutation spectrum:
Missense, frameshift, and splice site mutations have been reported, as well as in-frame deletions. Genotype-phenotype studies indicate that there is a relationship between mutation type and disease severity, with individuals harboring null alleles exhibiting a more severe clinical presentation than individuals with missense mutations.\textsuperscript{1,3,4}

Specimen Requirements and Shipping/Handling:
- **Blood**: A single tube with 1-5 mL whole blood in EDTA (1-2mL for infants). Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for one week prior to shipping.
- **Buccal Brushes**: Can be used as an alternative to blood for ACADVL sequencing only. Gene deletion/duplication testing requires submission of a venous blood sample. When sending a buccal sample, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children under 6 months of age.
- **Prenatal Diagnosis**: 10 mL amniotic fluid, 5 mg CVS, or 2 T25 flasks. Ship overnight at ambient temperature, using a cool pack in hot weather. Call to discuss requirements for parental blood. Keep backup cultures.

Required Forms:
Sample Submission (Requisition) Form – complete both sides
Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency” page on our website: www.genedx.com