

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

### 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.<sup>1,2</sup>

### Genetics:

VLCAD deficiency is caused by variants 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. Variants 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 acylcarnities. 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.

### Inheritance Pattern:

Autosomal Recessive

### Test Methods:

Variant 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 variant 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. Variants 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, variant analysis identified more than 90% of mutant alleles.<sup>1</sup> The methods used by

GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

**Variant Spectrum:**

Missense, frameshift, and splice site variants have been reported, as well as in-frame deletions. Genotype-phenotype studies indicate that there is a relationship between variant type and disease severity, with individuals harboring null alleles exhibiting a more severe clinical presentation than individuals with missense variants.<sup>1,3,4</sup>

**References:**

1. Andresen, B.S. et al, (1999) Am J Hum Genet 64:479-494
2. Liebig, M. et al, (2006) Pediatrics 118:1065-1069
3. Gregersen, N. et al, (2001) Hum Mutat 18:169-189
4. Mathur, A. et al, (1999) Circulation 99:1337-1343