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.[1,2]

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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the ACADVL gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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.[1,3,4]

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