ACADS Gene Analysis in Short-Chain Acyl-CoA Dehydrogenase (SCAD) Deficiency

CLINICAL FEATURES

Short-chain acyl-CoA dehydrogenase deficiency (SCAD) is a rare disorder of fatty acid oxidation. Previous reports of clinical findings in individuals with SCAD deficiency have been highly variable, ranging from asymptomatic to symptoms that include developmental delay, seizures, hypotonia, ketotic hypoglycemia, behavioral disorders and failure to thrive; some adults have been reported with signs of muscle weakness and progressive myopathy.[1,2,3] However, association of SCAD deficiency with a clinical phenotype has long been questioned, and most individuals identified with SCAD deficiency detected by newborn screening have had normal growth and development, as have relatives of probands ascertained by newborn screening.[1,3] Based on more recent data, in particular data from newborn screening, it is generally believed that SCAD deficiency is associated only with biochemical findings.[1] The incidence of SCAD deficiency has been estimated to be as high as 1/35,000 to 1/50,000.[1]

GENETIC

SCAD deficiency is caused by pathogenic variants in the ACADS gene that encodes a short-chain acyl-CoA dehydrogenase that is involved in the initial reaction of short-chain fatty acid oxidation. This enzyme catalyzes the mitochondrial beta-oxidation of C4-C6 straight-chain fatty acyl-CoAs. Pathogenic variants in the ACADS gene cause accumulation of short-chain fatty acids and their metabolites. Infants with SCAD deficiency may be identified through newborn screening programs. Follow-up testing for SCAD deficiency may include analysis of acylcarnitines and organic acids. Confirmation can be made by molecular analysis of the ACADS gene.

INHERITANCE PATTERN

Autosomal Recessive

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the ACADS 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.

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VARIANT SPECTRUM

Variants have been reported across the ACADS gene and include missense, nonsense, splicing defects and small deletions. Two very common missense changes in the ACADS gene, G209S (c.625G>A) and R171W (c.511C>T),can be associated with ethylmalonic aciduria when present in an individual who is homozygous or compound heterozygous.[5,6]

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