

ACADM Gene Analysis in Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

Clinical Features

Medium-chain acyl-CoA dehydrogenase deficiency (MCAD) is the most common disorder of fatty acid oxidation. Newborn screening by tandem mass spectrometry reveals the accumulation of octanoylcarnitine, which is characteristic of MCAD deficiency. Symptoms that typically occur between 6 months to two years include lethargy, hypoglycemia, vomiting, hypotonia, seizures and sudden infant death syndrome. Complications include hepatic dysfunction, respiratory difficulties, cardiac arrest, neurologic deficits and coma. The disorder is characterized by high mortality however milder variants exist and adult onset can occur. Significant phenotypic heterogeneity may occur even within a family. ^{1,2}

Genetics

MCAD deficiency is caused by pathogenic variants in the *ACADM* gene on chromosome 1p31, encoding medium chain acyl-CoA dehydrogenase that is involved in the initial reaction of the beta-oxidation of fatty acids. Pathogenic variants in the *ACADM* gene cause accumulation of medium-chain fatty acids and their metabolites. Most infants can be identified through newborn screening. After follow-up biochemical testing, analysis of the *ACADM* gene is recommended for diagnostic confirmation of MCAD deficiency. In the United States the incidence of MCAD deficiency is approximately 1/15,000 live births.³ Caucasians of northern European descent have the highest carrier frequency (approximately 1/80-1/100).¹

Inheritance Pattern

Autosomal Recessive

Test Methods

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *ACADM* 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 pathogenic variants encompass the majority of variants in *ACADM*, however small deletions/duplications have been reported. The K329E missense variant accounts for up to 67% of mutant

ACADM alleles, based on newborn screening in the United States.⁵ A T121I variant accounts for 95% of mutant *ACADM* alleles in Saudi Arabia, based on newborn screening in that country.^{3,4}

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