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. 

Genetics:
MCAD deficiency has an autosomal recessive inheritance pattern. 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. Caucasians of northern European descent have the highest carrier frequency (approximately 1/80-1/100).

Test Methods:
For full sequencing, variant analysis of the ACADM gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-12. Pathogenic variants in exon 11, including the common K329E variants (aka K304E), account for up to 85% of mutant ACADM alleles. For this reason, sequencing of exon 11 can be ordered first, followed by exons 1-10 and 12 if two variants are not identified in Tier 1. For individuals of Saudi-Arabian descent, variant specific testing for the p.T121I variant that has been identified in this population on 95% of mutant ACADM alleles is available as a separate test. If full sequencing identifies a variant on only one allele of the ACADM 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 patients whose initial newborn screening was confirmed using follow-up testing of plasma acylcarnitine and/or urinary organic acid analysis, variant analysis identified a sequence variant in over 95% of cases.\(^2\)

Variant Spectrum:
Missense pathogenic variants encompass the majority of variants in ACADM, however small deletions/duplications have been reported. The K329E missense pathogenic variant accounts for up to 85% of mutant ACADM alleles, based on newborn screening in the United States, while the T121I pathogenic variant accounts for 95% of mutant ACADM alleles in Saudi Arabia, based on newborn screening in that country.\(^3,4\)

References: