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:
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.[3] 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. 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] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

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 85% of mutant *ACADM* alleles, based on newborn screening in the United States. A T121I variant accounts for 95% of mutant *ACADM* alleles in Saudi Arabia, based on newborn screening in that country.[3,4]

References:

1. Andresen, B.S. et al, (2001) Am J Hum Genet 68:1408-1418.
2. Maier, E.M. et al, (2005) Hum Mutat 25:443-52.
3. Chace, D.H. et al, (2002) Annu Rev Genomics, Hum Genet 3:17-45.
4. Al-Hassnan et al., (2010) [Epub ahead of print]