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 ACADS 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 ACADS 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]

Genetics:
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:
Analysis of the *ACADS* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons, and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *ACADS* 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. Pathogenic variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing or another appropriate method.

Test Sensitivity:

In individuals diagnosed with SCAD deficiency on the basis of ethylmalonic aciduria and low SCAD activity in cultured fibroblasts, sequence analysis identified at least two reportable variants in more than 95% of cases.[4] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

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]

References:

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