Medium Chain Acyl-CoA Dehydrogenase (ACADM) 2 Mutations

Medium chain acyl-coenzyme A dehydrogenase (MCAD) deficiency is one of the most common inborn errors of metabolism and is the most frequently diagnosed fatty acid β-oxidation disorder.[1] Symptoms generally present between 3 and 24 months of age[1] and may include hypoketotic hypoglycemia, lethargy, seizure, coma, hepatomegaly, encephalopathy, Reye-like syndrome, or sudden death. These episodes may be triggered by prolonged fasting, infection, or surgery. Once diagnosed, patients generally have a good prognosis.[1] Genetic testing is typically indicated by a positive newborn screen or after positive biochemical tests in a newly symptomatic individual.[1]

Featured ARUP Testing

Medium Chain Acyl-CoA Dehydrogenase (ACADM) 2 Mutations 0051205

Method: Polymerase Chain Reaction/Fluorescence Monitoring

- Preferred initial molecular test to confirm a diagnosis or identify carriers of MCAD deficiency in individuals with suggestive clinical and/or biochemical findings such as:
  - Abnormal newborn screen for MCAD
  - Reye-like syndrome (in infants)
- Test for family members of a proband with the c.985A>G or c.199T>C variants
- Carrier test for reproductive partner of an affected individual or a carrier of MCAD deficiency

For additional biochemical and genetic test options, refer to the Laboratory Test Directory.

Testing Strategy

Biochemical tests are necessary for the initial diagnosis of MCAD deficiency and may include the following:

- Acylcarnitine Quantitative Profile, Plasma
- Carnitine Panel
- Acylglycines, Quantitative, Urine
- Organic Acids, Urine

Refer to the Laboratory Test Directory for available test options.

Genetics

Gene

ACADM

Pathogenic Variants

c.985A>G; p.K329E

- Most common pathogenic variant in individuals with MCAD deficiency

c.199T>C; p.Y67H

- Mild pathogenic variant associated with residual MCAD enzymatic activity
- Individuals heterozygous for this variant and another pathogenic variant on the opposite chromosome may have reduced acylcarnitine levels and may be at risk for metabolic crisis.[2]

Inheritance

Autosomal recessive

Test Interpretation

Clinical Sensitivity

Approximately 75% in White individuals[2,3]

Results

Result	Clinical Significance
Homozygosity for c.985A>G	Predicts MCAD deficiency
Heterozygosity for c.985A>G	Indicates individual is at least a carrier for classic MCAD deficiency
Compound heterozygosity for c.985A>G variant and the mild c.199T>C variant	May have reduced acylcarnitine levels and may be at risk for metabolic crisis
Heterozygosity for c.199T>C	Indicates individual is at least a carrier for mild MCAD deficiency
Homozygosity for c.199T>C	Predicts mild MCAD deficiency
No variants detected	Indicates likelihood of MCAD deficiency or carrier state is reduced

Limitations

- Diagnostic errors can occur due to rare sequence variations.
- *ACADM* variants other than c.985A>G and c.199T>C will not be detected.

References

1. Merritt JL II, Chang IJ. Medium-chain acyl-coenzyme A dehydrogenase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews: University of Washington; 1993-2021. [Updated: Jun 2019; Accessed: Nov 2021]

2. Gramer G, Haege G, Fang-Hoffmann J, et al. Medium-chain Acyl-CoA dehydrogenase deficiency: evaluation of genotype-phenotype correlation in patients detected by newborn screening. *JIMD Rep*. 2015;23:101-112.

3. Rhead WJ. Newborn screening for medium-chain acyl-CoA dehydrogenase deficiency: a global perspective. *J Inherit Metab Dis*. 2006;29(2-3):370-377.

Related Information

Fatty Acid Oxidation Disorders Panel, Sequencing

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