

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 age¹ 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

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

See [Related Tests](#).

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}

Tests to Consider

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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

Panel Test

Fatty Acid Oxidation Disorders Panel, Sequencing 3001851

Method: Massively Parallel Sequencing

May be used to confirm or rule out a diagnosis of a fatty acid oxidation disorder following clinical and/or biochemical presentation

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, Haegi 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 Inher Metab Dis. 2006;29(2-3):370-377.

Related Information

[Fatty Acid Oxidation Disorders Panel, Sequencing](#)

Related Tests

[Acylcarnitine Quantitative Profile, Plasma 0040033](#)

Method: Tandem Mass Spectrometry

[Carnitine Panel 0081110](#)

Method: Tandem Mass Spectrometry

[Acylglycines, Quantitative, Urine 0081170](#)

Method: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

[Organic Acids, Urine 0098389](#)

Method: Gas Chromatography-Mass Spectrometry (GC-MS)

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