

Medium-Chain Acyl-CoA Dehydrogenase Deficiency Genetic Testing

Indications for Ordering

Molecular testing to confirm diagnosis or identify carriers of medium chain acyl-CoA dehydrogenase (MCAD) deficiency for individuals with suggestive clinical and/or biochemical findings

Test Description

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

- Polymerase chain reaction (PCR) and fluorescence monitoring using hybridization probe for variants c.985A>G and c.199T>A in the *ACADM* gene

Medium Chain Acyl-CoA Dehydrogenase Deficiency (*ACADM*) Sequencing

- PCR followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *ACADM* gene

Tests to Consider

Typical testing strategy

- Biochemical tests
 - Acylcarnitine Quantitative Profile, Plasma
 - Carnitine Panel
 - Acylglycines, Quantitative, Urine
 - Organic Acids, Urine
- Molecular tests
 - Medium Chain Acyl-CoA Dehydrogenase Deficiency (*ACADM*) 2 Mutations
 - Medium Chain Acyl-CoA Dehydrogenase Deficiency (*ACADM*) Sequencing

Primary tests

[Medium Chain Acyl-CoA Dehydrogenase \(*ACADM*\) 2 Mutations 0051205](#)

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

[Medium Chain Acyl-CoA Dehydrogenase Deficiency \(*ACADM*\) Sequencing 0051758](#)

- Molecular test to confirm a diagnosis of MCAD deficiency for individuals with suggestive clinical and/or biochemical findings who have one or no pathogenic variants detected with 2 variants test
- Carrier testing for reproductive partner of an affected individual or carrier of MCAD deficiency

Disease Overview

Incidence –1/4,000-17,000

- Most frequently diagnosed fatty acid beta-oxidation disorder
- Carrier frequency in European Caucasians is ~1/50

Symptoms

- Hypoketotic hypoglycemia
- Coma
- Episodic emesis
- Lethargy
- Seizures
- Hepatomegaly
- Encephalopathy
- Reye-like syndrome
- Sudden death
- Maternal (if fetus has MCAD deficiency)
 - HELLP (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelet count) syndrome
 - Acute fatty liver of pregnancy
- Triggers of acute metabolic episodes
 - Prolonged fasting
 - Infection
 - Surgery

Pathophysiology

- MCAD
 - Enzyme involved in mitochondrial fatty acid beta-oxidation
 - Fuels ketogenesis during periods of high-energy usage after hepatic glycogen is depleted
- Deficiency of MCAD results in impaired beta-oxidation and accumulation of medium-chain fatty acids

- Expected laboratory test results
 - Plasma acylcarnitine
 - C6-C10 species – abnormalities
 - Urine organic acid analysis
 - Hexanolyglycine and suberylglycine – elevated
 - Medium-chain dicarboxylic acids in symptomatic individuals – elevated
 - Urine acylglycine
 - Hexanolyglycine and suberylglycine – elevated

Genetics

Gene – *ACADM*

Inheritance – autosomal recessive

Variants

- Most common – c.985A>G (Lys304Glu)
 - Accounts for 75% of disease-causing alleles
 - Half of individuals with MCAD deficiency are homozygous for this variant
 - Most remaining individuals with MCAD deficiency are compound heterozygotes
- Mild variant c.199T>C

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity (sequencing) – 95-99%
- Analytical sensitivity/specificity – 99%

Results

- Two severe *ACADM* gene variants
 - Predicts MCAD deficiency
- One severe *ACADM* gene variant
 - Individual is at least a carrier for classic MCAD deficiency
- Compound heterozygosity for c.985A>G variant and mild c.199T>C variant
 - May produce an abnormal acylcarnitine profile
 - Clinical consequences of this genotype are unknown
- One mild variant
 - Individual is at least a carrier for mild MCAD deficiency
- Compound heterozygotes for c.985A>G and another *ACADM* variant, or individuals homozygous for non-c.985A>G variants
 - Predicts MCAD deficiency
 - Genotype/phenotype correlations are not well established
- Lack of gene variant reduces likelihood of MCAD deficiency or carrier state
- Variants of unknown clinical significance may be identified

Limitations

- Not detected
 - Regulatory region or deep intronic variants
 - Large deletions/duplications
- Diagnostic errors can occur due to rare sequence variations