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>C 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
  o Acylcarnitine Quantitative Profile, Plasma
  o Carnitine Panel
  o Acylglycines, Quantitative, Urine
  o Organic Acids, Urine
• Molecular tests
  o Medium Chain Acyl-CoA Dehydrogenase Deficiency (ACADM) 2 Mutations
  o 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
  o Abnormal newborn screen for MCAD
  o Infants with Reye-like syndrome
• Testing for family members of a proband with the c.985A>G or c.199T>C 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)
  o HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome
  o Acute fatty liver of pregnancy
• Triggers of acute metabolic episodes
  o Prolonged fasting
  o Infection
  o 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
    - Hexanoylglycine and suberylglycine: elevated
    - Medium-chain dicarboxylic acids in symptomatic individuals: elevated
  - Urine acylglycine
    - Hexanoylglycine 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