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
  - 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>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 White individuals 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
    - Hexanolylglycine and suberylglycine: elevated
    - Medium-chain dicarboxylic acids in symptomatic individuals: elevated
  - Urine acylglycine
    - Hexanolylglycine 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