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
  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>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)
  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
  o Plasma acylcarnitine
    ▪ C6-C10 species – abnormalities
  o Urine organic acid analysis
    ▪ Hexanoylglycine and suberylglucose – elevated
    ▪ Medium-chain dicarboxylic acids in symptomatic individuals – elevated
  o Urine acylglycine
    ▪ Hexanoylglycine and suberylglucose – elevated

Genetics

Gene – ACADM

Inheritance – autosomal recessive

Variants
  ▪ Most common – c.985A>G (Lys304Glu)
    o Accounts for 75% of disease-causing alleles
    o Half of individuals with MCAD deficiency are homozygous for this variant
    o 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
  o Predicts MCAD deficiency
• One severe ACADM gene variant
  o Individual is at least a carrier for classic MCAD deficiency
• Compound heterozygosity for c.985A>G variant and mild c.199T>C variant
  o May produce an abnormal acylcarnitine profile
    ▪ Clinical consequences of this genotype are unknown
• One mild variant
  o 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
  o Predicts MCAD deficiency
  o 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
  o Regulatory region or deep intronic variants
  o Large deletions/duplications
• Diagnostic errors can occur due to rare sequence variations