

# Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

## *DNA TESTING TO PREDICT CARRIER STATUS OR DIAGNOSE MCAD DEFICIENCY*

### Disease Overview

- Medium-chain acyl-CoA dehydrogenase (MCAD) is an enzyme involved in mitochondrial fatty acid beta-oxidation, fueling hepatic ketogenesis during periods of high energy demand after hepatic glycogen stores have been depleted. MCAD deficiency results in the accumulation of medium-chain fatty acids and is the most frequently diagnosed beta-oxidation defect.
- Affected individuals appear normal at birth and typically experience their first acute metabolic episode before two years of age, although presentation in adulthood is possible.
- Triggers in infancy include prolonged fasting, or common illnesses or infections; adult cases may be precipitated by metabolic stressors like surgery, illness, or alcohol use.
- Signs and symptoms include episodic vomiting, lethargy, recurrent hypoglycemic coma, seizures, hypoketotic dicarboxylic aciduria, hepatomegaly, hepatic failure, encephalopathy, and low plasma carnitine.
- In nearly 20 percent of cases, the initial manifestation may be sudden, unexplained death.
- Maternal pregnancy complications such as HELLP syndrome (i.e., hemolysis, elevated liver enzymes, low platelets) and acute fatty liver of pregnancy (AFLP) are more common in women carrying affected fetuses.
- The prognosis is excellent for patients diagnosed presymptomatically. Low-cost clinical management, including avoidance of fasting, following a low-fat diet, and supplementation with L-carnitine, can help prevent morbidity and mortality.

### Epidemiology

- The incidence is one in 15,000 in the United States based on newborn-screening data.
- Carrier frequency in European Caucasians is approximately one in 50; less common in other populations.

### Genetics

- Autosomal recessive.
- Mutations in the *ACADM* gene are responsible for MCAD deficiency. The most common mutation, c.985A>G, results in a lysine-for-glutamate amino acid change (p.K304E), representing approximately 75 percent of disease-causing alleles from newborn-screening data.
- Approximately 50 percent of patients are homozygous for the c.985A>G mutation; however, 40 percent are compound heterozygotes with one copy of c.985A>G and a rare mutation on their other allele.

- The carrier frequency of the mild point mutation, c.199T>C (p.Y42H), is approximately one in 500. Compound heterozygotes for c.985A>G/c.199T>C may have an abnormal acylcarnitine profile. As the clinical consequences of this genotype are unknown; patient follow-up is recommended.
- Compound heterozygotes for c.985A>G and another *ACADM* mutation, or individuals homozygous for non- c.985A>G mutations, may present with mild MCAD deficiency; however, genotype/phenotype correlations in MCAD are not well established.

### Indications for Ordering

- Medium Chain Acyl-CoA Dehydrogenase Deficiency (*ACADM*) 2 Mutations
  - Testing for infants with early Reye-like syndrome.
  - Follow-up of an abnormal newborn screen for MCAD deficiency.
  - Diagnostic testing for parents and siblings of a proband homozygous for c.985A>G (due to intra-familial variability in presentation and apparently asymptomatic status of homozygous individuals).
  - Carrier testing for at-risk relatives after c.985A>G has been identified in an affected family member.
  - Carrier testing for the reproductive partner of an individual who is affected with, or a carrier of, MCAD deficiency.
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (*ACADM*) Sequencing
  - Diagnostic testing for patients with clinical and/or biochemical evidence of MCAD deficiency who have one or no identifiable mutations using the MCAD (*ACADM*) 2 Mutation test.
  - Carrier testing for the reproductive partner of an individual that is affected with, or a carrier of, MCAD deficiency.

### Contraindication for Ordering

Prenatal testing

### Additional Ordering Notes

- If there is a family history of MCAD deficiency, please provide the relationship of the proband to the individual being tested, as well as the specific mutations identified in the proband.
- In persons with clinical evidence of MCAD deficiency, plasma acylcarnitine profile testing is recommended to exclude this diagnosis.

### Interpretation

- The detection of two severe *ACADM* gene mutations predicts MCAD deficiency.
- Compound heterozygosity for the c.985A>G mutation and the mild c.199T>C may produce an abnormal acylcarnitine profile. As the

clinical consequences of this genotype are unknown; patient follow-up is recommended. When one severe mutation is detected in a clinically unaffected individual, the patient is predicted to be at least a carrier for classic MCAD deficiency.

- When one mild mutation is detected in a clinically unaffected individual, the patient is predicted to be at least a carrier for mild MCAD deficiency.
- Gene sequencing may identify novel mutation(s); thus, the determination of clinical significance (benign or deleterious) may be unclear.
- Lack of a detectable mutation by gene sequencing reduces the likelihood that the patient is neither affected with, nor a carrier of, MCAD deficiency.

### Methodology and Limitations

- Medium Chain Acyl-CoA Dehydrogenase Deficiency (*ACADM*) 2 Mutations
  - Mutations in the *ACADM* gene c.985A>G (p.K304E) and c.199T>C (p.Y42H) are assayed by polymerase chain reaction (PCR) and fluorescence monitoring using hybridization probes.
  - Clinical sensitivity is 75 percent for MCAD deficiency.
  - Analytical sensitivity and specificity is 99 percent.
  - Rare diagnostic errors may occur due to primer site mutations.
- 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.

- Clinical sensitivity is 95–99 percent.
- Analytical sensitivity and specificity is 99 percent.
- Regulatory region mutations, deep intronic mutations, and large deletion/duplications will not be detected.
- Rare diagnostic errors may occur due to primer site mutations.

### Related Tests

- Acylcarnitine Quantitative Profile, Plasma (0040033)
- Carnitine Panel (0081110)
- Acylglycine, Quantitative, Urine, (0081170)
- Organic Acids, Urine, (0098389)

### References

1. Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency Gene Reviews. <http://www.genetests.org> (accessed July 10, 2007).
2. Chace DH, et al. The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism. *Annu Rev Genomics Hum Genet* 2002; 3:17–45.
3. Andresean BS, et al. Medium-chain acyl-CoA dehydrogenase (MCAD) mutations identified by MS/MS-based prospective screening of newborns differ from those observed in patients with clinical symptoms. *Am J Hum Genet* 2001; 68:1408–18.
4. Waddell L, et al. Medium-chain acyl-CoA dehydrogenase deficiency: genotype-biochemical phenotype correlations. *Mol Genet Metab* 2006; 87:32–9.

## Test Information

0051205  
0051758

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

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).