

## Medium Chain Acyl-CoA Dehydrogenase Deficiency via *ACADM* Gene Sequencing (Test #180)

**Brief Description of Clinical Features:** Medium chain acyl-CoA dehydrogenase deficiency (MCADD, OMIM #201450) is a defect in the catabolism of fatty acids within the mitochondria. Currently, the majority of new patients are identified through tandem mass spectrometry in neonatal screening. Those patients who are identified clinically typically present within the first two years of life with an episode of lethargy and vomiting accompanied by hypoketotic hypoglycemia, commonly triggered by a viral infection. Some patients also have hepatomegaly and acute liver disease. These symptoms may progress to seizures, coma and death. If MCADD is diagnosed early, most mortality and morbidity can be prevented through relatively simple measures, such as frequent feedings to avoid any extended periods of fasting (Wilcken et al. *Lancet* 369:37-42, 2007). MCADD is one of the most common monogenic metabolic disorders with an incidence of about 1/15,000 newborns in the United States. A significant fraction of Sudden Infant Death victims have MCADD (Boles et al. *J. Pediatr* 132:924-933, 1998). For more information see Matern and Rinaldo, *GeneReviews* 2005 ([www.genetests.org](http://www.genetests.org)) and Grosse et al. *Genet Med* 8:205-212, 2006.

**Genetics:** MCADD is an autosomal recessive disease. Medium chain acyl-CoA dehydrogenase, encoded by the *ACADM* gene, catalyzes the first step in the breakdown of fatty acids with 4-12 carbon atoms. For patients with Northern European ancestry, one missense mutation in exon 11 (c.985A>G, p.Lys304Glu) is predominant, comprising up to about 76% of alleles in individuals with MCAD deficiency. This mutation tends to cause particularly severe disease. At least 45 other causative missense, frameshift, splicing, and nonsense mutations have been described throughout the length of the gene; most are private mutations. Individuals who are compound heterozygous for the p.Lys304Glu mutation, or homozygous for other mutations in the *ACADM* gene, tend to have less severe disease. It appears that diagnosis by tandem mass spectrometry is more sensitive than diagnosis by other clinical features and may identify subclinical cases (Andresen et al. *Am J Hum Genet* 68:1408-1418, 2001; Maier et al. *Hum Mut* 25:443-452, 2005; Matern and Rinaldo, *GeneReviews*, 2005; and Waddell et al. *Mol Genet Metab* 87:32-39, 2006).

**Description of This Particular Test:** Medium chain acyl-CoA dehydrogenase is encoded by the *ACADM* gene (OMIM #607008). Testing is accomplished by amplifying the 12 coding exons and ~50 bp of adjacent non coding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. Testing for the common p.Lys304Glu mutation can be performed for \$190 (test code 100).

**Reference Sequences:** Genomic: NC\_000001.9 mRNA and Protein: CCDS 668.1

**Indications for Test:** Newborns suspected to have MCADD based on clinical or by tandem mass spectroscopy findings.

**Sensitivity of Test:** Sensitivity of this test appears to be high. Approximately 50% of patients are homozygous for the p.Lys304Glu mutation, and 40% of affected individuals are heterozygous for this mutation (Matern and Rinaldo, *GeneReviews* 2005).

**Turn Around Time:** Maximum of 40 days, although many tests are completed in 2-3 weeks.

**Specimen Requirements:** See page 4 of Requisition Form.

<b>Prices:</b>	<b>Sequencing of <i>ACADM</i></b>		<b>\$ 540</b>	
<b>CPT Codes:</b>				
Sample Ascertainment	83890	\$ 30	DNA Isolation	83891 \$ 40
Amplification x11	83898	\$ 140	Sequencing x11	83904 \$ 220
Separation	83894	\$ 40	Interpretation/Report	83912 \$ 70

**Accreditation Info.** CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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