

Short Chain Acyl-CoA Dehydrogenase Deficiency via *ACADS* Gene Sequencing (Test #183)

Brief Description of Clinical Features: Short chain acyl-CoA dehydrogenase deficiency (SCADD, OMIM #201470) is a defect in the breakdown of fatty acids within the mitochondria causing accumulation of butyrylcarnitine and ethylmalonic acid in the blood and urine. Currently, the majority of new patients are identified through tandem mass spectrometry in neonatal screening, and they remain asymptomatic. However, older patients identified through clinical symptoms commonly have chiefly neuromuscular symptoms including hypotonia, developmental delay, and seizures. Other reported symptoms include speech delay, feeding difficulty, vomiting, hypoglycemia, and lethargy. Further studies are needed to clarify the relationship between mutations in the SCAD gene and disease, and the long term consequences of SCADD. (van Maldegem et al. *JAMA* 296:943-52, 2006; Jethva et al. *Mol Genet Metab* 95:195-200, 2008; Pedersen et al. *Hum Genet* 124:43-56, 2008).

Genetics: Short chain acyl-CoA dehydrogenase, encoded by the *ACADS* gene (OMIM #606886), catalyzes one of the steps in the breakdown of fatty acids with short carbon chains, particularly butyryl-CoA. SCADD is an autosomal recessive inborn error of metabolism. Unlike most other genetic diseases causing fatty acid oxidation defects, the vast majority of mutations reported to date in *ACADS* have been missense mutations. It may well be that complete absence of short chain acyl-CoA dehydrogenase activity is lethal. Two common sequence variants in *ACADS*, c.511C>T (p.Arg171Trp, rs1800556; frequency of T allele ~3%) and c.625G>A (p.Gly209Ser, rs17848088; frequency of A allele ~20%) impair folding and stability. These variants are thought to modify or even cause the disorder in combination with adverse cellular conditions, especially when homozygous for the rare alleles. Genotype-phenotype correlations have not been identified at this time, though genotype correlates well with biochemical profiles. (Corydon et al. *Pediatr Res* 49:18-23, 2001; van Maldegem et al. 2006; Waisbren et al. *Mol Genet Metab* 95:39-45, 2008).

Description of This Particular Test: Short chain acyl-CoA dehydrogenase is encoded by the exons 1 – 10 of the *ACADS* gene on chr 12q24. Testing is accomplished by amplifying the coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and capillary electrophoresis.

Reference Sequences: **Genomic:** NC_000012.1 **mRNA and Protein:** CCDS 9207.1

Indications for Test: Infants identified by newborn screening with SCADD.

Sensitivity of Test: Incidence of SCADD has been estimated at 1/33,000 births using a cut-off for butyrylcarnitine of 1.9µmol/L (Waisbren et al. 2008). Analytical sensitivity should be high because all mutations reported to date are expected to be detected by sequence analysis of genomic DNA.

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

Specimen Requirements: See bottom of page 2 of Requisition Form.

Price:	Sequencing of <i>ACADS</i>, Exons 1-10	\$ 540
CPT Codes:		
Sample Ascertainment	83890 \$ 30	DNA Isolation 83891 \$ 40
Amplification x8	83898 \$ 130	Sequencing x8 83904 \$ 210
Separation	83894 \$ 50	Interpretation/Report 83912 \$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/11) (CAP#: 7185561, AU ID: 1407125 expires 12/20/10)

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