

Very Long Chain Acyl-CoA Dehydrogenase Deficiency via *ACADVL* Gene Sequencing (Test #184)

Brief Description of Clinical Features: Very long chain acyl-CoA dehydrogenase deficiency (VLCADD, OMIM #201475) is a defect in the breakdown of very long chain (C14-C20) fatty acids within the mitochondria. The severity of VLCADD varies over a wide range and can be divided into three clinical groups: (1) Severe, early-onset, cardiac and multiorgan failure. Affected individuals present within the first few months of life with cardiomyopathy, arrhythmias, pericardial effusion, hepatomegaly, hypotonia, and episodes of hypoketotic hypoglycemia. (2) Hepatic or hypoketotic hypoglycemia. These individuals present in early childhood with hepatomegaly and hypoketotic hypoglycemia, but without the cardiac issues. (3) Later-onset episodic myopathic form. These individuals are diagnosed in adolescence or adult life with muscle weakness and pain, which can be induced by exercise. VLCADD may be detected through tandem mass spectrometry in routine neonatal screening, though affected individuals with milder phenotypes may not be identified during times of physiologic health. Incidence of VLCADD in the United States is estimated to be 1/30,000. For more information see Leslie et al. *GeneReviews* 2009 (www.genetests.org), Gregersen et al. *Hum Mut* 18:169-189, 2001 and Rinaldo et al. *Annu Rev Physiol* 64:477-502, 2002.

Genetics: Very long chain acyl-CoA dehydrogenase, encoded by the *ACADVL* gene, catalyzes the first step in the catabolism of fatty acids with 14-20 carbon atoms. VLCADD exhibits autosomal recessive inheritance. Hundreds of causative *ACADVL* mutations have been reported to date. Mutations are located throughout the gene and are roughly 60% missense and 40% frameshift, splicing, or nonsense. One mutation, p.Val283Ala, accounts for 20% of the pathologic alleles among those identified by newborn screening. Mutations which completely eliminate enzyme activity usually cause the most severe disease, while missense mutations resulting in some residual enzyme activity lead to milder childhood and adult onset forms (Andresen et al. *Am J Hum Genet* 64:479-494, 1999; Gregersen et al. 2001).

Description of This Particular Test: Very long chain acyl-CoA dehydrogenase is encoded by exons 1 – 20 of the *ACADVL* gene on chr 17p13. 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_000017.9 mRNA: NM_000018.2 mRNA and protein: CCDS 11090.1

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

Sensitivity of Test: Andresen et al. (1999) performed *ACADVL* gene sequencing on 55 VLCADD patients with demonstrated enzyme deficiency and found two likely causative mutations in 47 patients (85%) and one likely causative mutation in the remaining 8 patients. Boneh et al. (2006) found two causative mutations in 6 of 6 patients identified through neonatal screening. Analytical sensitivity should be high because nearly 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 page 4 of Requisition Form.

Price: Sequencing of *ACADVL*, Exons 1-20 \$ 740

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x12	83898 \$ 220	Sequencing x12	83904 \$ 320
Separation x1	83894 \$ 50	Interpretation/Report x1	83912 \$ 80

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

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