Very Long-Chain Acyl-CoA Dehydrogenase (ACADVL) Deficiency

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Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is an inherited disorder of mitochondrial long-chain fatty acid oxidation, resulting in an inability to properly break down very long-chain fatty acids into energy. This condition is associated with three phenotypes that vary in age of onset and severity. Morbidity and mortality are high in cases of acute presentation in a newborn. Testing for VLCAD deficiency may include biochemical testing (eg, acylcarnitine profile, carnitine profile, and organic acids) and genetic testing.

Disease Overview

Prevalence

Approximately 1/40,000

Phenotypes

Phenotype	Age of Onset	Signs and Symptoms
Severe early-onset cardiac and multiorgan failure VLCAD deficiency	First months of life	• Hypertrophic cardiomyopathy • Pericardial effusion • Arrhythmias • Hypoglycemia • Reye-like symptoms • Sudden infant death
Hepatic or hypoketotic hypoglycemic VLCAD deficiency	Early childhood	• Absence of cardiomyopathy • Fasting intolerance and Reye-like syndrome triggered by prolonged fasting or illness • Hepatomegaly • Increased liver function tests and elevated CPK
Later onset episodic myopathic VLCAD deficiency	Adolescence or adulthood	• Myopathy • Exercise-induced rhabdomyolysis • Myoglobinuria

CPK, creatine phosphokinase

Genetics

Gene

ACADVL (NM_000018)

Etiology

Pathogenic germline variants in the *ACADVL* gene

Featured ARUP Testing

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (ACADVL) Sequencing and Deletion/Duplication 3004419

Method: Massively Parallel Sequencing

- Preferred molecular test to diagnose VLCAD deficiency following clinical and/or biochemical presentations
- May also be used for carrier testing for the reproductive partner of an individual who is affected with or a carrier of VLCAD deficiency

Additional biochemical and genetic test options are available. If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate. Refer to the Laboratory Test Directory for more information.

Inheritance

Autosomal recessive

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and, in certain situations, to confirm variant calls.
- The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Sensitivity/Specificity

Clinical sensitivity: 95-97%[1]

Analytic sensitivity/specificity:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result as Listed in Patient Chart	Variant(s) Detected	Clinical Significance
Positive	Two pathogenic or likely pathogenic *ACADVL* variants detected	Confirms a diagnosis of VLCAD deficiency
See Note	One or more variants of uncertain significance detected	Unknown if variant(s) are disease causing or benign
	One pathogenic or likely pathogenic ACADVL variant detected	Individual is at least a carrier of VLCAD deficiency and may be affected if an undetected variant is present on the opposite chromosome

Result as Listed in Patient Chart	Variant(s) Detected	Clinical Significance
Negative	No pathogenic variants detected	Diagnosis of VLCAD deficiency is less likely, though not excluded

Limitations

- A negative result does not exclude a diagnosis of VLCAD deficiency.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the *ACADVL* gene
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants, due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions

References

1. Leslie ND, Valencia CA, Strauss AW, et al. Very long-chain acyl-coenzyme A dehydrogenase deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Last revision May 2021; accessed Sep 2021.

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