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

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 (e.g., acylcarnitine profile, carnitine profile, and organic acids) and genetic testing.

Disease Overview

Prevalence
Approximately 1/40,000

Phenotypes

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

CPK, creatine phosphokinase

Genetics

Gene
ACADVL (NM_000018)

Etiology
Pathogenic germline variants in the ACADVL gene

Inheritance
Autosomal recessive

Tests to Consider

**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

**Familial Targeted Sequencing 3005867**

**Method:** Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member’s test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

For additional genetic and biochemical tests, see Related Tests.
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%\(^1\)

Analytical sensitivity/specificity:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA Estimate(^a)) (% and 95% Credibility Region (%))</th>
<th>Analytical Specificity (NPA) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99 (96.9-99.4)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Deletions 1-10 bp(^b)</td>
<td>93.8 (84.3-98.2)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Insertions 1-10 bp(^b)</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Exon-level(^c) deletions</td>
<td>97.8 (90.3-99.8)  [2 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td></td>
<td>62.5 (38.3-82.6)  [single exon]</td>
<td></td>
</tr>
<tr>
<td>Exon-level(^d) duplications</td>
<td>83.3 (56.4-96.4)  [3 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

\(^a\) 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 analytical 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

<table>
<thead>
<tr>
<th>Result as Listed in Patient Chart</th>
<th>Variant(s) Detected</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Two pathogenic or likely pathogenic ACADVL variants detected</td>
<td>Confirms a diagnosis of VLCAD deficiency</td>
</tr>
<tr>
<td>See Note</td>
<td>One or more variants of uncertain significance detected</td>
<td>Unknown if variant(s) are disease causing or benign</td>
</tr>
<tr>
<td></td>
<td>One pathogenic or likely pathogenic ACADVL variant detected</td>
<td>Individual is at least a carrier of VLCAD deficiency and may be affected if an undetected variant is present on the opposite chromosome</td>
</tr>
<tr>
<td>Negative</td>
<td>No pathogenic variants detected</td>
<td>Diagnosis of VLCAD deficiency is less likely, though not excluded</td>
</tr>
</tbody>
</table>

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 allogenic 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


Additional Resources


Related Tests

Acylcarnitine Quantitative Profile, Plasma 0040033
Method: Tandem Mass Spectrometry

Carnitine Panel 0081110
Method: Tandem Mass Spectrometry

Organic Acids, Urine 0098389
Method: Gas Chromatography-Mass Spectrometry (GC-MS)