Capillary Malformation-Arteriovenous Malformation

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is a disorder of the vascular system characterized by enlarged capillaries that appear as small, round dots on the skin. Some affected individuals also have fast-flow vascular anomalies, including arteriovenous malformations (AVMs) or arteriovenous fistulas (AVFs) in the skin, muscle, bone, spine, or brain. These lesions may cause life-threatening complications such as bleeding, congestive heart failure, or neurological consequences. Additional manifestations include lymphatic abnormalities, recurrent epistaxis (CM-AVM2), dermal telangiectasias (CM-AVM2), and bier spots (CM-AVM2). Genetic testing can confirm diagnosis of RASA1-related CM-AVM disorder (CM-AVM1) or EPHB4-related CM-AVM disorder (CM-AVM2) in individuals with clinical findings suggestive of CM-AVM.

Disease Overview

Incidence

- Approximately 1/20,000 for CM-AVM1
- Approximately 1/12,000 for CM-AVM2

Genetics

Genes

- EPHB4 (NM_004444) and RASA1 (NM_002890)
- See Genes Tested table for more information

Inheritance

- Autosomal dominant
- De novo variants
  - Approximately 33% of cases for RASA1
  - Approximately 20% of cases for EPHB4
- Somatic mosaicism has been described

Penetrance

- EPHB4: 93%\(^1\)
- RASA1: 90-99%
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 next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

Clinical sensitivity is not well established but is estimated at 60%\(^2\)

- **EPHB4**
  - An estimated 10% of CM-AVM is attributed to EPHB4
    - Detected in 15% of individuals with sporadic or familial CMs with or without fast-flow lesions\(^1\)
  - To date, all described pathogenic variants are detectable by sequencing
  - Clinical sensitivity of deletion/duplication analysis is unknown
- **RASA1**
  - An estimated 50% of CM-AVM attributed to RASA1
  - Detected in approximately 30% of consecutive cases with or without CMs,\(^3\) with higher detection rate in individuals with multifocal CMs
  - Detected in 70% of individuals with multifocal CMs with or without fast-flow lesions\(^4\)
  - 92% of detectable RASA1 pathogenic variants are sequence variants and 8% are large deletions/duplications

Analytic Sensitivity

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate(^a) (%) and 95% Credibility Region</th>
<th>Analytic 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>
</tbody>
</table>

\(^a\)Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

\(^b\)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
### Variant Class

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<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate(a) (%) and 95% Credibility Region</th>
<th>Analytic Specificity (NPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertions 1-10 bp&lt;sup&gt;b&lt;/sup&gt;</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Exon-level&lt;sup&gt;c&lt;/sup&gt; deletions</td>
<td>97.8 (90.3-99.8) [2 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Exon-level&lt;sup&gt;c&lt;/sup&gt; duplications</td>
<td>83.3 (56.4-96.4) [3 exons or larger]</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

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<sup>b</sup>Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

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

### Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Variant(s) Detected</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Pathogenic <em>EPHB4</em> or <em>RASA1</em> variant detected</td>
<td>Confirms diagnosis of CM-AVM in a symptomatic individual</td>
</tr>
<tr>
<td>Negative</td>
<td>No known pathogenic <em>EPHB4</em> or <em>RASA1</em> variant detected</td>
<td>Reduces possibility of, but does not exclude, a diagnosis of CM-AVM</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Variant of uncertain clinical significance detected in <em>EPHB4</em> or <em>RASA1</em></td>
<td>Unclear if variant is disease causing or benign</td>
</tr>
</tbody>
</table>

### Limitations

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>MIM#</th>
<th>Disorder</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPB4</td>
<td>600011</td>
<td>CM-AVM2</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphatic malformation 7</td>
<td></td>
</tr>
<tr>
<td>RASA1</td>
<td>139150</td>
<td>CM-AVM1</td>
<td>AD</td>
</tr>
</tbody>
</table>

AD, autosomal dominant

References


Related Information

Hereditary Hemorrhagic Telangiectasia - HHT

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