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

Penetranace

- 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>
<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(^c) 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.

\(^b\)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

<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>
<th>Disorder Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHB4</td>
<td>600011</td>
<td>CM-AVM2</td>
<td>AD</td>
<td>Lymphatic malformation 7</td>
</tr>
<tr>
<td>RASA1</td>
<td>139150</td>
<td>CM-AVM1</td>
<td>AD</td>
<td></td>
</tr>
</tbody>
</table>

AD, autosomal dominant

References


Additional Resources


Hereditary Hemorrhagic Telangiectasia - HHT

Related Tests

Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing and Deletion/Duplication 2009337
Method: Massively Parallel Sequencing

Vascular Malformations Panel, Sequencing and Deletion/Duplication 2007384
Method: Massively Parallel Sequencing