# 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.

## Featured ARUP Testing

Capillary Malformation-Arteriovenous Malformation (CM-AVM) Panel, Sequencing and Deletion/Duplication 3003634

**Method:** Massively Parallel Sequencing

Use to detect CM-AVM. If vascular symptoms are expanded beyond CM-AVM, consider testing for a hereditary vascular malformation disorder. If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate. Refer to the Laboratory Test Directory for additional information.

## 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

| 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 |

[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 | Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region | Analytic Specificity (NPA) |
|---|---|---|
| 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]<br>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.

[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.

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Results

| Result | Variant(s) Detected | Clinical Significance |
|---|---|---|
| Positive | Pathogenic *EPHB4* or *RASA1* variant detected | Confirms diagnosis of CM-AVM in a symptomatic individual |
| Negative | No known pathogenic *EPHB4* or *RASA1* variant detected | Reduces possibility of, but does not exclude, a diagnosis of CM-AVM |
| Inconclusive | Variant of uncertain clinical significance detected in *EPHB4* or *RASA1* | Unclear if variant is disease causing or benign |

## 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

| Gene | MIM# | Disorder | Inheritance |
|---|---|---|---|
| *EPHB4* | 600011 | CM-AVM2<br>Lymphatic malformation 7 | AD |
| *RASA1* | 139150 | CM-AVM1 | AD |

AD, autosomal dominant

## References


1. Amyere M, Revencu N, Helaers R, et al. Germline loss-of-function mutations in EPHB4 cause a second form of capillary malformation-arteriovenous malformation (CM-AVM2) deregulating RAS-MAPK signaling. *Circulation*. 2017;136(11):1037-1048.

2. Bayrak-Toydemir P, Stevenson D. Capillary malformation-arteriovenous malformation syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Sep 2019; Accessed: Nov 2020]

3. Wooderchak-Donahue W, Stevenson DA, McDonald J , et al. RASA1 analysis: clinical and molecular findings in a series of consecutive cases. *Eur J Med Genet*. 2012;55(2):91-95.

4. Revencu N, Boon LM, Mendola A, et al. RASA1 mutations and associated phenotypes in 68 families with capillary malformation-arteriovenous malformation. *Hum Mutat*. 2013;34(12):1632-1641.


# Related Information

Hereditary Hemorrhagic Telangiectasia - HHT


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