

Capillary Malformation-Arteriovenous Malformation

Last Literature Review: December 2020 Last Update: July 2023

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.

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.

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 lesions¹
 - 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 lesions⁴
 - 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
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

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

^bVariants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

^cIn 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	Variant(s) Detected	Clinical Significance
Positive	Pathogenic <i>EPHB4</i> or <i>RASA1</i> variant detected	Confirms diagnosis of CM-AVM in a symptomatic individual
Negative	No known pathogenic <i>EPHB4</i> or <i>RASA1</i> variant detected	Reduces possibility of, but does not exclude, a diagnosis of CM-AVM
Inconclusive	Variant of uncertain clinical significance detected in <i>EPHB4</i> or <i>RASA1</i>	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
<i>EPHB4</i>	600011	CM-AVM2 Lymphatic malformation 7	AD
<i>RASA1</i>	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, eds. *GeneReviews*. University of Washington, Seattle. 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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