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. 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.

Tests to Consider

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

Method: Massively Parallel Sequencing/ Multiplex Ligation-dependent Probe Amplification

Preferred test to detect CM-AVM; assesses for *RASA1*-associated CM-AVM1 and *EPHB4*-associated CM-AVM2

See Related Tests

Disease Overview

Incidence

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

Symptoms/Manifestations

- Multifocal CMs; commonly localized on skin of the trunk, limbs, or face
  - Fast flow lesions
    - AVM, AVF, and vein of Galen malformation located in the brain, spine, skin, or muscle may cause life-threatening complications
      - Bleeding
      - Congestive heart failure
      - Neurological consequences
    - In Parkes Weber Syndrome (PKWS), diffuse subcutaneous/intramuscular micro AVFs associated with hypertrophy of the involved extremity
- Lymphatic abnormalities
- Recurrent epistaxis (CM-AVM2)
- Dermal telangiectasias (CM-AVM2)
- Bier spots (CM-AVM2)

Genetics

Genes

EPHB4 and *RASA1*

Inheritance

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

Penetrance

- *EPHB4*: 93%[1]
- *RASA1*: 90-99%

Test Interpretation

Genes Tested

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

Sensitivity/Specificity

- Clinical sensitivity is not well established but is estimated at 65%
  - *EPHB4*
    - An estimated 15% of CM-AVM 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 0-70% of CM-AVM attributed to *RASA1*
    - Detected in ~30% of consecutive cases with or without CMs,[2] with higher detection rate in individuals with multifocal CMs
    - Detected in 70% of individuals with multifocal CMs with or without fast-flow lesions[3]
    - 92% of detectable *RASA1* pathogenic variants are sequence variants
    - 8% of detectable *RASA1* pathogenic variants are large deletions/duplications
- Analytical sensitivity
  - For multiplex ligation-dependent probe amplification (MLPA) of *RASA1*: 99%
  - For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

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

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

Limitations

- A negative result does not exclude a diagnosis of CM-AVM.
- 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
  - Large deletions/duplications in *EPHB4* gene
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - 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

AD, autosomal dominant; CM-AVM, capillary malformation-arteriovenous malformation

Gene	MIM#	Disorder	Inheritance
EPHB4	600011	CM-AVM2 Lymphatic malformation 7	AD
RASA1	139150	CM-AVM1	AD

AD, autosomal dominant; CM-AVM, capillary malformation-arteriovenous malformation

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. PubMed

2. 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. PubMed

3. 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. PubMed

4. 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]

Additional Resources

Wooderchak-Donahue WL, Johnson P, McDonald J, et al. Expanding the clinical and molecular findings in RASA1 capillary malformation-arteriovenous malformation. Eur J Hum Genet. 2018;26(10):1521-1536. PubMed

Related Information

Hereditary Hemorrhagic Telangiectasia - HHT

Related Tests

Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing and Deletion/Duplication 2009337

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Vascular Malformations Panel, Sequencing and Deletion/Duplication 2007384

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review December 2020 | Last Update January 2021