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. Genetic testing can confirm diagnosis of a *RASA1*-related CM-AVM disorder (CM-AVM1), or an *EPHB4*-related CM-AVM disorder (CM-AVM2), in individuals with symptoms suggestive of CM-AVM.

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, arteriovenous fistula (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, but uncommon)
- Telangiectasias: dermal (CM-AVM2, but less common than CMs)

Genetics

Genes

EPHB4 and *RASA1*

Inheritance

Autosomal dominant

Penetrance

- *EPHB4*: 93%[1]
- *RASA1*: 90-95%

De novo Variants

~33% of cases for *RASA1*

Variants

- 92% of *RASA1* pathogenic variants detectable by sequencing
- 8% of *RASA1* pathogenic variants detectable by deletion/duplication analysis

Tests to Consider

Capillary Malformation-Arteriovenous Malformation (EPHB4 and RASA1) Sequencing, and (RASA1) Deletion/Duplication 3001132

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Most comprehensive DNA test for CM-AVM (CM-AVM1 and CM-AVM2)

RASA1-Related Disorders (RASA1) Sequencing and Deletion/Duplication 2007852

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Preferred DNA test for *RASA1*-related disorders (CM-AVM1) only

Capillary Malformation-Arteriovenous Malformation 2 (EPHB4) Sequencing 3001129

Method: Polymerase Chain Reaction/Sequencing

DNA test for *EPHB4*-related CM-AVM (CM-AVM2) only

Related Tests

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

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

Most comprehensive test to determine the cause of a telangiectasia/AVM disorder

Vascular Malformations Panel, Sequencing and Deletion/Duplication 2007384

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

Preferred DNA test to confirm clinical diagnosis of a heritable vascular malformation disorder

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity for CM-AVM is not well established and varies based on clinical manifestations; estimates based on available publications
  - *EPHB4*
    - Sequencing: at least 15%
      - Detected in 15% of individuals with sporadic or familial CMs with or without fast-flow lesions[1]
    - Deletion/duplication: unknown
  - *RASA1*
    - Sequencing: ~30-70%
      - 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]
    - Deletion/duplication: ~8%[4]
- Analytical sensitivity/specificity for sequencing of *EPHB4* and *RASA1*, and MLPA of *RASA1*: 99%

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
  - Large deletions/duplications in *EPHB4*
  - Regulatory region and deep intronic variants
  - Breakpoints for large deletions/duplications identified in *RASA1*
  - Variants in genes other than *EPHB4* and *RASA1*

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

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
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