Capillary Malformation-Arteriovenous Malformation

Capillary malformation-arteriovenous malformation syndrome (CM-AVM) 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 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

Tests to Consider

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

**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**

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

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

**RASA1-Related Disorders (RASA1) Sequencing**

**Method:** Polymerase Chain Reaction/Sequencing

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

**Capillary Malformation-Arteriovenous Malformation 2 (EPHB4) Sequencing**

**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**

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

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

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity for CM-AVM: 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


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
Content Review January 2019 | Last Update February 2020
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