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

**Penetrance**
- EPHB4 – 93% (Amyere, 2017)
- 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

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<tr>
<th>Test Description</th>
<th>Method Details</th>
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<tr>
<td>Capillary Malformation-Arteriovenous Malformation</td>
<td>Sequencing and Deletion/Duplication 2001132</td>
<td>Most comprehensive DNA test for CM-AVM (CM-AVM1 and CM-AVM2)</td>
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<tr>
<td>(EPHB4 and RASA1)</td>
<td>Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification</td>
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<td>RASA1-Related Disorders (RASA1)</td>
<td>Sequencing and Deletion/Duplication 2007852</td>
<td>Preferred DNA test for RASA1-related disorders (CM-AVM1) only</td>
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<td>Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification</td>
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<td>RASA1-Related Disorders (RASA1)</td>
<td>Sequencing 2002730</td>
<td>DNA test for RASA1-related disorders (CM-AVM1) only</td>
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<td>Method: Polymerase Chain Reaction/Sequencing</td>
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<td>Capillary Malformation-Arteriovenous Malformation 2</td>
<td>Sequencing 3001129</td>
<td>DNA test for EPHB4-related CM-AVM (CM-AVM2) only</td>
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<tr>
<td>(EPHB4)</td>
<td>Method: Polymerase Chain Reaction/Sequencing</td>
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**Related Tests**
- Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing and Deletion/Duplication 2009337
- Vascular Malformations Panel, Sequencing and Deletion/Duplication 2007384
**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 (Amyere, 2017)
    - Deletion/duplication – unknown
  - **RASA1**
    - Sequencing – ~30-70%
      - Detected in 30% of consecutive cases with or without CMs (Wooderchak-Donahue, 2012), with higher detection rate in individuals with multifocal CMs
      - Detected in 70% of individuals with multifocal CMs with or without fast-flow lesions (Revencu, 2013)
    - Deletion/duplication – ~8% (Bayrak-Toydemir, 2016)
  - 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