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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

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

RASA1-Related Disorders (RASA1) Sequencing 2002730
Method: Polymerase Chain Reaction/Sequencing

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

TEST INTERPRETATION

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

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*

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RELATED INFORMATION

Hereditary Hemorrhagic Telangiectasia - HHT

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