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

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**


