RASA1-Related Disorders

Indications for Ordering

Confirm diagnosis in individuals with findings suggestive of capillary malformation-arteriovenous malformation (CM-AVM) syndrome or Parkes Weber syndrome (PKWS)

Test Description

- Polymerase chain reaction followed by bidirectional sequencing of *RASA1* coding regions and intron/exon boundaries
- Multiplex ligation-dependent probe amplification to detect large coding region deletions/duplications

Tests to Consider

Primary tests

RASA1-Related Disorders (*RASA1*) Sequencing and Deletion/Duplication 2007852
- Preferred DNA test for *RASA1*-related disorders

RASA1-Related Disorders (*RASA1*) Sequencing 2002730
- Acceptable DNA test for *RASA1*-related disorders

Related tests

Vascular Malformations Panel, Sequencing and Deletion/Duplication, 14 Genes 2007384
- Preferred DNA test to confirm clinical diagnosis of a heritable vascular malformation disorder

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence – ~1/100,000

Symptoms

Multifocal capillary malformations and/or telangiectases
- Commonly localized on limbs/face
- May be associated with a fast-flow lesion
  - Arteriovenous malformation (AVM)
  - Arteriovenous fistula (AVF)
    - In PKWS, diffuse subcutaneous/intramuscular micro-AVFs associated with hypertrophy of the involved extremity
  - AVM/AVF in the brain, spine, skin, or muscle may cause life-threatening complications
    - Bleeding
    - Congestive heart failure
    - Neurological consequences

Genetics

Gene – *RASA1*

Inheritance – autosomal dominant

Penetrance – 90-95%

De novo variants – ~1/3 of cases

Variants – ~50 identified

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity
  - Sequencing – ~70%
  - Deletion/duplication – ~5%
- Analytical sensitivity/specificity – 99%

Results
- Positive
  - Diagnosis confirmed
  - Clinical diagnoses may include
    - CM-AVM syndrome
    - PKWS
- Negative – diagnosis of a *RASA1*-related disorder unlikely but has not been excluded
- Inconclusive – gene variant detected, but it is unclear whether variant is benign or pathogenic

Limitations
- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
  - Regulatory region and deep intronic variants
  - Single base-pair substitutions
  - Small deletions/duplications
  - Breakpoints for large deletions/duplications
  - Variants in genes other than *RASA1*

References

- Bayrak-Toydemir P, Stevenson D. RASA1-Related Disorders. 2011 Feb 22 [Updated 2013 Dec 19]. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015 (www.ncbi.nlm.nih.gov/books/NBK52764/)
- Wooderchak-Donahue W, Stevenson D, et al. Expanding the clinical and molecular findings in RASA1 cases. Presented at American College of Medical Genetics and Genomics, Annual Clinical Genetics Meeting, March 24-28, 2015, Salt Lake City, UT (publication in progress)