

RASA1 Sequencing

TO DETERMINE THE ETIOLOGY OF CAPILLARY- ARTERIOVENOUS MALFORMATIONS

Disease Overview

- Vascular malformations are often identified at birth, grow proportionally with the child, and may become more pronounced at puberty.
- Capillary malformations (CM or port-wine stain) affect approximately 0.3 percent of newborns and are characterized by flat red, pink, or purple cutaneous lesions.
- Arteriovenous malformations (AVM) and arteriovenous fistula (AVF) result from abnormal connections of arteries and veins. Screening and/or treatment for these fast-flow lesions is often recommended, as life-threatening complications such as bleeding, congestive heart failure, or neurologic consequences may result.
- Determining the etiology of CM is important, as morbidity, prognosis, and treatment may differ based on their association with other vascular malformations or an underlying syndrome. The distribution of CM may suggest an association with other vascular abnormalities or a hereditary condition, including:
 - CM-AVM syndrome: characterized by small, multifocal, randomly-distributed CM, which are usually pink or red in color and commonly associated with an AVM/AVF. CM-AVM often affects the limbs and face. CM-AVM syndrome is associated with *RASA1* germline mutations.
 - Parkes-Weber syndrome: a segmental overgrowth syndrome characterized by large cutaneous vascular stain with multiple underlying micro-AVF. Parkes-Weber syndrome is associated with *RASA1* germline mutations when multi-focal CM are present; otherwise, it's believed to be sporadic.¹
 - Klippel-Trenaunay syndrome: characterized by capillary malformations, venous malformations or varicose veins, and hypertrophy of the affected tissues. Phenotype overlaps with Parkes-Weber syndrome, but association with *RASA1* germline mutations is not well defined.
 - Hereditary hemorrhagic telangiectasia (HHT): characterized by pulmonary, hepatic, or brain AVM in combination with telangiectases, typically on the lips, fingers, and oral mucosa. The skin of the limbs and trunk is typically unaffected. The punctuate appearance and location of the oral/dermal telangiectases differ from the CM of CM/AVM syndrome. HHT is associated with *ACVRL1* and *ENG* germline mutations.
 - *PTEN* hamartoma tumor syndrome (PHTS): AVMs are often intramuscular and multifocal, associated with ectopic fat, and destroy tissue architecture. PHTS is associated with *PTEN* germline mutations.

Epidemiology

Vascular lesions have an equal sex distribution.

Genetics

- Autosomal dominant.
- Approximately two thirds of *RASA1* mutations are inherited, and one third are suspected to be de novo in CM-AVM syndrome in two small series.^{1,2}
- Germline *RASA1* mutations are more likely to be detected in familial (~90 percent) versus sporadic (~60 percent) cases, according to one series.¹
- Animal models suggest homozygosity is embryonic lethal.
- *RASA1* encodes the p120RasGAP protein, which regulates the Ras/MAPkinase pathway involved with vascular development and cellular apoptosis. Phenotypic variability may be explained by p120RasGAP function in signaling growth factors involved with proliferation, migration, and cell death.
- Other findings associated with *RASA1* mutations include tumors of the nervous system (e.g., neurofibroma or optic glioma).¹

Indication for Ordering

Diagnostic confirmation in individuals with characteristic findings.

Contraindications

- Prenatal testing.
- Testing for individuals with a previously identified familial *RASA1* mutation (please order [Targeted Sequencing, Familial Mutation, ARUP test #2001961](#)).

Interpretation

- Negative: No *RASA1* gene mutations are detected.
- Positive: The detection of a *RASA1* gene mutation previously reported in individuals with a *RASA1*-related syndrome (CM-AVM, Parkes-Weber syndrome, etc.).
- Gene sequencing may reveal novel mutation(s); thus, the determination of clinical significance (benign or deleterious) may be unclear.

Limitations

- Genes associated with CM other than *RASA1* will not be tested.
- Large deletions, deep intronic mutations, and promoter mutations in the *RASA1* gene will not be detected.
- Rare diagnostic errors may occur due to primer-site mutations.

Methodology

- PCR followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *RASA1* gene.
- Clinical sensitivity is 75 percent for CM-AVM based on one study; unknown for other *RASA1*-related conditions.¹
- Analytical sensitivity and specificity are 99 percent.

Related Test

Familial Mutation, Targeted Sequencing (2001961)

References

1. Revencu N, et al. Parkes Weber syndrome, vein of Galen aneurismal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Hum Mut* 2008;29:959–65.
2. Boon LM, et al. RASA1: variable phenotype with capillary and arteriovenous malformations. *Curr Opin Genet Dev* 2005;15:265–9.
3. Brunetti-Pierri N, et al. Parkes Weber syndrome occurring in a family with capillary malformations. *Clin Dysmorphol* 2007; 16:167–171.
4. Eerola I, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. *Am J Hum Gen* 2003;73:1240–9.
5. Brouillard P and Vikkula M. Genetic causes of vascular malformations. *Hum Mol Genet* 2007;16:R140–9.

Test Information

2002730

RASA1-Related Disorders (*RASA1*)

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.