Vascular Malformations Panel, Sequencing and Deletion/Duplication

Last Literature Review: May 2022 Last Update: October 2023

Vascular malformation syndromes are caused by defects of blood vessels, which can affect multiple vessel types (venous, arterial, capillary, or combined). Examples include capillary malformation, arteriovenous malformation, cerebral cavernous malformation (CCM), glomuvenous malformation, hereditary hemorrhagic telangiectasia (HHT), multiple cutaneous and mucosal venous malformations, pulmonary arterial hypertension, and hereditary lymphedema syndromes. Potential findings of vascular malformation syndromes include hemorrhage and/or epistaxis, localized pain and/or lymphedema, destruction or deformation of surrounding tissue, localized intravascular coagulopathy (LIC), stroke, and congestive heart failure. If no single specific diagnosis is strongly suspected, a multigene panel test can confirm a clinical diagnosis of a hereditary vascular malformation disorder.

Featured ARUP Testing

Vascular Malformations Panel, Sequencing and Deletion/Duplication 2007384

Method: Massively Parallel Sequencing

- Use to confirm a clinical diagnosis of a hereditary vascular malformation disorder if no single specific diagnosis is strongly suspected.
- If an individual meets clinical criteria for a specific disorder or if a specific diagnosis is suspected, consider more targeted gene testing first.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Genetics

Genes

Analysis includes the coding regions and intron-exon boundaries of the genes tested (see Genes Tested table), the 5' untranslated region of *ENG*, a region of *ACVRL1* intron 9 encompassing the CT-rich variant hotspot region, and select *PTEN* promoter variants.

Etiology

Pathogenic variants in vascular malformation genes lead to defects of blood vessels that can cause fast-flow or slow-flow lesions, shunting, swelling, or skin findings. For some disorders, this may lead to potentially life-threatening hemorrhage, stroke, or heart failure.

Prevalence

Syndrome	Prevalence
HHT	1 in 5,000 to 1 in 10,000[1,2]
CCM	1 in 2,000 to 1 in 10,000[3]
CM-AVM	*RASA1*-CM-AVM: 1 in 20,000[4] *EPHB4*-CM-AVM: 1 in 12,000[4]
PTEN hamartoma tumor syndrome:	1 in 200,000[5]
AKT1-related proteus syndrome	1 in 1 million[6]

CM-AVM, capillary malformation-arteriovenous malformation syndrome

Sources: McDonald, 2017[1]; Faughnan, 2020[2]; Zafar, 2019[3]; Amyere, 2017[4]; Nelen, 1999[5]; Biesecker, 2019[6]

Genotype-Phenotype Correlation

- Vascular malformation syndromes are typically categorized according to vessel type affected and fast- versus slow-flow lesions.
- Most vascular malformations are sporadic.
- Inherited forms are characterized by multiple lesions, which are often smaller and less often congenital than their sporadic counterparts.
- Penetrance is often age-related and variable.

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.
- Bidirectional Sanger sequencing is performed on the following gene(s):
  - *PTEN* (NM_000314) 9

Clinical Sensitivity

Variable and dependent upon specific disorder

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [Single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; PPA, positive percent agreement; NPA, negative percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a heritable form of a vascular malformation disorder.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:

- Variants outside the coding regions and intron-exon boundaries of the targeted genes
- Regulatory region variants and deep intronic variants
- Breakpoints of large deletions/duplications
- The following exons are not sequenced due to technical limitations of the assay:
  - *CCM2* (NM_001363458) exon(s) 7
  - *CCM2* (NM_001363459) exon(s) 6
  - *FLT4* (NM_001354989) exon(s) 30
  - *GJC2* (NM_020435) partial exon(s) 2(Chr1:228346380-228346419)
  - *PTEN* (NM_000314) exon(s) 9
  - *PTEN* (NM_001304717) exon(s) 10
  - *PTEN* (NM_001304718) exon(s) 9
  - *SOX18* (NM_018419) partial exon(s) 1(Chr20:62680707-62680791)
  - *STAMBP* (NM_001353969) exon(s) 10
  - *STAMBP* (NM_001353970) exon(s) 11
  - *STAMBP* (NM_001353976) exon(s) 10
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - *CCM2* (NM_001363458) 7; *CCM2* (NM_001363459) 6; *ENG* (NM_001114753) 1; *ENG* (NM_000118) 1; *FLT4* (NM_001354989) 30; *GLMN* (NM_053274) 16; *GLMN* (NM_001319683) 15; *PIEZO1* (NM_001142864) 1,25,47; *PTEN* (NM_000314) 9; *PTEN* (NM_001304717) 1,10; *PTEN* (NM_001304718) 9; *STAMBP* (NM_001353969) 10; *STAMBP* (NM_001353970) 11; *STAMBP* (NM_001353976) 10

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ACVRL1	601284	Hereditary hemorrhagic telangiectasia, type 2	AD
AKT1	164730	Proteus syndrome	AD with somatic mosaicism
BMPR2	600799	Primary pulmonary hypertension 1 Pulmonary venoocclusive disease 1, autosomal dominant	AD
CCBE1	612753	Hennekam lymphangiectasia-lymphedema syndrome 1	AR
CCM2	607929	Cerebral cavernous malformations 2	AD
EIF2AK4	609280	Pulmonary venoocclusive disease 2, autosomal recessive	AR
ELMO2	606421	Primary intraosseous vascular malformation	AR
ENG	131195	Hereditary hemorrhagic telangiectasia type 1	AD
EPHB4	600011	Capillary malformation-arteriovenous malformation syndrome	AD
FAT4	612411	Van Maldergem syndrome 2	AR

AD, autosomal dominant; AR, autosomal recessive

Gene	MIM Number	Disorder	Inheritance
		Hennekam lymphangiectasia-lymphedema syndrome 2	
FLT4	136352	Hereditary lymphedema IA Capillary infantile hemangioma	AD
FOXC2	602402	Lymphedema-distichiasis syndrome	AD
GATA2	137295	Primary lymphedema with myelodysplasia Emberger syndrome	AD
GDF2 (BMP9)	605120	Hereditary hemorrhagic telangiectasia type 5	AD
GJC2	608803	Hereditary lymphedema IC	AD
GLMN	601749	Glomuvenous malformations	AD
KCNK3	603220	Primary pulmonary hypertension 4	AD
KRIT1	604214	Cerebral cavernous malformations	AD
PDCD10	609118	Cerebral cavernous malformations 3	AD
PIEZO1	611184	Hereditary lymphedema III	AR
PTEN	601728	*PTEN* hamartoma tumor syndrome *PTEN*-related Proteus syndrome	AD
RASA1	139150	Capillary malformation-arteriovenous malformation syndrome Parkes Weber syndrome	AD
SMAD4	600993	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome	AD
SMAD9	603295	Primary pulmonary hypertension 2	AD
SOX18	601618	Hypotrichosis-lymphedema-telangiectasia-renal defect syndrome	AD
		Hypotrichosis-lymphedema-telangiectasia syndrome	AR
STAMBP	606247	Microcephaly-capillary malformation syndrome	AR
TEK	600221	Multiple cutaneous and mucosal venous malformations	AD
VEGFC	601528	Hereditary lymphedema ID	AD

AD, autosomal dominant; AR, autosomal recessive

References

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2. Faughnan ME, Mager JJ, Hetts SW, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *Ann Intern Med*. 2020;173(12):989-1001.

3. Zafar A, Quadri SA, Farooqui M, et al. Familial cerebral cavernous malformations. *Stroke*. 2019;50(5):1294-1301.

4. Amyere M, Revencu N, Helaers R, et al. Germline loss-of-function mutations in EPHB4 cause a second form of capillary malformation-arteriovenous malformation (CM-AVM2) deregulating RAS-MAPK signaling. *Circulation*. 2017;136(11):1037-1048.

5. Nelen MR, Kremer H, Konings IB, et al. Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations. *Eur J Hum Genet*. 1999;7(3):267-73.

6. Biesecker LG, Sapp JC. Proteus syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Last update Jan 2019; accessed Mar 2022.

Related Information

Hereditary Hemorrhagic Telangiectasia - HHT
Pulmonary Arterial Hypertension Panel, Sequencing and Deletion/Duplication

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