

Vascular Malformations Panel, Sequencing and Deletion/Duplication

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.

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	<i>RASA1</i> -CM-AVM: 1 in 20,000 ⁴ <i>EPHB4</i> -CM-AVM: 1 in 12,000 ⁴
<i>PTEN</i> hamartoma tumor syndrome:	1 in 200,000 ⁵
<i>AKT1</i> -related proteus syndrome	1 in 1 million ⁶

CM-AVM, capillary malformation-arteriovenous malformation syndrome

Sources: McDonald, 2017¹; Faughnan, 2020²; Zafar, 2019³; Amyere, 2017⁴; Nelen, 1999⁵; Biesecker, 2019⁶

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.

Tests to Consider

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.

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Assess for a known familial sequence variant previously identified in a family member

See [Related Tests](#)

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

^aPPA 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.

^bVariants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

^cIn 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
<i>ACVRL1</i>	601284	Hereditary hemorrhagic telangiectasia, type 2	AD
<i>AKT1</i>	164730	Proteus syndrome	AD with somatic mosaicism
<i>BMPR2</i>	600799	Primary pulmonary hypertension 1 Pulmonary venoocclusive disease 1, autosomal dominant	AD
<i>CCBE1</i>	612753	Hennekam lymphangiectasia-lymphedema syndrome 1	AR
<i>CCM2</i>	607929	Cerebral cavernous malformations 2	AD
<i>EIF2AK4</i>	609280	Pulmonary venoocclusive disease 2, autosomal recessive	AR
<i>ELMO2</i>	606421	Primary intraosseous vascular malformation	AR
<i>ENG</i>	131195	Hereditary hemorrhagic telangiectasia type 1	AD
<i>EPHB4</i>	600011	Capillary malformation-arteriovenous malformation syndrome	AD
<i>FAT4</i>	612411	Van Maldergem syndrome 2 Hennekam lymphangiectasia-lymphedema syndrome 2	AR
<i>FLT4</i>	136352	Hereditary lymphedema IA Capillary infantile hemangioma	AD
<i>FOXC2</i>	602402	Lymphedema-distichiasis syndrome	AD
<i>GATA2</i>	137295	Primary lymphedema with myelodysplasia Emberger syndrome	AD
<i>GDF2 (BMP9)</i>	605120	Hereditary hemorrhagic telangiectasia type 5	AD
<i>GJC2</i>	608803	Hereditary lymphedema IC	AD
<i>GLMN</i>	601749	Glomuvenous malformations	AD

Gene	MIM Number	Disorder	Inheritance
<i>KCNK3</i>	603220	Primary pulmonary hypertension 4	AD
<i>KRIT1</i>	604214	Cerebral cavernous malformations	AD
<i>PDCD10</i>	609118	Cerebral cavernous malformations 3	AD
<i>PIEZO1</i>	611184	Hereditary lymphedema III	AR
<i>PTEN</i>	601728	<i>PTEN</i> hamartoma tumor syndrome <i>PTEN</i> -related Proteus syndrome	AD
<i>RASA1</i>	139150	Capillary malformation-arteriovenous malformation syndrome Parkes Weber syndrome	AD
<i>SMAD4</i>	600993	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome	AD
<i>SMAD9</i>	603295	Primary pulmonary hypertension 2	AD
<i>SOX18</i>	601618	Hypotrichosis-lymphedema-telangiectasia-renal defect syndrome	AD
		Hypotrichosis-lymphedema-telangiectasia syndrome	AR
<i>STAMBP</i>	606247	Microcephaly-capillary malformation syndrome	AR
<i>TEK</i>	600221	Multiple cutaneous and mucosal venous malformations	AD
<i>VEGFC</i>	601528	Hereditary lymphedema ID	AD

AD, autosomal dominant; AR, autosomal recessive

References

- McDonald J, Peyerit RE. [Hereditary hemorrhagic telangiectasia](#). In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Updated: Feb 2017; Accessed: Oct 2020]
- Faughnan ME, Mager JJ, Hetts SW, et al. [Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia](#). *Ann Intern Med*. 2020. [Published online ahead of print Sep 2020].
- Zafar A, Quadri SA, Farooqui M, et al. [Familial cerebral cavernous malformations](#). *Stroke*. 2019;50(5):1294-1301.
- 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.
- 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.
- Biesecker LG, Sapp JC. [Proteus syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Jan 2019; Accessed: Mar 2022]

Additional Resources

Bayrak-Toydemir P, Stevenson D. [Capillary malformation-arteriovenous malformation syndrome](#). In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Sep 2019; Accessed: Nov 2020]

Related Information

[Hereditary Hemorrhagic Telangiectasia - HHT](#)
[Pulmonary Arterial Hypertension Panel, Sequencing and Deletion/Duplication](#)

Related Tests

[Capillary Malformation-Arteriovenous Malformation \(CM-AVM\) Panel, Sequencing and Deletion/Duplication 3003634](#)

Method: Massively Parallel Sequencing/ Multiplex Ligation-dependent Probe Amplification

[Cerebral Cavernous Malformation Panel, Sequencing and Deletion/Duplication 3002286](#)

Method: Massively Parallel Sequencing

[Hereditary Hemorrhagic Telangiectasia \(HHT\) Panel, Sequencing and Deletion/Duplication 2009337](#)

Method: Massively Parallel Sequencing

[Pulmonary Arterial Hypertension \(PAH\) Panel, Sequencing and Deletion/Duplication 2009345](#)

Method: Massively Parallel Sequencing

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology, 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
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