# 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). If no single specific diagnosis is strongly suspected, a DNA test can confirm clinical diagnosis of a genetic-related vascular malformation disorder.

## Tests to Consider

Vascular Malformations Panel, Sequencing and Deletion/Duplication 2007384

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Preferred DNA test to confirm clinical diagnosis of a genetic-related vascular malformation disorder, such as a capillary malformation, arteriovenous malformation, cerebral cavernous malformation, glomuvenous malformation, hereditary hemorrhagic telangiectasia, multiple cutaneous and mucosal venous malformations, pulmonary arterial hypertension, or hereditary lymphedema syndrome, if no single specific diagnosis is strongly suspected.

See Related Tests

## Disease Overview

### Findings

- Hemorrhage and/or epistaxis
- Localized pain and/or lymphedema
- Destruction/deformation of surrounding tissue
- Localized intravascular coagulopathy (LIC)
- Stroke or congestive heart failure
- Pulmonary arterial hypertension (PAH)

### Etiology

Pathogenic variants in vascular malformation genes lead to defects of blood vessels, causing 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

- Hereditary hemorrhagic telangiectasia (HHT): 1 in 10,000
- Familial cerebral cavernous malformation (CCM): 1 in 2,000 to 10,000
- *RASA1*-related disorders (CM-AVM, Parkes Weber): approximately 1 in 100,000
- Pulmonary Arterial Hypertension (PAH): 1-2/100,000
- *PTEN*-related Proteus syndrome (PS)/Proteus-like syndrome (PLS): estimated <1 in 1,000,000
- Juvenile polyposis/hereditary hemorrhagic telangiectasia (JP/HHT) syndrome: approximately 1 in 100,000

### Inheritance

- Autosomal recessive for *CCBE1*, *EIF2AK4*, *ELMO2*, *FAT4*, *PIEZO1*, and *STAMBP*
- Autosomal dominant and autosomal recessive for *SOX18*
- Autosomal dominant with somatic mosaicism for *AKT1* and *PIK3CA*
- Autosomal dominant for all other genes

### Genotype-Phenotype Correlation

- Vascular malformation syndromes are typically categorized according to vessel type affected and fast- vs. 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 Description

See the Genes Tested table for the coding regions and intron-exon boundaries of 30 genes, the 5' untranslated region of *ENG*, and a region of *ACVRL1* intron 9 encompassing the CT-rich variant hotspot region.

## Clinical Sensitivity

Variable and dependent upon specific disorder

## Testing Strategy

If an individual meets clinical criteria for a specific disorder or if a specific diagnosis is suspected, consider more targeted gene testing first. (See Related Tests.)

## 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
  - Deletions/duplications in *AKT1*, *EIF2AK4*, *ELMO2*, *EPHB4*, *FAT4*, *GATA2*, *PIEZO1*, *PIK3CA*, *SMAD9*, *SOX18*, *STAMBP*, *VEGFC*
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *PIK3CA* (NM_006218) 10,11,12,13,14
    - *SOX18* (NM_018419) 1
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - *FLT4* (NM_002020) 30; *FLT4* (NM_182925) 20, 22; *GLMN* (NM_053274) 11; *PTEN* (NM_000314) 8, 9; *PTEN* (NM_001304717) 1; *TEK* (NM_000459) 1

## Analytical Sensitivity

For massively parallel sequencing:

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) | Analytical Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|
| SNVs | 99.2 | 96.9-99.4 |
| Deletions 1-10 bp | 93.8 | 84.3-98.2 |
| Deletions 11-44 bp | 100 | 87.8-100 |
| Insertions 1-10 bp | 94.8 | 86.8-98.5 |
| Insertions 11-23 bp | 100 | 62.1-100 |

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

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

## Genes Tested

| Gene | MIM Number | Disorder | Inheritance |
|---|---|---|---|

| 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<br>Pulmonary venoocclusive disease 1, autosomal dominant | AD |
| *CAV1* | 601047 | Primary pulmonary hypertension 3<br>Partial lipodystrophy, congenital cataracts, and neurodegeneration<br>Congenital generalized lipodystrophy type 3 | 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<br>Hennekam lymphangiectasia-lymphedema syndrome 2 | AR |
| *FLT4* | 136352 | Hereditary lymphedema IA<br>Capillary infantile hemangioma | AD |
| *FOXC2* | 602402 | Lymphedema-distichiasis syndrome | AD |
| *GATA2* | 137295 | Primary lymphedema with myelodysplasia<br>Emberger syndrome | AD |
| *GDF2 (BMP9)* | 605120 | Hereditary hemorrhagic telangeictasia 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 |

AD, autosomal dominant; AR, autosomal recessive

| Gene | MIM Number | Disorder | Inheritance |
|---|---|---|---|
| *PIK3CA* | 171834 | Megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP)<br>Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal/spinal abnormalities (CLOVES)<br>Capillary malformation of the lower lip, lymphatic malformation of face and neck, asymmetry of face and limbs, and partial/generalized overgrowth (CLAPO) | AD with somatic mosaicism |
| *PTEN* | 601728 | *PTEN*-related Proteus syndrome<br>*PTEN* hamartoma tumor syndrome | AD |
| *RASA1* | 139150 | Capillary malformation-arteriovenous malformation<br>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

## 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]

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: Feb 2020]

McDonald J, Pyeritz RE. Hereditary hemorrhagic telangiectasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Last update: Feb 2017; Accessed: Oct 2020]

Tournier-Lasserve E. Familial cerebral cavernous malformation. Orphanet. [Last update: Mar 2014; Accessed: Nov 2018]

Peacock AJ, Murphy NF, McMurray JJV, et al. An epidemiological study of pulmonary arterial hypertension. Eur Respir J. 2007;30(1):104-109. PubMed

Williams JCB, Hamilton K, Shiller M, et al. Combined juvenile polyposis and hereditary hemorrhagic telangiectasia. Proc (Bayl Univ Med Cent). 2012;25(4):360-364. PubMed


## Related Information

Hereditary Hemorrhagic Telangiectasia - HHT
Pulmonary Arterial Hypertension - PAH

## 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 / Genomic Microarray (Oligo-based Array)

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

**Method:** Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

### PTEN-Related Disorders (PTEN) Sequencing and Deletion/Duplication 2002470

**Method:** Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

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

**Method:** Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

### Familial Mutation, Targeted Sequencing 2001961

**Method:** Polymerase Chain Reaction/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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