

# Vascular Malformations, 14 Genes

## Indications for Ordering

Confirm clinical diagnosis of a vascular malformation disorder

- Capillary malformation-arteriovenous malformation syndrome (CM-AVM)
- Cerebral cavernous malformation (CCM)
- Glomuvenous malformation (GVM)
- Hereditary hemorrhagic telangiectasia (HHT)
- Juvenile polyposis syndrome/hereditary hemorrhagic telangiectasia (JPS/HHT)
- Multiple cutaneous and mucosal venous malformations (VMCM)
- Parkes Weber syndrome (PKWS)
- *PTEN*-related Proteus syndrome
- Pulmonary arterial hypertension (PAH)

## Test Description

- Next generation sequencing for targeted capture of all coding exons and exon/intron junctions followed by massively parallel sequencing
  - Sequence variants reported are confirmed by Sanger sequencing
- Deletion/duplication analysis by custom-designed comparative genomic hybridization (CGH) array

## Tests to Consider

### Primary tests

[Vascular Malformations Panel, Sequencing and Deletion/Duplication, 14 Genes 2007384](#)

- Preferred DNA test to confirm clinical diagnosis of a genetic-related vascular malformation disorder

### Related tests

Consider if patient/family has classic symptoms of HHT

- [Hereditary Hemorrhagic Telangiectasia \(HHT\) Panel, Sequencing Deletion/Duplication, 5 Genes 2009337](#)
- [Hereditary Hemorrhagic Telangiectasia \(ACVRL1 and ENG\) Sequencing and Deletion/Duplication with Reflex to Juvenile Polyposis \(SMAD4\) Sequencing and Deletion/Duplication 2009008](#)
- [Hereditary Hemorrhagic Telangiectasia \(ACVRL1 and ENG\) Sequencing and Deletion/Duplication 0051382](#)
- [Hereditary Hemorrhagic Telangiectasia \(ACVRL1 and ENG\) Sequencing 0051381](#)

Consider if clinical suspicion for *PTEN*-related disorder is high

- [PTEN-Related Disorders \(PTEN\) Sequencing and Deletion/Duplication 2002470](#)
- [PTEN-Related Disorders \(PTEN\) Sequencing 2002722](#)

Consider if clinical suspicion for CM-AVM syndrome is high

- [RASA1-Related Disorders \(RASA1\) Sequencing 2002730](#)

Consider for individuals with a clinical phenotype of juvenile polyposis

- [Juvenile Polyposis \(SMAD4\) Sequencing and Deletion/Duplication 2001971](#)
- [Juvenile Polyposis \(SMAD4\) Sequencing 0051510](#)

Consider for individuals with PAH and no other vascular findings

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

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a pathogenic familial variant identifiable by sequencing is known

## Disease Overview

Vascular malformation syndromes are caused by defects of blood vessels

- Typically categorized according to
  - Vessel type affected (venous, arterial, capillary, or combined)
  - 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

## Symptoms

- Hemorrhage
- Effects of shunting through high-flow lesions (eg, cases of congestive heart failure)
- Localized pain
- Destruction/deformation of surrounding tissue
- Localized intravascular coagulopathy (LIC)
- Stroke
- Effects of resistance through occluded vessels

## Genetics

**Genes** – see table

- Clinical variability is high and penetrance is often age related and reduced

## Test Interpretation

**Clinical sensitivity** – dependent upon specific disorder

### Results

- Positive – one copy of a pathogenic variant detected in *ACVRL1*, *BMP9/GDF2*, *BMPR2*, *CAV1*, *CCM1/KRIT1*, *CCM2*, *CCM3/PDCD10*, *ENG*, *GLMN*, *KCNK3*, *PTEN*, *RASA1*, *SMAD4*, or *TEK* gene
  - Confirms affected status for related disorder
- Negative – no pathogenic variant detected in *ACVRL1*, *BMP9/GDF2*, *BMPR2*, *CAV1*, *CCM1/KRIT1*, *CCM2*, *CCM3/PDCD10*, *ENG*, *GLMN*, *KCNK3*, *PTEN*, *RASA1*, *SMAD4*, or *TEK* gene
  - Decreases but does not exclude likelihood of diagnosis of a heritable vascular malformation disorder in a clinically affected individual
- Inconclusive – variants of unknown clinical significance may be identified in any of the 14 genes tested

### Limitations

- Some small deletions or insertions may not be detected by massively parallel sequencing
- Not determined or evaluated
  - Variants in genes not listed
  - Deep intronic or regulatory region variants
  - Breakpoints of large deletions/duplications
- Copy number variants <1,000 base pairs may or may not be detected in the targeted genes
- Diagnostic errors may occur due to rare sequence variations

Gene Symbol	Gene Description	NM #	OMIM #	Condition	Inheritance
<i>ACVRL1</i>	Activin receptor-like kinase 1	000020	601284	HHT type 2	AD
<i>BMP9/GDF2</i>	Growth/differentiation factor 2	016204	605120	HHT type 5	AD
<i>BMPR2</i>	Bone morphogenetic protein receptor, type II	001204	600799	PAH1	AD
<i>CAV1</i>	Caveolin 1	001753	601047	PAH2	AD
<i>CCM1/KRIT1</i>	Ankyrin repeat containing	194456	604214	CCM1	AD
<i>CCM2</i>	Cerebral cavernous malformation 2	031443	607929	CCM2	AD
<i>CCM3/PDCD10</i>	Programmed cell death 10	007217	609118	CCM3	AD
<i>ENG</i>	Endoglin	001114753	131195	HHT type 1	AD
<i>GLMN</i>	Glomulin	053274	601749	Glomuvenous malformation	AD
<i>KCNK3</i>	Potassium channel, subfamily K, member 3	002246	603220	PAH4	AD
<i>PTEN</i>	Phosphatase and tensin homolog	000314	601728	PTEN-related Proteus syndrome	AD
<i>RASA1</i>	Ras p21 protein activator 1	002890	139150	CM-AVM	AD
<i>SMAD4</i>	SMA- and MAD-related protein 4	005359	600993	JP/HHT	AD
<i>TEK</i>	TEK tyrosine kinase, endothelial	000459	600221	VMCM	AD

AD = autosomal dominant