Vascular Malformations Panel, Sequencing and Deletion/Duplication

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
  - Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants
- Deletion/duplication analysis by custom-designed comparative genomic hybridization (CGH) array

Tests to Consider

Primary tests

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