Hereditary Hemorrhagic Telangiectasia Panel, Sequencing and Deletion/Duplication

Indications for Ordering

Confirm diagnosis of a hereditary telangiectasia/arteriovenous malformation (AVM) disorder
- Hereditary hemorrhagic telangiectasia (HHT)
- Juvenile polyposis syndrome (JPS)
- Capillary malformation (CM)

Test Description

- Targeted capture of all coding exons and intron/exon junctions followed by massively parallel sequencing
  - Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants
- Custom-designed comparative genomic hybridization (CGH) array to detect deletions/duplications

Tests to Consider

Primary tests

Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing and Deletion/Duplication 2009337
- Most comprehensive test to determine the cause of a telangiectasia/AVM disorder

Related tests

Hereditary Hemorrhagic Telangiectasia (*ACVRL1* and *ENG*) Sequencing and Deletion/Duplication with Reflex to Juvenile Polyposis (*SMAD4*) Sequencing and Deletion/Duplication 2009008
- Appropriate test when clinical/family history is classic for HHT

Hereditary Hemorrhagic Telangiectasia (*ACVRL1* and *ENG*) Sequencing and Deletion/Duplication 0051382
- Acceptable test when clinical/family history is classic for HHT
  - If negative, consider Juvenile Polyposis (*SMAD4*) Sequencing and Deletion/Duplication

Hereditary Hemorrhagic Telangiectasia (*ACVRL1* and *ENG*) Sequencing 0051381
- Alternative test when clinical/family history is classic for HHT

Juvenile Polyposis (*SMAD4*) Sequencing and Deletion/Duplication 2001971
- Diagnostic and predictive testing for JPS/HHT

Telangiectasia Syndrome (*BMP9/GDF2*) Sequencing 2010015
- Use for individuals suspected of having a telangiectasia syndrome without a variant in the *ACVRL1*, *ENG*, or *SMAD4* gene

RASA1-Related Disorders (*RASA1*) Sequencing and Deletion/Duplication 2007852
- Preferred molecular test for *RASA1*-related disorders
- Use if cutaneous vascular lesions include CMs
- Use if no variants in the *ACVRL1, ENG,* or *SMAD4* gene

Disease Overview

Manifestations
- Cutaneous and/or mucosal telangiectasia/CMs
- Cerebral and spinal AVMs
- Lung and liver AVMs – HHT
- Extremities, face, neck AVMs – CM/AVM
- AVMs and juvenile polyps –JPS/HHT

Symptoms
- Bleeding/hemorrhage from telangiectases/AVM
- Effects related to high-flow shunting of blood through AVMs
  - Congestive heart failure
  - Embolic stroke/brain abscess secondary to pulmonary AVM

Genetics

See table

Test Interpretation

Clinical sensitivity

- HHT Panel, Sequencing and Deletion/Duplication
  - ~87% for individuals meeting consensus clinical diagnostic criteria for HHT (Bossler, 2006; Gedge, 2007; Prigoda, 2006; Richards-Yutz, 2010; Wooderchak-Donahue, 2013)
  - Variable for those with symptoms but who do not meet diagnostic criteria
  - *ACVRL1* and *ENG* genes are causative for ~85% of HHT (Bossler, 2006; Gedge, 2007; Prigoda, 2006; Richards-Yutz, 2010)
    - 75% detectable by sequencing
    - 10% detectable by large deletion/duplication
  - *SMAD4* causative for ~1-3% HHT (Prigoda, 2006)
  - *BMP9/GDF2* variants detected in <1% of individuals suspected to have a hereditary telangiectasia syndrome, but with no variant in the *ACVRL1*, *ENG* or *SMAD4* genes (Wooderchak-Donahue, 2013)

Results

- Positive – one copy of a pathogenic variant in the *ACVRL1, BMP9, ENG*, *RASA1*, or *SMAD4* gene detected
  - Predictive of a telangiectasia/AVM disorder
- Negative – no pathogenic variant found in the *ACVRL1, BMP9, ENG*, *RASA1*, or *SMAD4* gene in a clinically affected individual
  - Diagnosis of a telangiectasia/AVM disorder is unlikely but not excluded
- Inconclusive – variants of unknown clinical significance may be identified in any of the genes tested

Limitations

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

References

- Bossler AD, Richards J, et al. Novel mutations in ENG and ACVRL1 identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia (HHT): correlation of genotype with phenotype. Hum Mutat. 2006;27(7):667-675
- Gedge F, McDonald J, et al. Clinical and analytical sensitivities in hereditary hemorrhagic telangiectasia testing and a report of de novo mutations. J Mol Diagn. 2007;9(2):258-265
- Prigoda NL, Savas S, et al. Hereditary haemorrhagic telangiectasia: mutation detection, test sensitivity and novel mutations. J Med Genet. 2006;43(9):722-728
- Richards-Yutz J, Grant K, et al. Update on molecular diagnosis of hereditary hemorrhagic telangiectasia. Hum Genet. 2010;128(1):61-77
- Wooderchak-Donahue WL, McDonald J, et al. BMP9 mutations cause a vascular-anomaly syndrome with phenotypic overlap with hereditary hemorrhagic telangiectasia. Am J Hum Genet. 2013;93(3):530-537

Gene Symbol	Gene Description	NM #	OMIM #	Condition	Inh.	Prevalence	De Novo Variants
ACVRL1/ALK1	Activin receptor-like kinase 1	000020	601284	HHT type 2/HHT2	AD	~1/5,000	Rare
BMP9/GDF2	Growth/ differentiation factor 2	016204	605120	HHT type 5/HHT5	AD	Unknown	Unknown
ENG	Endoglin	001114753	131195	HHT type 1/HHT1	AD	~1/5,000	Rare
RASA1	Ras p21 protein activator 1	002890	139150	CM/AVM or *RASA1*-related	AD	~1/100,000 in northern Europeans	~25%
SMAD4	SMA- and MAD-related protein 4	005359	600993	JPS/HHT	AD	Unknown	~25%

AD, autosomal dominant; CM/AVM, capillary malformation/arteriovascular malformation; HHT, hereditary hemorrhagic telangiectasia; Inh., inheritance; JPS/HHT, juvenile polyposis syndrome/hereditary hemorrhagic telangiectasia