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

RASAI-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
  o ~87% for individuals meeting consensus clinical diagnostic criteria for HHT (Bossler, 2006; Gedge, 2007; Prigoda, 2006; Richards-Yutz, 2010; Wooderchak-Donahue, 2013)
  o Variable for those with symptoms but who do not meet diagnostic criteria
  o 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
    o SMAD4 causative for ~1-3% HHT (Prigoda, 2006)
    o 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)
  ▪ Inconclusive – variants of unknown clinical significance may be identified in any of the genes tested

Results
• Positive – one copy of a pathogenic variant in the ACVRL1, BMP9, ENG, RASA1, or SMAD4 gene detected
  o 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
  o 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
  o Variants in genes not tested
  o Deep intronic or regulatory region variants
  o 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

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Description</th>
<th>NM #</th>
<th>OMIM #</th>
<th>Condition</th>
<th>Inh.</th>
<th>Prevalence</th>
<th>De Novo Variants</th>
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<td>CM/AVM or RASA1-related</td>
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<td>~1/100,000 in northern Europeans</td>
<td>~25%</td>
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<td>600993</td>
<td>JPS/HHT</td>
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</tbody>
</table>

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

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