Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant genetic disorder that leads to abnormal blood vessel formation in the skin, mucous membranes, and often in organs such as the lungs, liver, and brain. Genetic testing can confirm a diagnosis.

Disease Overview

Symptoms
- Spontaneous and recurring nosebleeds
- Cutaneous and/or mucosal telangiectases, predominantly on the face, lips, hands, and in oral, nasal, and gastrointestinal mucosa
- Arteriovenous malformations (AVMs) affecting the lungs, liver, and brain
- HHT symptoms and juvenile polyps are present with juvenile polyposis syndrome (JPS)/HHT (SMAD4)

Penetration
- Approximately 95% of individuals will develop nosebleeds or telangiectases.
- Penetration is age dependent.

Prevalence
1/10,000

Inheritance
Autosomal dominant

Test Description

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

Clinical sensitivity
- 87% of individuals meeting consensus clinical diagnostic criteria for HHT will have a causative variant in one of the genes tested.
  - Variable for those with symptoms but who do not meet diagnostic criteria
- ACVRL1 and ENG are causative for ~85% of HHT. 1,2,3,4
  - 75% detectable by sequencing
  - 10% detectable by large deletion/duplication analysis
- SMAD4 is causative for 1-3% of HHT 3
- BMP9/GDF2 mutations are detected in <1% of individuals with no other causative variants. 5
- The clinical sensitivity for EPHB4 is unknown.

Limitations
- A negative result does not exclude a diagnosis of HHT or overlapping disorders.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.

Tests to Consider

Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing and Deletion/Duplication 2009337
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray
Recommended test for symptomatic individuals who do not meet clinical criteria for HHT

Hereditary Hemorrhagic Telangiectasia (ACVRL1 and ENG) Sequencing and Deletion/Duplication 0051382
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification
Recommended test for symptomatic individuals who meet clinical criteria for HHT

Hereditary Hemorrhagic Telangiectasia (ACVRL1 and ENG) Sequencing and Deletion/Duplication with Reflex to Juvenile Polyposis (SMAD4) Sequencing and Deletion/Duplication 2009008
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification
Recommended test for symptomatic individuals who meet clinical criteria for HHT

Hereditary Hemorrhagic Telangiectasia (ACVRL1 and ENG) Sequencing 0051381
Method: Polymerase Chain Reaction/Sequencing

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial sequence variant previously identified in a family member.
- A copy of the family member’s test results documenting the known familial variant is required.
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 EPHB4

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

### Analytical Sensitivity

For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate (%)</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
</tr>
<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
</tr>
<tr>
<td>Deletions 11-44 bp</td>
<td>100</td>
<td>87.8-100</td>
</tr>
<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
</tr>
<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACVRL1</td>
<td>ACVRLK1, ORW2, HHT2, ALK1, HHT</td>
<td>601284</td>
<td>HHT, type 2</td>
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<tr>
<td>ENG</td>
<td>ORW1, ORW, END, HHT1, CD105</td>
<td>131195</td>
<td>HHT, type 1</td>
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<tr>
<td>EPHB4</td>
<td>HTK, Tyro11</td>
<td>600011</td>
<td>CM-AVM</td>
</tr>
<tr>
<td>GDF2</td>
<td>BMP-9, BMP9</td>
<td>605120</td>
<td>HHT, type 5</td>
</tr>
<tr>
<td>RASA1</td>
<td>RASA, GAP, CM-AVM, p120GAP, p120RASGAP, p120</td>
<td>139150</td>
<td>CM-AVM, Parkes Weber syndrome</td>
</tr>
<tr>
<td>SMAD4</td>
<td>MADH4, DPC4</td>
<td>600993</td>
<td>JPS, JPS/HHT</td>
</tr>
</tbody>
</table>

CM-AVM, capillary malformation-arteriovenous malformation

### REFERENCES


RELATED INFORMATION
Hereditary Hemorrhagic Telangiectasia - HHT

RELATED TESTS
- Juvenile Polyposis (SMAD4) Sequencing and Deletion/Duplication 2001971
  Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification
- Telangiectasia Syndrome (BMP9/GDF2) Sequencing 2010015
  Method: Polymerase Chain Reaction/Sequencing
- RASA1-Related Disorders (RASA1) Sequencing and Deletion/Duplication 2007852
  Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification
- Capillary Malformation-Arteriovenous Malformation (EPHB4 and RASA1) Sequencing, and (RASA1) Deletion/Duplication 3001132
  Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification
- Capillary Malformation-Arteriovenous Malformation 2 (EPHB4) Sequencing 3001129
  Method: Polymerase Chain Reaction/Sequencing