# Hereditary Hemorrhagic Telangiectasia Panel

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. Overlapping disorders include *BMP9*/*GDF2*-related vascular-anomaly syndrome, *BMPR2*-related disorders, capillary malformation-arteriovenous malformation (CM-AVM), and *SMAD4*-related juvenile polyposis syndrome (JPS)/HHT. Genetic testing can confirm a diagnosis.

## Featured ARUP Testing

Hereditary Hemorrhagic Telangiectasia (HHT) Panel, Sequencing and Deletion/Duplication 2009337

**Method:** Massively Parallel Sequencing

Recommended diagnostic test for individuals with clinical features of HHT

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

## Disease Overview

### Symptoms

- HHT (*ACVRL1* and *ENG*)[1]
  - 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
- Related disorders with HHT clinical overlap, including cutaneous AVMs and/or telangiectases[1]
  - HHT symptoms and juvenile polyps are present with juvenile polyposis syndrome (JPS)/HHT (*SMAD4*)
  - CM-AVM (*RASA1* and *EPHB4*)
  - *BMP9*/*GDF2*-related vascular-anomaly syndrome
  - *BMPR2*-related disorders

## Genetics

### Genes

See the Genes Tested table. Additional targeted regions include the 5' untranslated region of *ENG*, and a region of *ACVRL1* intron 9 encompassing the CT-rich variant hotspot region.

### Penetrance

Approximately 95% of individuals with HHT will develop symptoms by late adulthood.[1]

### Prevalence

1/5,000 to 1/10,000[1,2]

### Inheritance

Autosomal dominant for all genes tested

## Test Interpretation

### Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

## Clinical Sensitivity

- Approximately 97% of individuals meeting consensus clinical diagnostic criteria for HHT will have a causative variant in *ACVRL1*, *ENG*, or *SMAD4*.
  - *ACVRL1* and *ENG* are causative for approximately 96% of HHT.[1,3]
    - 90% detectable by sequencing
    - 10% detectable by large deletion/duplication analysis
  - *SMAD4* is causative for 1% of HHT.[1,3]
  - 3% unknown[1,3]
- *BMP9*/*GDF2* pathogenic variants are detected in <1% of individuals with suspected HHT and no other causative variants.[4]
- Approximately 60% of individuals with capillary malformation-arteriovenous malformation (CM-AVM) have detectable pathogenic variants in the *EPHB4* and *RASA1* genes.[5]
- The clinical sensitivity of *BMPR2*-related disorders in individuals with suspected HHT is unknown.

## Analytic Sensitivity

For massively parallel sequencing:

| Variant Class | Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%) | Analytic Specificity (NPA) (%) |
|---|---|---|
| SNVs | >99 (96.9-99.4) | >99.9 |
| Deletions 1-10 bp[b] | 93.8 (84.3-98.2) | >99.9 |
| Insertions 1-10 bp[b] | 94.8 (86.8-98.5) | >99.9 |
| Exon-level[c] Deletions | 97.8 (90.3-99.8) [2 exons or larger]<br>62.5 (38.3-82.6) [single exon] | >99.9 |
| Exon-level[c] Duplications | 83.3 (56.4-96.4) [3 exons or larger] | >99.9 |

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

## Results

| Result | Variant(s) Detected | Clinical Significance |
|---|---|---|
| Positive | One pathogenic variant detected | Confirms a diagnosis; see Genes Tested table for disease association |
| Negative | No pathogenic variants detected | Reduces risk for HHT and other hereditary conditions tested, but not excluded |
| Uncertain | Variant of unknown clinical significance detected | It is unknown whether variant is benign or pathogenic |

## 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.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes (excluding the 5' untranslated region of *ENG*, and a region of *ACVRL1* intron 9 encompassing the CT-rich variant hotspot region)
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than 3 exons in size
  - Single exon deletions/duplications in the following exons:
    - *ENG* (NM_001114753, NM_000118) 1
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

## Genes Tested

| Gene | Alias Symbol(s) | MIM Number | Disorder |
|---|---|---|---|
| *ACVRL1* | ACVRLK1, ORW2, HHT2, ALK1, HHT | 601284 | HHT, type 2 |
| *BMPR2* | n/a | 600799 | *BMPR2*-related disorders; familial primary pulmonary hypertension with or without HHT |
| *ENG* | ORW1, ORW, END, HHT1, CD105 | 131195 | HHT, type 1 |
| *EPHB4* | HTK, Tyro11 | 600011 | CM-AVM |
| *GDF2* | BMP-9, BMP9 | 605120 | *BMP9* / *GDF2*-related vascular-anomaly syndrome |
| *RASA1* | RASA, GAP, CM-AVM, p120GAP, p120RASGAP, p120 | 139150 | CM-AVM, Parkes Weber syndrome |
| *SMAD4* | MADH4, DPC4 | 600993 | JPS, JPS/HHT |

CM-AVM, capillary malformation-arteriovenous malformation; n/a, not available

## References


1. McDonald J, Pyeritz RE. Hereditary hemorrhagic telangiectasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Updated: Feb 2017; Accessed: Oct 2020]

2. Faughnan ME, Mager JJ, Hetts SW, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *Ann Intern Med*. 2020. [Published online ahead of print Sep 2020].

3. McDonald J, Bayrak-Toydemir P, DeMille D, et al. Curaçao diagnostic criteria for hereditary hemorrhagic telangiectasia is highly predictive of a pathogenic variant in ENG or ACVRL1 (HHT1 and HHT2). *Genet Med*. 2020;22(7):1201-1205.

4. Wooderchak-Donahue WL, McDonald J, O'Fallon B , 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.

5. Bayrak-Toydemir P, Stevenson D. Capillary malformation-arteriovenous malformation syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Sep 2019; Accessed: Nov 2020]

## Related Information

Hereditary Hemorrhagic Telangiectasia - HHT

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review May 2022 | Last Update September 2023