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*)

Penetrance

- Approximately 95% of individuals will develop nosebleeds or telangiectases.[1]
- Penetrance is age dependent.[1]

Prevalence

1/5,000[2]

Inheritance

Autosomal dominant

Tests to Consider

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

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Recommended diagnostic test for individuals with clinical features of HHT

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

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

- Useful for confirming a diagnosis when a pathogenic deletion/duplication variant has been identified in family member
- A copy of the family member's lab report documenting the familial variant is required

See Related Tests

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.[3,4,5,6]
  - 75% detectable by sequencing
  - 10% detectable by large deletion/duplication analysis
- *SMAD4* is causative for 1-3% of HHT[5]
- *BMP9*/*GDF2* mutation are detected in <1% of individuals with no other causative variants.[7]
- 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.
- 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:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]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

Gene	Alias Symbol(s)	MIM Number	Disorder
ACVRL1	ACVRLK1, ORW2, HHT2, ALK1, HHT	601284	HHT, type 2
ENG	ORW1, ORW, END, HHT1, CD105	131195	HHT, type 1
EPHB4	HTK, Tyro11	600011	CM-AVM
GDF2	BMP-9, BMP9	605120	HHT, type 5
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

References

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Related Information

Hereditary Hemorrhagic Telangiectasia - HHT

Related Tests

Telangiectasia Syndrome (BMP9/GDF2) Sequencing 2010015

Method: Polymerase Chain Reaction/Sequencing

Vascular Malformations Panel, Sequencing and Deletion/Duplication 2007384

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

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