

Hereditary Hemorrhagic Telangiectasia Panel

Disorder also known as: Osler-Weber-Rendu Syndrome

Panel Gene List: *ACVRL1, ENG, GDF2, RASA1, SMAD4*

Additional genes from our cardiology test menu may be added to this panel by selecting test code 697C.

Clinical Features:

Hereditary hemorrhagic telangiectasia (HHT) affects 1 in 5,000 to 1 in 10,000 individuals.^{1,2} It is a vascular disorder characterized by telangiectasias, arteriovenous malformations (AVMs), and recurrent nose bleeds (epistaxis). Telangiectasias are commonly detected on the buccal mucosa, tongue, lips, face, fingers, and chest, while AVMs are often found in the lung, liver, or brain.^{3,4} Diagnostic criteria, called the Curacao criteria, have been established for HHT. Diagnosis requires the presence of at least three of the following: epistaxis, telangiectasias, a visceral lesion, and family history of HHT in a first degree relative.⁴ HHT is often diagnosed in adolescence or adulthood. However, cases of severely affected infants have been reported.⁴ Clinical features and age of onset of HHT may vary considerably, even within a family.

Inheritance Pattern/Genetics: Autosomal Dominant

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the HHT Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined hemorrhagic telangiectasias and a family history of disease. The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions

or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Gene	Protein	Inheritance	Disease Association(s)
<i>ACVRL1</i>	ACTIVIN A RECEPTOR TYPE II-LIKE 1	AD	HHT
<i>ENG</i>	ENDOGLIN	AD	HHT
<i>GDF2</i>	GROWTH/DIFFERENTIATION FACTOR 2	AD	HHT
<i>RASA1</i>	RAS P21 PROTEIN ACTIVATOR 1	AD	Capillary malformation-arteriovenous malformation, Parkes Weber syndrome, Basal cell carcinoma
<i>SMAD4</i>	SMAD FAMILY MEMBER 4	AD	Juvenile polyposis, HHT, Myhre syndrome

Abbreviations: AD – Autosomal dominant; HHT - Hereditary Hemorrhagic Telangiectasia

References:

1. Kjeldsen et al. (1999) J. Intern. Med. 245 (1):31-9 (PMID: 10095814)
2. Marchuk et al. (1998) Am. J. Med. Genet. 76 (3):269-73 (PMID: 9508248)
3. McDonald J, Pyeritz RE. Hereditary Hemorrhagic Telangiectasia. 2000 Jun 26 [Updated 2014 Jul 24]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1351/>
4. Shovlin et al. (2010) Blood Reviews 24 (6):203-19 (PMID: 20870325)