THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Hereditary Hemorrhagic Telangiectasia (HHT)

Clinical Features

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant condition characterized by the presence of telangiectases and arteriovenous malformations (AVMs) of the skin, mucosa, and viscera. The most common presenting manifestation of HHT is recurrent nosebleeds (epistaxis). Gastrointestinal bleeding occurs in roughly 25% of patients with HHT, with a typical age of onset after 50 years. Larger AVMs in the brain, liver or lungs can cause more serious complications that may be sudden and/or fatal. HHT has nearly complete penetrance by age 40, with over 90% of individuals exhibiting symptoms prior to age 21 (2).

Some patients with HHT also exhibit features consistent with juvenile polyposis syndrome (JPS); this condition is named juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT) [OMIM#175050]. JPHT is characterized by HHT, the presence of hamartomatous polyps (which occur throughout the gastrointestinal tract), and increased risk for gastrointestinal cancer.

Molecular Genetics

HHT is caused by heterozygous mutations in the *ENG, ACVRL1* (previously known as *ALK1)*, *SMAD4*, and *GDF2* genes. Mutations in *ENG* and *ACVRL1* are the most common causes of HHT. Heterozygous mutations in *SMAD4* are related to juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, and are present in 1-2% of patients with HHT. Mutations in *GDF2* are a rare cause of HHT, and occur in less than 1% of affected individuals.

Heterozygous mutations in *RASA1* are associated with capillary malformation-arteriovenous malformation syndrome [OMIM#608354] and Parkes Weber syndrome [OMIM#608355], which are both characterized by vascular abnormalities and AVMs. Parkes Weber syndrome is further defined by overgrowth of one limb, most commonly a leg. In these *RASA1*-related conditions, AVMs have not been reported in viscera, which distinguishes these conditions from HHT (1).

Test Methods

Comprehensive sequence coverage of the coding regions and splice junctions of the *ENG, ACVRL1, SMAD4, GDF2* and *RASA1* genes is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Hereditary Hemorrhagic Telangiectasia (HHT) panel (5 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81406
	81407

Turn-around time: 8 weeks

Results

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References

1. Bayrak-Toydemir P, Stevenson D. RASA1-Related Disorders. 2011 Feb 22 [Updated 2016 Oct 6]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

2. 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

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555

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