impact genetics

HHT Hereditary Hemorrhagic Telangiectasia

Genetic Test

Transparent | Precise testing | Exceptional service

Test Description

Genes tested

- *ENG (endoglin)*. Hereditary hemorrhagic telangiectasia type 1 (HHT1).
- *ACVRL1 (ALK1)*. Hereditary hemorrhagic telangiectasia type 2 (HHT2).
- *SMAD4 (MADH4)*. Some patients with JP-HHT may show only symptoms of HHT with occult manifestation of juvenile polyposis (JP). The mutations leading to JP-HHT are most often found in the COOH-terminus of *SMAD4*.

Copy number changes

Our lab uses Multiplex Ligation-dependent Probe Amplification (MLPA) to look for whole-exon and multi-exon deletions and duplications.

Sequence analysis

Our sequence analysis is highly sensitive and is able to detect mosaic mutations at the level of 15% or greater. We consider reported polymorphisms when designing our sequencing assays to ensure the accuracy of our sequence results.

We sequence a minimum of 25 nucleotides flanking each exon to detect changes in splice sites. We use *in silico* analysis and scoring to determine whether a particular change is likely to cause missplicing. In the case of a suspicious intronic variant of uncertain significance we perform RNA transcript analysis on a fresh blood sample at no added charge.

For missense amino acid changes of uncertain significance we employ several *in silico* conservation analysis programs to predict whether a particular missense change is likely to be pathogenic. In addition, when appropriate we will test known affected and unaffected relatives at no charge to clarify variant classification.

RNA Analysis

In the event that no HHT mutation is found for patients who have a clinical diagnosis or a strong family history we will pursue transcript analysis to look for deep intronic changes that may impact slicing; this is performed at no added charge.

Genetic Counseling Services (U.S. patients only)

Comprehensive pre and/or post test counseling is available via telegenetics

Board certified, licenced genetic counselors will:

- Lead patients through a discussion to evaluate medical history;
- Construct a 3 generation pedigree (family tree);
- Discuss the genetic testing options that may be appropriate for that family or individual.

To access the online booking system go to **http://impactgenetics.com/genetic-counseling/**
or by calling **1-855-422-2557**.

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Choose Impact | *Excellence and expertise*

- **Reports:** We strive to provide as much useful information as possible. World-renowned medical experts contribute to cases involving complex interpretation.
- **Sensitivity: Consider sensitivity when comparing total costs.** Higher sensitivity in detecting mutations reduces unnecessary clinical screening for non-carriers. Impact Genetic's diagnostic sensitivity for HHT probands is 89%. Suspected probands with no mutation found who meet less than three Curaçao criteria are excluded.
- **Re-tests:** If no mutation is found, we bank any remaining DNA and RNA and re-test in the future when new science or test methods are available. For any new findings, we re-issue our report at no added charge.
- **Experience:** We have completed analysis for hundreds of HHT families, building a knowledge base that allows us to provide more accurate interpretation.
- **Ascribing value to variants:** We analyze all variants of unknown significance using current *in silico* methods and take into account the knowledge we have gained from our previous test experience. In addition, we search HHT mutation databases for previous reports of the variant in question. Where needed to define a causative mutation, we request family member samples to test at no added charge.
- **Clinically appropriate turn-around time:**
  Proband turn-around time is 6-9 weeks.
  Known familial mutation turn-around time is 2-3 weeks.
  Prenatal turn-around time is 7 business days.
- **Certified lab:** Our lab is fully accredited and certified:
  College of American Pathologists (CAP) and CLIA '88
  Institute for Quality Management in Healthcare (IQMH) ISO 15189
- **Service excellence:** Impact is committed to exceptional customer service. Our team happily provides genetic counseling and test order support so you can spend more time with your patients.
- **Logistics:** Impact provides genetic testing services to over 25 countries and samples are routinely shipped from across the world without disruption. We provide the necessary paperwork and recommend a courier service that will reliably deliver samples. **We are able to provide sample collection kits** with prepared and pre-paid courier envelopes.

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Our Research | *On the leading edge of HHT genetics*

In addition to using the latest research to constantly improve our test methods, we perform and publish our own research to ensure we are at the leading edge of HHT genetics. We share our mutation information in registered mutation databases for use by other researchers and clinicians. Our referring specialists have access to the data from our banked patient samples including detailed clinical information. We are open to modifying requisitions as needed to collect new and important clinical phenotype information. Our CAP compliant ethics and privacy policies ensure that appropriate consent is in place.

Examples of papers our team has authored:

- Prigoda-Lee, N. et al. 2011. **Identification of clinically relevant mosaicism in type 1 hereditary haemorrhagic telangiectasia**. *J Med Genet*. May; 48(5): 353-7.

  Our lab identified three patients with mosaic mutations in the *ENG* gene. Each of these patients was the first person in the family recognized as having HHT. We discuss the difficulty in identifying mosaic mutations in HHT patients, and the rarity of mosaicism in HHT. We recommend that in isolated cases of HHT with no mutation found mosaicism should be suspected.

- Prigoda-Lee, N. et al. 2006. **Hereditary haemorrhagic telangiectasia: mutation detection, test sensitivity and novel mutations**. *J Med Genet*. Sep; 43(9): 722-8.

  This is a description of our methods for HHT mutation discovery. Our strategy for understanding variants of unknown significance includes several methods, and correctly predicts significance for most published variants.

Our team has contributed to these papers:

- Gallione, C. et al. 2006. ***SMAD4* mutations found in unselected HHT patients**. *J Med Genet*. Oct;43(10): 793-7.
- Abdalla, S. et al. 2006. **Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease**. *J Med Genet*. Feb; 43(2): 97-110.
- Cohen, J. et al. 2005. **Cost comparison of genetic and clinical screening in families with hereditary hemorrhagic telangiectasia**. *Am J Med Genet A*. Aug 30; 137(2): 153-60.
- Abdalla, S. et al. 2005. **Novel mutations and polymorphisms in genes causing hereditary hemorrhagic telangiectasia**. *Hum Mutat*. Mar; 25(3): 320-1.

Please visit impactgenetics.com for more information and updates on our research.