SickKids | Genome Diagnostics

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) results from the presence of multiple arteriovenous malformations (AVMs) in which intervening capillaries between arteries and veins are absent, resulting in direct connections between them. Small AVMs or telangiectases near the skin surface and surface of oral and gastrointestinal (GI) mucosa membranes often rupture and bleed with minor trauma. Large AVMs often cause more severe symptoms when they occur in the brain, lungs, GI tract or more rarely the liver and spine. Complications from bleeding or shunting may be sudden and catastrophic.

Genetics

HHT is an autosomal dominant disorder caused by mutations in the gene *ENG*, *ACVRL1* (*ALK1*), and rarely SMAD4. Although penetrance is high (~100%), clinical expression is variable and age-dependent. There is a 50% chance that individuals with a mutation will pass it on and a 50% chance they will not pass the mutation to offspring.

In approximately ~80% of cases, HHT is caused by mutations in the ENG (67%) or ACVRL1 (31%) gene. HHT1 is caused by defects in the endoglin protein encoded by the *ENG* gene on chromosome 9q34.1. HHT2 is caused by defects in the serine/ threonine receptor kinase R3 encoded by the *ACVRL1* (*ALK1*) gene on chromosome 12q11-q14. Approximately 85% of HHT1 or HHT2 are caused by point mutations or small insertions/deletions. Mutations in SMAD4 account for 1-3% of cases and are associated with juvenile polyposis. In ~20% of HHT clinically diagnosed patients no mutated genes have been identified.

Test Sensitivity

Approximately 80% of all *ENG or ACVRL1* (*ALK1*) mutations (*SMAD4* frequency unknown) can be detected by molecular analysis in the Genome Diagnostics Laboratory.

Test Methods

- Complete sequencing of the coding region and flanking exon/ intron boundaries of the *ENG*, *ACVRL1* or *SMAD4* gene (upon request) to identify point mutations or small insertions/deletions.

- Quantitative testing of the *ENG or ACVRL1* gene to detect larger deletions, using Multiplex Ligation dependent Probe Amplification (MLPA).

It is often helpful to first identify the mutation(s) in an affected family member or parent of the affected family member. In families where an *ENG, ACVRL1* or *SMAD4* mutation has previously been identified, samples from relatives are analyzed only for the familial mutation.

Who Should Be Tested?

- Individuals clinically suspected of being affected with HHT

- Individuals with a family history of HHT, to determine carrier status

Potential Outcomes & Interpretation of Test Results

***ENG, ACVRL1 or SMAD 4* Gene Mutations**	**Explanation**
None detected	This result does not support a diagnosis of Hereditary hemorrhagic telangiectasia
Mutation detected	This result supports a diagnosis of Hereditary hemorrhagic telangiectasia

For More Information

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/ Item # 187300

GeneReviews online clinical information resource http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book =gene&part=hht

To locate a genetics centre near you, visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Current molecular testing may not detect all possible mutations in the ENG, ACVRL1 (ALK1) or SMAD4 genes. A negative test does not rule out the diagnosis of HHT, nor eliminate the possibility the individual is a carrier.

2. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.