

Hereditary Hemorrhagic Telangiectasia (*ENG* and *ACVRL1*) Sequencing and Deletion/Duplication

TO IDENTIFY A FAMILIAL MUTATION OR CONFIRM DIAGNOSIS IN SYMPTOMATIC INDIVIDUALS

Disease Overview

- HHT is characterized by:
 - Telangiectases appearing as red spots on the lips, tongue, fingers, GI tract, and/or nasal mucosa.
 - Recurrent, spontaneous nosebleeds.
 - Larger arteriovenous malformations (AVMs) in the internal organs, most commonly the lungs, liver, or brain.
- AVMs are usually congenital, while nosebleeds and external telangiectases often do not present until the second or third decade of life.
- Undetected and untreated lung or brain AVMs are a significant cause of morbidity and mortality and may present prior to the onset of recurrent nosebleeds and/or externally apparent telangiectases.
- Appropriate early screening and treatment for internal AVMs can dramatically improve outcome.

Epidemiology

- Prevalence is approximately one in 5,000–10,000.
- HHT affects individuals of all ethnicities.

Genetics

- Autosomal dominant; penetrance approaches 100 percent by age 40.
- A mutation in either the Endoglin (*ENG*) or activin A receptor type II-like 1 (*ACVRL1*) gene causes over 85 percent of HHT.
- De novo mutations in *ENG* and *ACVRL1* are rare, but have been reported.
- Approximately 75 percent of HHT mutations are point mutations or small deletions/duplications detectable by sequencing *ACVRL1* and *ENG*; approximately 10 percent are large deletions/duplications in *ACVRL1* and *ENG* detectable by multiplex ligation-dependent probe amplification (MLPA).
- A small percentage (1–3 percent) of HHT is caused by a mutation in the *SMAD4* gene. Mutations in *SMAD4* have been associated with combined HHT/juvenile polyposis syndrome, as well as juvenile polyposis without symptoms of HHT.
- There are at least two unidentified HHT genes (suggested by linkage in affected families).

Indications for Ordering

- To identify the familial mutation in clinically affected individuals, which enables diagnostic testing of at-risk relatives.
- For confirmation of HHT in symptomatic individuals.

Contraindications

- Presymptomatic or diagnostic testing for at-risk family members when a causative HHT mutation has previously been identified in the family. For these cases, order HHT FSM: Hereditary Hemorrhagic Telangiectasia (*ACVRL1* or *ENG*) Familial Mutation (ARUP test# 2001961).
- Prenatal testing, which requires knowledge of familial mutation. For fetal cases, order HHT FE-FSM: Hereditary Hemorrhagic Telangiectasia (*ACVRL1* or *ENG*) Familial Mutation, Fetal (ARUP test# 2001980).

Interpretation

For optimal test interpretation, please submit a patient history form detailing patient symptoms and family history of HHT.

- A positive result means a gene mutation predicted to cause HHT was detected.
- A negative result does not rule out HHT, due to the possibility of an undetectable *ENG* or *ACVRL1* mutation or a mutation in another HHT-related gene. Medical management should rely on clinical findings and family history.
- An uncertain result means a gene mutation was detected, but it is unknown whether it is deleterious or benign. Medical management should rely on clinical findings and family history.

Limitations

- Although sequence and deletion/duplication analyses of the *ENG* and *ACVRL1* genes will detect approximately 85 percent of HHT mutations, mutations in intronic or regulatory regions, or mutations in other genes, including *SMAD4*, will not be detected.
- Gene mutations of uncertain significance are common in *ENG* and *ACVRL1*.
- Breakpoints of large deletions/duplications detected in *ENG* and *ACVRL1* will not be determined.

Methodology

- Bi-directional sequencing of the entire coding region and intron-exon borders of the *ENG* and *ACVRL1* genes.
- Multiplex ligation-dependent probe amplification (MLPA) is performed for large deletion/duplication analysis of *ENG* and *ACVRL1*.

Related Tests

- Hereditary Hemorrhagic Telangiectasia (*ACVRL1* and *ENG*) Deletion/Duplication (0051348)
- Hereditary Hemorrhagic Telangiectasia (*ACVRL1* or *ENG*) Familial Mutation, Targeted Sequencing (2001961)
- Hereditary Hemorrhagic Telangiectasia (*ACVRL1* or *ENG*) Familial Mutation, Targeted Sequencing, Fetal (2001980)
- Juvenile Polyposis (*SMAD4*) Sequencing and Deletion/Duplication (2001971)
- Juvenile Polyposis (*SMAD4*) Sequencing (0051510)
- Juvenile Polyposis (*SMAD4*) Deletion/Duplication (2001976)

References

1. Bayrak-Toydemir P, et al. Hereditary hemorrhagic telangiectasia: an overview of diagnosis and management in the molecular era for clinicians. *Genet Med* 2004; 6(4):175–91.
2. Bayrak-Toydemir P, et al. Genotype-phenotype correlation in HHT: mutations and manifestations. *Am J Med Gen* 2006; 140A:463–70.
3. Bossler A, et al. Novel mutations in *ENG* and *ACVRL1* identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia. *Hum Mutat* 2006; 27(7):667–75.
4. Morgan T, et al. Intracranial hemorrhage in infants and children with hereditary hemorrhagic telangiectasia. *Pediatrics* 2002; 109(1):1–7.

Test Information

0051382 **Hereditary Hemorrhagic Telangiectasia (*ACVRL1* and *ENG*)
Sequencing & Deletion/Duplication**

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.