

Hereditary Hemorrhagic Telangiectasia Type 1 (HHT1) / Osler-Weber-Rendu Disease via *ENG* Gene Sequencing (Test #861)

Brief Description of Clinical Features: Hereditary Hemorrhagic Telangiectasia (HHT, OMIM 187300) is a disease of vascular dysplasia. HHT is characterized by the presence of arteriovenous malformations (AVMs) that involve direct connections between arteries and veins with no intervening capillary bed. AVMs can be located throughout the body and have a greater tendency towards rupture than normal blood vessels; this is often visible as telangiectases (small red or purple spots) on the lips, hands, or face of HHT patients. Recurrent nosebleeds are the most common symptom of HHT. About 20-25% of patients develop GI bleeding later in life that may lead to severe anemia (Abdalla et al. *J Med Genet* 40:494-502, 2003). Hepatic AVMs are found in up to 32% of patients and are often asymptomatic, but can cause cirrhosis and affect cardiac output (Plauchu et al. *Am J Med Genet* 32:291, 1989; Garcia-Tsao et al. *New Eng J Med* 343:931, 2000). Cerebral AVMs (5-20% of patients) and Pulmonary AVMs (30-50% of patients) are usually present at birth and may cause headaches, seizures, ischemia, hypoxemia, and hemothorax (see Shovlin and Letarte *Thorax* 54:714-729, 1999). The penetrance of HHT varies depending upon type (see below), and symptoms usually present by age 16 (Porteous et al. *J Med Genet* 29:527, 1992). The severity of HHT can vary widely even within families and can go unnoticed in affected individuals.

Genetics: HHT is an autosomal dominant disorder caused by mutations in genes encoding proteins that modulate the normally inhibitory transforming growth factor (TGF)- β signaling pathway during cell proliferation and differentiation. The incidence of HHT is ~ 1:5-8,000. HHT affects men, women and all ethnic groups (Govani and Shovlin *Eur J Hum Genet* 17:860, 2009). Mutations in the *ENG* gene (OMIM 131195) account for ~50-60% of HHT cases (HHT1; OMIM 187300). *ENG* encodes the endothelial cell surface co-receptor endoglin that binds (TGF)- β and is essential for vascular integrity (Rius et al. *Blood* 92:4677, 1998). HHT1 is associated with a high incidence of pulmonary and cerebral AVMs and a higher penetrance than HHT2 in which hepatic AVMs are more common (Letteboer et al. *Journal of Medical Genetics* 43:371 -377, 2006). HHT1 is thought to have a more severe phenotype than other forms of HHT. Causative mutations are found throughout the *ENG* gene and include primarily missense/nonsense mutations. Large whole or multi-exon deletions are also common (Prigoda et al. *J Med Genet* 43:722, 2006) as are splice site mutations and insertions. No predominant mutation has been identified.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 15 exons encoded in the two *ENG* gene transcripts plus ~50 bp of flanking non-coding DNA on either side of each exon. We will also sequence any single exon (Test #100, \$190) in family members of patients with known mutations, or to confirm research results.

Reference Sequences:

Isoform 1: Genomic: NC_000009.11 mRNA: NM_001114753.1 Protein: NP_001108225.1 (CCDS 48029.1)

Isoform 2: Genomic: NC_000009.11 mRNA: NM_000118.2 Protein: NP_000109.1 (CCDS 6880.1)

Indications for Test: Individuals with frequent nosebleeds, telangiectases, or any degree of GI, pulmonary, or cerebral bleeding.

Sensitivity of Test: Mutations in the *ENG* gene are found in ~50-60% of HHT patients.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2 – 3 weeks.

Specimen Requirements: See page 4 of Requisition Form

Price: Sequencing of *ENG* \$ 940

CPT Codes							
Test	83890 x1	83891 x1	83898 x17	83904 x17	83894 x1	83912 x1	Total
<i>ENG</i>	\$ 30	\$ 40	\$280	\$430	\$ 50	\$110	\$940

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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