

Hereditary Hemorrhagic Telangiectasia Type 1 (HHT1) / Osler-Weber-Rendu Disease via *ENG*, *ACVRL1/ALK1* and *SMAD4* Gene Sequencing (Test #860)

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. Recurrent nosebleeds are common. 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 ~ 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 cases) and Pulmonary AVMs (30-50% of cases) are usually present at birth and may cause headaches, seizures, ischemia, hypoxemia, and hemothorax (see Shovlin and Letarte *Thorax* 54:714-729, 1999). HHT penetrance varies depending upon type (see below), but 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 and affects men, women and all ethnic groups (Govani and Shovlin *Eur J Hum Genet* 17:860, 2009). HHT is caused by mutations in at least three genes: *ENG* (HHT1, OMIM 187300, ~ 50-60 % of cases), *ACVRL1/ALK1* (HHT2, OMIM 600376, ~30-40% of cases), and *SMAD4* (OMIM 175050, ~2% of all cases, or ~10% of cases not attributed to *ENG* or *ACVRL1/ALK1*). Pulmonary and cerebral AVMs are more common in HHT1, while hepatic AVMs are more common in HHT2 (Letteboer et al. *J Med Genet* 43:371 -377, 2006). Causative mutations are found throughout the *ENG*, *ACVRL1*, and *SMAD4* genes and include primarily missense/nonsense mutations and both small and large, often multi-exon, deletions. Splice site mutations and insertions are also common, but no predominant mutation has been identified in any of these genes.

Description of This Particular Test: This test involves bidirectional DNA sequencing of the *ENG*, *ACVRL1/ALK1*, and *SMAD4* genes plus ~50 bp of flanking non-coding DNA on either side of each exon. Genes will be tested in the order specified by the client. Tests for the individual genes are also available. 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:

Gene:	HHT Type	Genomic: NC_	mRNA: NM_	Protein: NP_	CCDS
<i>ENG</i>	HHT1	000009.11	001114753.1 / 000118.2	001108225.1 / 000109.1	48029.1 / 6880.1
<i>ACVRL1/AKI1</i>	HHT2	000012.11	000020.2	000011.2	31804.1
<i>SMAD4</i>	JP-HHT	000018.9	005359.5	005350.1	11950.1

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

Sensitivity: > 80% of HHT patients have mutations in *ACVRL1*, *ENG* or *SMAD4* (Prigoda et al. *J Med Genet* 43:722, 2006).

Turnaround Time: Maximum of 60 calendar days, although many tests are completed in 2 – 3 weeks.

Specimen Requirements: See page 4 of Requisition Form

(See next page for pricing information)

Price: Sequencing of *ENG*, *ACVRL1/ALK1* and *SMAD4*: \$690-\$1970

CPT Codes							
Test	83890 x1	83891 x1	83898	83904	83894 x1	83912 x1	Totals
<i>ENG</i> only	\$ 30	\$ 40	x17 = \$280	x17 = \$430	\$ 50	\$110	\$ 940
<i>ACVRL1</i> only	\$ 30	\$ 40	x10 = \$200	x10 = \$300	\$ 30	\$ 90	\$ 690
<i>SMAD4</i> only	\$ 30	\$ 40	x10 = \$200	x10 = \$280	\$ 50	\$ 90	\$ 690
All Three Genes	\$ 30	\$ 40	x37 = \$680	x37 = \$990	\$ 90	\$140	\$1970*

* When all three of the genes are tested, a 15% discount will apply to the sum of the prices of the individual tests.

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

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