

Juvenile Polyposis Syndrome (JPS) and Hereditary Hemorrhagic Telangiectasia (HHT) via SMAD4 Gene Sequencing --Test #709

Brief Description of Clinical Features: Juvenile Polyposis Syndrome (JPS; OMIM 608456) is a rare, inherited hamartomatous polyposis syndrome with increased susceptibility to colorectal cancer. Hereditary Hemorrhagic Telangiectasia (HHT; OMIM 187300) is a disease of vascular dysplasia characterized by the presence of arteriovenous malformations (AVMs). Clinical diagnosis of JPS is typically made when one of the following criteria is met: more than five juvenile polyps in the colorectum; multiple juvenile polyps throughout the GI tract; or any number of juvenile polyps and a family history of gastrointestinal polyps (Chow & Macrae *J Gastroenterol Hepatol* 20:1634-1640, 2005). In JPS, 'juvenile' refers to the developmentally immature nature of the polyp, not the age of disease onset. In addition to polyposis, 10-20% of JPS patients also have extracolonic abnormalities such as congenital heart defects, cleft lip or palate, microcephaly and malrotations (Eng et al. *Annu Rev Med* 52:371-400, 2001). Patients with HHT often have frequent nosebleeds and telangiectases on the lips, hands, and face. About 20-25% of HHT patients develop GI bleeding later in life that may lead to severe anemia (Abdalla et al. *J Med Genet* 40:494-502, 2003). 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). Confirming a diagnosis of JPS or HHT is important for the appropriate surveillance and management of cancer in individuals with juvenile polyps, and AVMs in patients with HHT.

Genetics: Both JPS and HHT can be caused by heterozygous germline mutations in the *SMAD4* gene (OMIM 600993) (Howe et al. *Science* 280:1086-1088, 1998; Howe et al. *Nat Genet* 28:184-187, 2001). Mutations in *SMAD4* are also found in patients with a combined syndrome of JPS and HHT (JP-HHT). *SMAD4* mediates the biological effects of the Transforming Growth Factor- β (TGF- β) superfamily of cytokines (Miyazono et al. *J Biochem* 147:35-51, 2010). In epithelial cells, the TGF- β pathway normally inhibits growth and proliferation; mutations in *SMAD4* decrease TGF- β signaling and can lead to AVMs, neoplasia and carcinoma.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 11 coding exons (3-13) of the *SMAD4* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. We will also sequence a single exon (Test #100; \$190) in family members of patients with a known mutation, or to confirm research results.

Reference Sequences: Genomic: NC_000018.9 mRNA: NM_005359.5 Protein: NP_005350.1 CCDS 11950.1

Indications for Test: Candidates for this test are patients with a clinical diagnosis of JPS or AVMs. This test is specifically designed to detect germline mutations and is not appropriate for the detection of somatic mutations in tumors.

Sensitivity of Test: This test is predicted to identify a *SMAD4* mutation in ~20% of patients diagnosed with JPS (Calva-Cerqueira et al. *Clin Genet* 75:79-85, 2009), or ~ 10% of patients with HHT who do not have mutations in other known HHT genes (Gallione et al. *J Med Genet* 43:793, 2006).

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

Specimen Requirements: See page 4 of the Requisition Form.

Price:	Sequencing of the <i>SMAD4</i> Gene:	\$690
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x10	83898 \$ 200	Sequencing x10 83904 \$ 280
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 90

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

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