

Juvenile Polyposis Syndrome (JPS) via *BMPRIA* Gene Sequencing --Test #708

Brief Description of Clinical Features: Juvenile Polyposis Syndrome (JPS; OMIM 608456) is a rare, inherited hamartomatous polyposis syndrome with increased susceptibility to colorectal cancer. 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). 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). Although a solitary juvenile polyp in the general population has very little malignant potential (Nugent et al. *Gastroenterol* 105:698-700, 1993), patients with JPS have a 68% chance of developing gastrointestinal cancer by the age of 60 (Chow & Macrae *J Gastroenterol Hepatol* 20:1634-1640, 2005). Thus, confirming a diagnosis of JPS is important for the appropriate surveillance and management of cancer in individuals with juvenile polyps.

Genetics: JPS is caused by heterozygous germline mutations in one of two genes: *BMPRIA* (OMIM 601299) or *SMAD4* (OMIM 600993) (Howe et al. *Science* 280:1086-1088, 1998; Howe et al. *Nat Genet* 28:184-187, 2001). Both genes mediate 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 *BMPRIA* or *SMAD4* decrease TGF- β signaling and lead to neoplasia and carcinoma. *BMPRIA* encodes a transmembrane serine/threonine kinase receptor that binds the Bone Morphogenetic Protein (BMP) subfamily of TGF- β ligands (Heldin et al. *Nature* 390:465-471, 1997). Approximately 70 pathogenic variations have been identified throughout the *BMPRIA* gene and most (~90%) are detectable by DNA sequencing (Human Gene Mutation Database; www.hgmd.cf.ac.uk). In addition to causing JPS, one *BMPRIA* mutation (p.Ala338Asp) has also been identified in a family with Cowden Syndrome (CS; OMIM 158350), indicating *BMPRIA* mutations might also define a small subset of CS cases (Zhou et al. *Am J Hum Genet* 69:704-711, 2001).

Description of This Particular Test: This test involves bidirectional DNA sequencing of coding exons 3 – 13 of the *BMPRIA* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, 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_000010.10** mRNA: **NM_004329.2** Protein: **NP_004320.2** **CCDS 7378.1**

Indications for Test: Candidates for this test are patients diagnosed with JPS, and relatives of patients with a known *BMPRIA* mutation. Cowden Syndrome patients who have tested negative for a *PTEN* mutation are also candidates. This test is specifically designed to detect germline mutations and is not appropriate for the detection of somatic mutations in tumor tissue.

Sensitivity of Test: This test is predicted to identify a *BMPRIA* mutation in ~20% of patients diagnosed with JPS (Calva-Cerqueira et al., *Clin Genet* 75:79-85, 2009).

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 BMPRIA Gene:	\$660
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x9	83898 \$ 190	Sequencing x9 83904 \$ 280
Separation x1	83894 \$ 40	Interpretation/Report x1 83912 \$ 80

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

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