

Familial Adenomatous Polyposis via APC Gene Sequencing – Test #710

Brief Description of Clinical Features: Familial Adenomatous Polyposis (FAP) (OMIM 175100) is an inherited cancer syndrome characterized clinically by the development of hundreds to thousands adenomatous polyps in the colon and rectum. If not treated, nearly all FAP patients will develop colorectal cancer (CRC) by age 40 (Fearhead et al. *Hum Mol Genet* 10:721-733, 2001). In addition to CRC, FAP patients are also predisposed to desmoid tumors, small bowel cancer, thyroid cancer, hepatoblastoma and medulloblastoma (Galiatsatos et al. *Am J Gastroenterol* 101:385-398, 2006). About 60% of families with FAP also display congenital hypertrophy of the retinal pigment epithelium (CHRPE), a condition that does not affect sight or have malignant potential but can be easily detected by ophthalmoscopy at any age. CHRPE is highly diagnostic of FAP and can be useful for identifying FAP patients and at-risk family members, well before the appearance of polyps (Diaz-Llopis and Menezo *Arch Ophthalmol* 106:412-413, 1988).

Genetics: FAP is an autosomal dominant disorder caused by germline mutations in the *Adenomatous Polyposis Coli (APC)* gene. More than 1200 mutations have been reported in *APC* (Human Gene Mutation Database, www.hgmd.cf.ac.uk) and >90% are nonsense or frameshift mutations that result in a dysfunctional truncated protein product (Nagase and Nakamura *Hum Mut* 2:425-434, 1993). Germline mutations are spread evenly throughout the coding region (Beroud and Soussi *Nucleic Acids Res* 24:121-124, 1996). Several pathogenic mutations have also been documented in the promoter, 3' untranslated region (UTR) and deep within intron 14 (Heinimann et al. *Cancer Res* 61:7616-7622, 2001; De Rosa et al. *Dis Colon Rectum* 52:268-274, 2009). Severe FAP (i.e. more than 1000 polyps) typically occurs in patients with mutations between codons 1250 and 1464 (Caspari et al. *Lancet* 343:629-632, 1994). In contrast, patients with attenuated FAP (i.e. fewer than 100 colorectal polyps) usually have mutations at the very 5' and 3' ends of the gene, or in an alternatively spliced region of exon 9 (Young et al. *Hum Mut* 11:450-455, 1998; Soravia et al. *Am J Hum Genet* 62:1290-1301, 1998). CHRPE is limited to patients with mutations between codons 457 and 1444 (Caspari et al. *Hum Mol Genet* 4:337-340, 1995). Two missense variants, p.Ile1307Lys and p.Glu1317Lys, commonly found in Ashkenazi Jewish populations predispose carriers to multiple colorectal adenomas (generally less than 100) and carcinoma, but with low and variable penetrance (Frayling et al. *PNAS* 95:10722-10727, 1998).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 15 coding exons (2-16) of the *APC* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. Sequencing of the promoter, 3' UTR, alternate exon 9 and intron 14 regions for documented mutations is also performed. As indicated, we will sequence a single exon or regulatory region in family members of patients with a known mutation, or to confirm research results (Test #100; \$190).

Reference Sequences: Genomic: NC_000005.9 mRNA: NM_000038.5 Protein: NP_000029.2 CCDS 4107.1

Indications for Test: Candidates for this test are FAP patients and relatives of patients with a known *APC* mutation. This test is designed for heritable germline mutations and is not appropriate for the detection of somatic mutations in tumor tissue.

Sensitivity of Test: This test is predicted to detect >90% of causative FAP mutations (Laken et al. *PNAS* 96:2322-2326, 1999).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of Requisition Form.

Price:	Sequencing of the APC Gene:	\$ 1590
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x43	83898 \$ 500	Sequencing x43 83904 \$ 750
Separation x1	83894 \$ 140	Interpretation/Report x1 83912 \$ 130

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

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