

MUTYH Associated Polyposis (MAP) Syndrome via *MUTYH* Gene Sequencing --Test #706

Brief Description of Clinical Features: *MUTYH* Associated Polyposis (MAP) (OMIM 608456) is an autosomal recessive condition of Familial Adenomatous Polyposis (FAP) (OMIM 175100) caused exclusively by mutations in the *MUTYH* gene (OMIM 604933) (Al-Tassan et al. Nat Genet 30:227-232, 2002; Sieber et al. New Eng J Med 348:791-799, 2003). Individuals with MAP typically present by age 55 with multiple (between 10 and 1000) colorectal adenomas, some of which have or will become colorectal tumors (Poulsen & Bisgaard Curr Genomics 9:420-435, 2008). The *MUTYH* gene encodes a vital component of the Base Excision Repair (BER) system, which protects DNA from oxidative damage and the misincorporation of adenines opposite guanines during DNA replication (Lu et al. Front Biosci 11:3062-3080, 2006). As such, the molecular profile of colorectal adenomas and carcinomas taken from MAP patients includes G:C → T:A transversions in the adenomatous polyposis coli (*APC*) and *K-ras* tumor suppressor (*KRAS*) genes, among others (Lipton et al. Cancer Res 63:7595-7599, 2003; Jones et al. Br J Cancer 90:1591-1593, 2004).

Genetics: To date, about 100 pathogenic mutations have been reported in the *MUTYH* gene, nearly all (~99%) of which are single nucleotide variations, small insertions or deletions, or splice-site mutations (www.insight-group.org, www.hgmd.org). While MAP occurs in patients from various ethnic groups, specific *MUTYH* mutations are found in different populations. In European and North American MAP populations, two missense mutations, p.Tyr179Cys and p.Gly396Asp, are most common; both homozygous and compound heterozygous mutations contribute to the disease (Jones et al. Hum Mol Genet 11:2961-2967, 2002). In Asian MAP populations, common mutations include the missense mutation p.Arg245Cys, splice-site mutation c.934-2A>G, and p.Glu480Stop nonsense mutation; in these cases only homozygous mutations have been reported to contribute to disease (Tao et al. Carcinogenesis 25:1859-1866, 2004; Miyaki et al. Mutat Res 578:430-433, 2005). The penetrance of colorectal cancer (CRC) for biallelic carriers of *MUTYH* mutations is nearly 100% by the age of 60 (Farrington et al. Am J Hum Genet 77:112-119, 2005).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 16 exons of the *MUTYH* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000001.10 mRNA: NM_012222.2 Protein: NP_036354.1 (CCDS 520.1)

Indications for Test: Candidates for this test are patients with multiple colorectal adenomas—especially if no germ-line *APC* mutations have been identified or with recessive inheritance of colorectal adenomatous polyposis as suggested by family history. Relatives, particularly siblings, of patients with a verified *MUTYH* germline mutation are also candidates.

Sensitivity of Test: By definition, all MAP patients have biallelic germline mutations in *MUTYH*. However, mutations in *MUTYH* are also found in ~25% of patients initially diagnosed with FAP (Sampson et al. Lancet 362:39-41, 2003).

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

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of the *MUTYH* Gene: \$780

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x13	83898	\$ 220	Sequencing x13	83904	\$ 340
Separation x1	83894	\$ 50	Interpretation/Report x1	83912	\$ 100

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

Contact: Dr. Keith Nykamp, keith.nykamp@preventiongenetics.com, www.preventiongenetics.com