

Assay Summary

MUTYH Gene Mutation Analysis

MUTYH-Associated Polyposis

Synopsis

MUTYH-associated polyposis (MAP) (OMIM #608456) is an autosomal recessive disorder characterized by multiple colorectal adenomas and carcinomas. Individuals with MAP have an extremely high risk of developing colorectal cancer. MAP is caused by biallelic germline mutations in the mutY homolog (MUTYH) gene.^{1,2,4} The mean age of colorectal cancer diagnosis in untreated individuals is 45 years, several years later than in APC-related familial adenomatous polyposis (FAP).⁹ The phenotype is often undistinguishable from that of autosomal dominant FAP or attenuated FAP (AFAP) caused by mutations in adenomatous polyposis coli (APC) gene. The number of polyps in MAP patients is usually between 10 and 100, and affected individuals are often sporadic cases. However, biallelic MUTYH mutations have also been detected in patients affected with early-onset colorectal cancer without polyps and in one with more than 1000 polyps.^{7,8} The two most common mutations in Caucasians, accounting for about 75%-80% of mutant alleles, are Y165C (or Tyr165Cys) and G382D (or Gly382Asp).⁵ Prevalence of *MUTYH* mutations in other ethnic groups is currently unknown. The exact risk of colorectal cancer associated with monoallelic *MUTYH* mutation carriers remains uncertain; most large studies have described an odds ratio of <1.5.⁶

MUTYH gene is located on the short arm of chromosome 1 between positions 34.3 and 32.1.³ MUTYH is frequently also termed MYH. MUTYH is part of the Base Excision System which is responsible for the repair of oxidative DNA damage. Since 2002, biallelic germline mutations in the MUTYH gene were found to result in the accumulation of G:C→T:A transversion mutations in genes such as APC and KRAS, both of which have major roles in colorectal tumorigenesis.¹

Indications for testing

- 1) Individuals with FAP-like and AFAP-like phenotypes and in whom no inherited APC mutation could be identified
- 2) Predictive testing for at-risk family members of an individual diagnosed with polyposis and who tested negative for mutations in APC gene.

Methodology

Full gene sequencing of MUTYH: All of the 16 coding exons and associated intron junctions of the MUTYH gene are amplified using MUTYH specific primers, followed by direct DNA sequence analysis using an automated fluorescent sequencer. When a mutation is detected, confirmation is carried out by sequencing an independent PCR amplification in the opposite direction. If no mutation is found, sequence analysis is performed in both directions. Testing of at risk family members can be offered by DNA sequence analysis of only the region of the gene with the previously identified mutation.

Limitations

This method will not detect mutations located in regions of the genes that are not analyzed (non-coding exon sequences, intron sequences other than the splice junctions, and upstream and downstream sequences). The

method also will not detect inversions. Some sequence alterations that may be detected (such as those causing missense or synonymous changes) will be of unknown clinical significance. Interpretation of test results should be in the context of the patient's diagnosis, ethnicity, clinical and family histories, and other laboratory test results.

Specimen Requirements

(a) Blood samples: 2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes. Keep at ambient temperature and ship by overnight courier. Samples must be received in our laboratory within 72 hours of draw.

Note:

- i) for infants, a minimum of 3 ccs is sufficient.
- ii) we accept DNA; at least 10 micrograms is required.

(b) Prenatal samples: 2 T25 flasks of confluent cells sent padded to arrive on M/Tu/W. A blood sample from the mother maybe required (2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes) for use as positive control. Maternal cell contamination studies are not done here but are required for autosomal disorders and dosage analysis on X-linked disorders. We would be happy to assist in coordinating sending out a specimen for this purpose.

Test Request Form (TRF)

a) A completed MDL [TRF](#) is required for each specimen. Please submit the completed TRF with the specimen. Complete testing and billing information must be provided before the specimen is processed.

b) [General Cancer Patient Information Form](#): Include a completed General Cancer Patient Information for the proband and a complete pedigree.

<i>Order Codes</i>	<i>CPT Codes</i>	<i>TAT</i>
MUTYH –SEQ (MUTYH gene, full gene sequencing)	83890, 83898(x9), 83894, 83904(x9), 83912	4 wks
MUTYH –CAS (MUTYH gene, targeted mutation analysis, known mutation)	83890, 83898, 83894, 83904, 83912	3 wks
MUTYH-E07_E12 (MUTYH gene, sequencing (Exons 07, 12))	83890, 83898, 83894, 83904, 83912	3 wks
MUTYH –PD (MUTYH gene, known mutation detection, prenatal)	83890, 83898, 83894, 83904, 83912	2 wks
APC_MUTYH-COMP (APC and MUTYH: Full gene sequencing, APC: MLPA)	83890, 83898(x42), 83904(x42), 83894(x2), 83912(x3), 83896(x26), 83909	4 wks

References

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2. Jones S et al. Hum Mol Genet. 2002 Nov 1;11(23):2961-7.
3. Cheadle JP et al. Hum Mol Genet. 2003 Oct 15;12 Spec No 2:R159-65.
4. Sieber OM et al. N Engl J Med. 2003 Feb 27;348(9):791-9.
5. Gismondi V et al. Int J Cancer. 2004 May 1;109(5):680-4.
6. Peterlongo P et al. Carcinogenesis. 2006 Nov;27(11):2243-9.
7. Croitoru ME et al. J Natl Cancer Inst. 2004;96:1631-4.
8. Isidro G et al. Hum Mutat. 2004;24:353-4.
9. Nielsen M et al. J Med Genet. 2005 Sep;42(9):e54.

NOTE: This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.

