

Familial Adenomatous Polyposis, APC Sequencing and Deletion/Duplication, and *MUTYH* (*MYH*) 2 Mutations

FOR DIAGNOSTIC OR PRESYMPTOMATIC TESTING FOR FAMILIAL ADENOMATOUS POLYPOSIS, ATTENUATED FAP, TURCOT SYNDROME, GARDNER SYNDROME, AND MUTYH-ASSOCIATED POLYPOSIS

Disease Overview

- Colorectal cancer is the third most common form of cancer in the United States; individuals have a 6 percent lifetime risk of developing this disease.
- Most colorectal cancer is caused by somatic mutations and is not hereditary.
- *APC* is a tumor-suppressor gene. *APC* mutations may cause the following disorders: familial adenomatous polyposis (FAP), attenuated FAP, Gardner syndrome, and Turcot syndrome, all of which predispose individuals to colon cancer.
- FAP is characterized by the development of hundreds to thousands of adenomatous colonic polyps, usually beginning during early adolescence (7–36 years). Without a preventative colectomy, all individuals with FAP will develop colon cancer during their lifetime, with a mean diagnosis age of 39.
- Additional characteristics of FAP may include dental anomalies, polyps of the gastric fundus and duodenum, and congenital hypertrophy of the retinal pigment epithelium (CHRPE).
- Attenuated FAP differs from FAP in that affected individuals typically have 10–100 (average of 30) more proximally located polyps, and cancer generally occurs at a later age than for individuals with FAP.
- Gardner syndrome occurs in 20 percent of families with classic FAP and is associated with benign osteomas, desmoid tumors, and soft-tissue tumors.
- Turcot syndrome consists of colon polyps and central nervous system (CNS) tumors. Turcot syndrome associated with medulloblastoma is often caused by *APC* mutations, while Turcot with glioblastoma multiforme is usually caused by mismatch repair gene mutations.
- *MUTYH*-associated polyposis (MAP) is associated with 10–100 polyps, with an age of onset in the third decade or later.

Epidemiology

- FAP accounts for less than 1 percent of colorectal cancer cases.
- Approximately 1 percent of Caucasians are predicted to carry a *MUTYH* mutation.

Genetics

- Inheritance is autosomal dominant for *APC*-associated polyposis; 25 percent of cases are de novo.
- Penetrance of classic FAP is 100 percent in untreated individuals.
- Sequencing will detect approximately 90 percent of *APC* mutations; large deletion/duplication analysis is necessary to detect 10 percent of *APC* mutations.
- MAP is inherited in an autosomal recessive fashion and occurs due to biallelic mutations in the *MUTYH* (formerly *MYH*) gene.
- Approximately 20–30 percent of patients with 10–100 polyps have biallelic *MUTYH* mutations.
- Two *MUTYH* mutations, Y165C and G382D, account for 85 percent MAP in Caucasians.

Indications for Ordering

- Confirmation of a clinical diagnosis of FAP, attenuated FAP, Gardner syndrome, Turcot syndrome, or MAP.
- Individuals at risk for an *APC*-associated polyposis or MAP due to family history but without a known familial mutation.

Additional Ordering Notes

For optimal test interpretation, please complete the FAP Patient Information Form and submit with the sample.

Contraindications

- Prenatal testing.
- If testing relatives for a known familial *APC* mutation, please order Familial Mutation, Targeted Sequencing (ARUP test code 2001961).

Interpretation

- Identification of a single pathogenic mutation in the *APC* gene is predictive of FAP or *APC*-associated polyposis.

- Detection of two *MUTYH* mutations on opposite chromosomes is predictive of MAP. *MUTYH* sequencing is recommended for symptomatic individuals with only one identifiable *MUTYH* mutation.
- A negative result does not rule out FAP, *APC*-associated polyposis, or MAP due to the possibility of an undetectable mutation in the specific gene(s) analyzed or a mutation in another gene. *MUTYH* gene sequencing should be considered in this case.
- An uncertain result means that although a gene mutation was detected, it is unknown whether it is pathogenic or benign. Medical management should rely on clinical findings and family history.

Methodology

- Bidirectional sequencing of the entire coding region and intron-exon borders of the *APC* gene. Analytical sensitivity and specificity are 99 percent.
- Multiplex ligation-dependent probe amplification (MLPA) is performed to detect large deletions/duplications in the *APC* gene. Analytical sensitivity and specificity are 90 percent.
- Two *MUTYH* mutations, Y165C and G382D, are tested by PCR followed by fluorescence monitoring. Analytical sensitivity and specificity are approximately 99 percent. Clinical sensitivity for MAP is 85 percent in Caucasians.

Limitations

- Deep intronic or regulatory region mutations in the *APC* gene will not be identified.

- *APC* variants of uncertain significance may be detected.
- *APC* breakpoints of large deletions/duplications will not be determined.
- Only two targeted *MUTYH* mutations, Y165C and G382D, will be tested.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.

Related Tests

- Familial Adenomatous Polyposis (*APC*) Sequencing ([2004863](#))
- Familial Adenomatous Polyposis (*APC*) Deletion/Duplication ([2004920](#))
- Familial Mutation, Targeted Sequencing ([2001961](#))

References

1. GeneTests: *APC*-Associated Polyposis Conditions. <http://www.genetests.org> (accessed on April 5, 2011).
2. Half E, et al. Familial adenomatous polyposis. *Orphanet J Rare Dis* 2009;4:22.
3. Lindor NM, et al. Concise handbook of familial cancer susceptibility syndromes, 2nd ed. *J Natl Cancer Inst Monogr* 2008;38:1–93.

Test Information

2004915 **Familial Adenomatous Polyposis Panel: *APC* Sequencing, *APC* Deletion/Duplication, and *MYH 2* Mutations**

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.