City of Hope

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Assay Summary

APC (Adenomatous Polyposis Coli) Gene Mutation Analysis

Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP), Turcot Syndrome, Gardner Syndrome

Synopsis

APC-associated polyposis conditions result from germline mutations in the adenomatous polyposis coli (*APC*, OMIM# 611731*)* gene and cause a predisposition for colorectal cancer.[1,8] APC is a tumor suppressor gene located on the long arm of chromosome 5 in band q21. Most cases of Familial adenomatous polyposis (FAP) are caused by germ-line mutations in the APC gene.[1]

FAP is an autosomal dominant inherited disorder characterized by hundreds to thousands of adenomatous polyps multiple polyps in the internal lining of the colon and the rectum. However, up to 30 % of FAP cases arise from new mutations in APC gene.[1] Generally, polyps begin to develop during the second decade of life and 95% of individuals have polyps by age 35.[2] Almost 100% of individuals who carry an APC mutation will develop colorectal cancer if treatment is not provided at early stage.1 The mean age of colorectal cancer diagnosis in untreated individuals is 35-40 years.[3] FAP accounts for <1% of all colorectal cancers and it affects 1 in 8,000-10,000 individuals.[1]

The clinical criteria for diagnosis of FAP includes individuals that have i) more than 100 colorectal adenomatous polyps or ii) fewer than 100 colorectal adenomatous polyps and a family relative with FAP.

The variants of FAP are characterized by the number of polyps or by the extracolonic manifestation. The FAP variants are attenuated FAP, Gardner syndrome, and Turcot syndrome. Attenuated FAP is characterized by presence of fewer colonic polyps (average of 30), more proximally located polyps, and diagnosis of colon cancer at a later age; however, individuals still have a high risk of developing colorectal cancer.[7] AFAP is caused by germline mutations in the extreme 5′ or 3′ ends of APC or in the alternatively spliced region of exon 9.[12] Gardner syndrome is characterized by colonic polyposis typical of FAP together with osteomas and soft tissue tumors such as epidermal skin cysts, fibromas, desmoid tumors.8 Turcot syndrome is characterized by the association of colonic polyposis and central nervous system (CNS) tumors (medullablastoma).[5,6]

Extracolonic manifestations of classical FAP and its variants may include polyps in the gastric fundus and duodenum, dental anomalies, congenital hypertrophy of the retinal pigment epithelium (CHRPE), osteomas, and other malignant changes such as thyroid tumors, small bowl cancer, hepatoblastoma, and brain tumor.[1,4, 9]

Indications for testing

1) Confirmation of a clinical diagnosis of Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP), Turcot Syndrome, or Gardner Syndrome.
2) Predictive testing for at-risk family members of an individual diagnosed with FAP or APC-associated polyposis syndrome.

Methodology

Sequence analysis: Coding exons and associated intron junctions are captured and enriched using custom Agilent SureSelect technology. Next-generation sequencing is performed on Illumina MiSeq. Additional Sanger sequencing is performed for any regions with insufficient depth of coverage or for verification of suspect variant calls. Targeted testing for known familial mutation is performed by Sanger sequencing.

MLPA analysis for large deletions or duplications: Multiplex Ligation-Dependent Probe Amplification (MLPA, MRC-Holland) technology is used for detection of large deletions and duplications of one or more exons of the APC gene, including promoters 1A and 1B.

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

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.

Test Request Form (TRF)

a) A completed CMDL 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.

Order Codes	***CPT Codes***	***TAT***
APC-SEQ (APC gene, full gene sequencing by NGS)	81201, G0452	3 wks
APC-CAS (APC gene, targeted mutation analysis, known mutation)	81202, G0452	2 wks
APC-DEL (APC gene, MLPA analysis)	81203, G0452	3 wks
APC-DEL-CAS (APC gene, MLPA analysis, known deletions/duplications)	81203, G0452	3 wks

References

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7. Leppert M et al. *Science.* 1987; 238(4832): 1411–3.
8. Groden J et al. *Cell*. 1991; 66(3): 589–600.
9. Abdel-Rahman WM et al. *Ann Med*. 2004; 36(5):379-88.
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11. Sieber OM et al. *Proc Nati Acad Sci*. 2002; 99(5):2954-2958.
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NOTE: This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.