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Familial Adenomatous Polyposis and MUTYH-Associated Polyposis

Familial adenomatous polyposis (FAP) is caused by pathogenic variants in the *APC* gene resulting in the development of hundreds to thousands of adenomatous colonic polyps beginning in early adolescence. The lifetime risk for cancer in individuals with FAP is 100 percent. Additional symptoms may include dental anomalies, polyps of the gastric fundus and duodenum, and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Pathogenic *APC* variants may also cause other related syndromes, including attenuated FAP (AFAP), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), Gardner syndrome, and Turcot syndrome.

MUTYH-associated polyposis (MAP), caused by biallelic pathogenic variants in the *MUTYH* gene, can result in the development of colon polyps that are less numerous (typically 10-100) and is often diagnosed later in life. Genetic testing may be used to assess individuals at risk for FAP, other *APC*-associated polyposis, or MAP due to a suggestive personal or family history.

DISEASE OVERVIEW

Incidence/Prevalence

- Colorectal cancer (CRC): ~140,000/year in U.S.
  - Lifetime risk of developing CRC: 6%
  - Majority of CRC is not hereditary or inherited
  - FAP and MAP each account for <1% of CRC cases
- ~1% of Caucasians are predicted to carry a single pathogenic *MUTYH* variant

Age of Onset

- FAP: early adolescence
- MAP: third decade of life or later

Symptoms

FAP

- Development of hundreds to thousands of adenomatous colonic polyps
- Dental anomalies
- Polyps of gastric fundus and duodenum
- Congenital hypertrophy of retinal pigment epithelium (CHRPE)
- Begins generally during early adolescence
- Overall age range of 7-36 years
- Without a preventive colectomy, all individuals with FAP will develop colon cancer during their lifetime
- Mean age at time of diagnosis is 39 years

AFAP

Differs from FAP:

- Typically fewer polyps; 10-100, with an average of 30
- More proximally located polyps
- Cancer generally occurs at a later age

Gardner Syndrome

- Occurs in 20% of families with classic FAP

TESTS TO CONSIDER

Familial Adenomatous Polyposis Panel: (APC) Sequencing and Deletion/Duplication, (MUTYH) 2 Mutations 2004915
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Preferred diagnostic or predictive test for FAP and MAP

Familial Adenomatous Polyposis (APC) Sequencing 2004863
Method: Polymerase Chain Reaction/Sequencing

Acceptable diagnostic or predictive test for FAP
For classic FAP, consider *APC* sequencing and deletion/duplication testing

MUTYH-Associated Polyposis (MUTYH) Sequencing 2006191
Method: Polymerase Chain Reaction/Sequencing

Diagnostic or predictive test for MAP

Related Tests

Hereditary Gastrointestinal Cancer Panel, Sequencing and Deletion/Duplication 2013449
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray/Sequencing/Multiplex Ligation-dependent Probe Amplification

Recommended test to confirm a diagnosis of hereditary gastrointestinal (GI) cancer in individuals with a personal or family history of GI cancer and/or polyposis

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

- Associated with
  - Benign osteomas
  - Desmoid tumors
  - Soft-tissue tumors

Turcot Syndrome
- Colon polyps
- Central nervous system tumors
- Associated with medulloblastoma
- Often caused by pathogenic variants in *APC* gene
- Turcot with glioblastoma multiforme is usually caused by pathogenic variants in a mismatch repair gene

GAPPS
- Associated with pathogenic variants in promoter 1B of the *APC* gene
- Fundic gland polyposis
- Increased risk for gastric cancer

MAP
- 10-100 polyps
- ~20-30% of patients with 10-100 polyps have biallelic pathogenic *MUTYH* variants
- Age of onset is third decade or later

GENETICS

Genes

APC, MUTYH

Inheritance

- *APC* is autosomal dominant
- *MUTYH* is autosomal recessive

Penetrance

- Classic FAP: 100% in untreated individuals
- Individuals with MAP and colorectal cancer
  - 20% by age 50
  - 43% by age 60 [1]

De novo Variants

APC: 25% of cases

TEST INTERPRETATION

Sensitivity/Specificity

Analytical sensitivity/specificity: 99% for *APC* and *MUTYH*

Clinical Sensitivity

- Classic FAP: ~95%
  - ~90% of pathogenic variants detected by sequencing [2,3]
  - ~8-12% of pathogenic variants detected by deletion/duplication testing [4,5]
- Attenuated FAP: <30% [6]
- GAPPS: unknown
- MAP
  - 85% of pathogenic *MUTYH* variants in Northern European Caucasians detected by the 2 pathogenic variants test (Y165C and G382D) [7,8]
  - 98% of pathogenic *MUTYH* variants detected by full gene sequencing [9,10]

Results

Positive
- Identification of a single pathogenic variant in *APC* gene
  - Predictive of FAP or *APC*-associated polyposis
- Detection of two pathogenic *MUTYH* variants on opposite chromosomes

- Predictive of MAP
- Identification of a single pathogenic *MUTYH* variant
  - Individual is a carrier of MAP
  - Individual could be affected if another unidentified pathogenic *MUTYH* variant is present on the opposite chromosome
  - Possible increased risk for cancer has been associated but is not well defined

Negative

- No pathogenic variants were detected in *APC* or *MUTYH* genes
- Does not rule out FAP, *APC*-associated polyposis, or MAP

Inconclusive

- Variant(s) of unknown clinical significance may be detected

Limitations

Diagnostic errors can occur due to rare sequence variations

APC Gene

- Deep intronic or regulatory region variants will not be identified
- Breakpoints of large deletions/duplications will not be determined

MUTYH Gene

- FAP panel: only two pathogenic *MUTYH* variants will be tested (Y165C and G382D)
- Not detected on the *MUTYH* Sequencing test:
  - Large deletions or duplications
  - Deep intronic, regulatory region, or promoter pathogenic variants

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