REVIEW

# The genetic basis of familial adenomatous polyposis and its implications for clinical practice and risk management

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**Abstract:** Familial adenomatous polyposis (FAP) is an inherited disorder that represents the most common gastrointestinal polyposis syndrome. Germline mutations in the *APC* gene were initially identified as responsible for FAP, and later, several studies have also implicated the *MUTYH* gene as responsible for this disease, usually referred to as *MUTYH*-associated polyposis (MAP). FAP and MAP are characterized by the early onset of multiple adenomatous colorectal polyps, a high lifetime risk of colorectal cancer (CRC), and in some patients the development of extracolonic manifestations. The goal of colorectal management in these patients is to prevent CRC mortality through endoscopic and surgical approaches. Individuals with FAP and their relatives should receive appropriate genetic counseling and join surveillance programs when indicated. This review is focused on the description of the main clinical and genetic aspects of FAP associated with germline *APC* mutations and MAP.

**Keywords:** colorectal cancer, familial adenomatous polyposis, MAP, *APC*, *MUTYH*

## Introduction

Familial adenomatous polyposis (FAP) refers to an inherited syndrome characterized by the development of multiple adenomas in the colorectum, a high risk of colorectal cancer (CRC), and the existence of extracolonic manifestations. Germline *adenomatous polyposis coli (APC)* mutations were firstly described in 1991[1,2] as causing FAP with an autosomal dominant pattern of inheritance. Since then, a great body of evidence has been generated, including pathophysiology, genetics, clinical phenotype, and prevention. In 2002, another polyposis gene was identified, the *mutY homolog (MUTYH)* gene, in which biallelic mutations cause an autosomal recessive pattern of inheritance, usually referred to as *MUTYH*-associated polyposis (MAP).[3] This review is focused on the description of the key clinical and genetics aspects of FAP associated with germline *APC* mutations and MAP.

## *APC*-associated FAP

*APC*-FAP (OMIM #175100) is an autosomal-dominant inherited disease characterized by the development of multiple adenomas throughout the colorectum.[4] It represents less than 1% of all CRC cases, and is the most common gastrointestinal polyposis syndrome, with an incidence of one case per 10,000 subjects.[5]

## *APC* gene

*APC* is a tumor-suppressor gene that is located on chromosome 5q21-q22. The gene has 15 exons, with exon 15 individually representing >75% of the coding sequence and the most common target of both germline and somatic mutations. The *APC* gene encodes a

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protein of 2,843 aminoacids (310 kDa) that plays an outright role in the *Wnt* signaling pathway.[6] This multifunctional protein occurs in several isoforms within cells, containing several aminoacid motifs and domains allowing it to oligomerize, as well as interact with numerous other molecules (Figure 1A).[7,8] The APC protein functions as a tumor suppressor by negatively regulating the β-catenin oncoprotein. The APC protein leads to ubiquitination and degradation of β-catenin; so in the absence of it, β-catenin accumulates in the nucleus and interacts with factors that up-regulate the transcription of genes involved in cell cycle entry, proliferation, differentiation, migration, apoptosis, and progression.[9] In addition, APC stabilizes microtubules, leading to chromosomal stability.[10] Inactivation of APC can lead to defective chromosome segregation and aberrant mitosis.

Germline mutations in the *APC* gene are responsible for most cases of FAP. Individuals with a germline *APC* mutation develop multiple adenomas as a result of inactivation of the remaining allele in the colorectum by additional somatic *APC* mutations or loss of heterozygosity (LOH) at this locus.

In a recent large cross-sectional study, *APC* mutations were found in 80% (95% CI 71%–87%) of individuals with more than 1,000 adenomas, 56% (95% CI 54%–59%) in those with 100–999 adenomas, 10% (95% CI 9%–11%) in those with 20–99 adenomas, and 5% (95% CI 4%–7%) in those with 10–19 adenomas.[11] Inheritance of FAP is autosomal dominant although up to 25% of FAP patients carry de novo germline mutations.[12,13]

## Mutational landscape

Since the identification of the *APC* gene, more than 1,100 unique likely pathogenic germline mutations have been reported (http://www.lovd.nl/apc). The majority of them represent truncating mutations, being nonsense mutations

(28%), small insertions (10%) or small deletions (46%) that lead to a truncated protein.[14] Although infrequent, there are also missense mutations (3%) and gross alterations (ie, single or multiexon deletions and duplications) (13%).[14]

a.  Truncation mutations: As mentioned earlier, the great majority of FAP-associated *APC* mutations lead to a truncated protein, mainly due to a frameshift or nonsense variant. The most common nonsense changes are C>T mutations,[15] and the majority of germline mutations in *APC* occur in the 5′ half of the gene, leading to the elimination of most, if not all, of the 20-aminoacid repeats involved in regulating β-catenin levels and SAMP repeats involved in axin binding (Figure 1A).[16,17]

b.  Missense mutations: Although rare, more than 60 different missense variants of *APC* have been described in the literature as potentially pathogenic. The two missense variants most frequently reported are I1307K and E1317Q. The I1307K variant, present in 6% of all individuals of Ashkenazi Jewish ancestry, does not lead to a polyposis phenotype, but it carries an increased (10%–20%) lifetime risk of developing CRC.[16] The E1317Q missense variant has also been associated with a moderate risk for colorectal adenomas and CRC.[18]

c.  Splicing mutations and gross alterations: Splice altering mutations and large deletions/duplications have also been described, and recent data suggest that especially gross alterations affecting the promoter of coding regions may have been underreported, accounting for up to 20% of FAP families.[19–21]

d.  De novo mutations and germline mosaicism: Most of the *APC* germline mutations are inherited, but can also occur de novo in a patient with no family history of the disease, representing between 11% and 25% of all FAP cases.[22] The estimated rate of *APC* new mutations is between 4
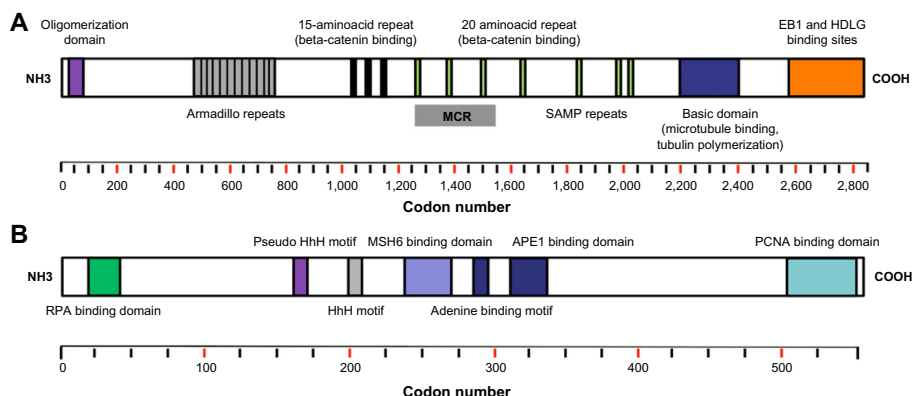


**Figure 1** The functional domains of the APC and MUTYH proteins.
**Notes:** (**A**) The APC protein consists of an oligomerization domain and an armadillo region in the N-terminus, a number of 15- and 20-aminoacid repeats in its central portion, and a C-terminus that contains a basic domain and binding sites for EB1 and the human disc large (HDLG) protein; (**B**) The MUTYH protein and its different domains.
**Abbreviations:** RPA, replication protein A; HhH, helix-hairpin-helix; APE1, apurinic endonuclease 1; PCNA, proliferating-cell nuclear antigen; MCR, mutation cluster region.

and $9\times10^6$ mutations/gametes/generation,[23] and equal susceptibility for mutagenesis during spermatogenesis and oogenesis has been described. A significant percentage of the de novo cases arise in the mosaic form, affecting only a subset of cells in the affected individual (it is estimated that one-fifth of the de novo cases of FAP are mosaic).[24,25]

e. Mutational hotspots: The mutational hotspots in the *APC* gene are located in the 5′ part of exon 15 at codons 1,309 and 1,061, accounting for approximately 17% and 11% of all germline *APC* mutations, respectively. Because of the accumulation of mutations from codon 1,250 to 1,464, this region is termed the mutation cluster region (MCR) (Figure 1A).[26]

The type of germline mutation in the *APC* gene determines the nature of the second hit. If the germline mutation occurs between codons 1,194 and 1,392, then there is a strong association with allelic loss of *APC* as the second hit. If the germline mutation occurs outside this region, the second hit is most likely to induce a truncating mutation in the MCR.[27]

## Phenotypes: classic and attenuated FAP (AFAP)

According to the number of polyps and the age of onset, two major phenotypes have been described for FAP (Table 1):

a. Classic FAP: It is characterized by the presence of hundreds to thousands of adenomatous polyps throughout the colon and the rectum. At the time of adolescence, the polyps are usually identified in the recto-sigmoid as small polyps, and thereafter, increase in size and number. About half of FAP patients develop adenomas by 15 years of age and 95% by 35 years.[28,29] CRC inevitably occurs at an earlier age than sporadic CRC (average age of 35 years), but only rarely before the age of 20 years.

b. AFAP: It is a variant of FAP with a mild disease course, characterized by a reduced number of polyps (10–100), later age of onset, frequently right-sided distribution of polyps, and lower CRC risk (up to 70%). The clinical definition of AFAP is controversial and should be considered in any patient with 10–99 adenomas, although a precise diagnosis is often difficult in a single patient.[11] *APC*-associated AFAP can mimic MAP or even sporadic polyp development. Examination of multiple family members can often determine the phenotype.

## Extracolonic manifestations

In many FAP patients, extracolonic manifestations are present, including gastric and duodenal polyps, desmoid tumors (DT) thyroidal and brain tumors, osteomas, congenital hypertrophy of the retinal pigmented epithelium, supernumerary teeth, and epidermoid cysts.

## Gastroduodenal polyps

The most common extracolonic manifestations in FAP patients are upper gastrointestinal polyps. They are located in the stomach, duodenum, and the periampullary region. Gastric polyps are usually benign fundic gland polyps (FGP), and occur in 20%–84% of FAP patients.[30] Although FAP-associated FGPs have been traditionally thought of as nonneoplastic and usually do not require intervention, cases of high-grade dysplasia and gastric carcinoma arising from FGPs in FAP have been reported.[31] Gastric adenomatous polyps represent around 10% of gastric polyps, and when they occur, they are most commonly located in the antrum.

**Table 1** Clinical phenotypes of *APC*-associated FAP and *MUTYH*-associated polyposis

| *APC* | *MUTYH* |
|---|---|
| Classic FAP | Attenuated FAP-classic FAP |
| • >100 colorectal adenomas | • Usually attenuated FAP phenotype and in some cases classic FAP |
| • Dominant pattern of inheritance (although 25% of cases mutation de novo) | • Recessive pattern of inheritance |
| • Early onset (adolescence) | Patients with >10 colorectal polyps (adenomatous and serrated) |
| • CRC risk of 100% | • A minority of MAP patients fulfill SPS criteria usually with synchronous adenomatous polyposis |
| AFAP | CRC without polyposis |
| • 10–99 colorectal adenomas | • Early onset of CRC (≤50 years old) |
| • Right-sided distribution in the colon | • Some cases with MMR deficiency has been reported |
| • Later age of onset | Extracolonic manifestations |
| • Lower CRC risk (up to 70%) | • Duodenal polyposis – duodenal cancer |
| Extracolonic manifestations | • Increased risk for some extraintestinal cancers |
| • Gastric and duodenal polyps, desmoids tumors, thyroidal and brain tumors, osteomas, congenital hypertrophy of the retinal pigmented epithelium, supernumerary teeth, and epidermoid cysts | |

**Abbreviations:** FAP, familial adenomatous polyposis; CRC, colorectal cancer; AFAP, attenuated familial adenomatous polyposis; MAP, *MUTYH*-associated polyposis; SPS, serrated polyposis syndrome; MMR, mismatch repair.

Despite the malignant potential of gastric dysplastic FGP and adenomas, gastric carcinoma is very rare in FAP patients (incidence <1%).[31]

After the colorectum, the duodenum is the second most common site of polyps in FAP patients. Duodenal adenomas arise in most patients with FAP with a lifetime risk of almost 100%.[32] These polyps have a predilection for the second and third portion of the duodenum, especially the periampullary region. This pattern probably reflects the exposure of duodenal mucosa to bile acids, suggesting a role for these compounds in duodenal carcinogenesis. Duodenal cancer is the second cause of cancer death in FAP patients, with a cumulative lifetime risk of 5%.[33]

## Extraintestinal manifestations

Both benign and malignant extracolonic manifestations are common in FAP patients. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is the most common extracolonic manifestation of FAP (70%–80%). It appears as gray-brown to black round or oval lesions in the retina, and is not known to cause any clinical problems. Epidermoid cysts (50%) and fibromas (25%–50%) are considered subcutaneous lesions, and may cause cosmetic problems. Other benign manifestations include dental abnormalities (79%–90%), osteomas (50%–90%), and desmoid tumors (DT) (10%–15%).[34,35]

DTs are slow-growing mesenchymal neoplasms characterized by the lack of metastatic potential but an aggressive local behavior due to their infiltrative growth and a high local recurrence rate following complete resection. Compared to the general population, FAP patients are at approximately 1,000-fold increased risk of developing DT.[36] Most DTs in FAP patients arise in the abdomen, most frequently in the abdominal wall or intra-abdominal. Risk factors for DT development include abdominal surgery, a positive family history for desmoids, and as explained below, the site of the mutation in the *APC* gene. Although benign histologically, they represent one of the main causes of death in patients with FAP.[37]

Extracolonic malignancies include thyroid cancer (2%–3%), pancreatic mucinous adenocarcinomas (1%), hepatoblastoma (1%), and brain tumors (ie, medulloblastoma; <1%).

Papillary thyroid carcinoma is the third most common malignancy associated with FAP (after CRC and duodenal cancer). The lifetime risk of developing thyroid cancer is low, and estimated to be 2%–3% with a rate of approximately 160 times that of the general population.[37] There is a remark-

able female preponderance (female to male ratio 17:1), and the average age at diagnosis is 27 years.[35] Although thyroid cancer in FAP patients can be multifocal and regional lymph node involvement may occur, prognosis is usually very favorable.

Hepatoblastoma is an embryonal neoplasm that predominantly occurs in children between 6 months and 3 years of age, but the age at diagnosis can range from prenatal stages to 16 years. Although the combination of chemotherapy and surgery is very successful, an estimated 25% of all patients do not survive this disease.

The combination of colorectal and extracolonic manifestations is known as Gardner's syndrome, whereas the association between colorectal polyposis and brain tumors corresponds to Turcot's syndrome.

## Genotype–phenotype correlation

The existence of a spectrum of polyposis caused by mutations located in different regions of the *APC* gene was suggested by Leppert et al in 1990.[38] Since then, several studies have observed an association between the clinical manifestation and the location of the germline mutation. Broadly, the classic phenotype of more than 100 adenomas is associated with mutations between codons 178 and 309, and between codons 409 and 1,580, corresponding to exons 5–8, 9–14 and the first half of the large final exon 15.[6] Based upon the genotype–phenotype correlation, FAP can be classified into three categories. Profuse or aggressive polyposis (characterized by an earlier onset and greater number of polyps) has been associated with mutations from codons 1,250 to 1,464, mainly in codon 1,309. AFAP is usually associated with mutations at the extreme 5′ (before codon 157) and 3′ (after codon 1,595) ends of the *APC* gene, and in the alternatively spliced region of exon 9 (codons 213–412). Finally, in classic FAP, the intermediate phenotype, mutations are located in the remainder of the *APC* gene, in particular the 5′ end between codon 157 and 1,595 excluding codon 1,309.[6,26,39,40] (Figure 2).

Extracolonic manifestations have been also associated with specific *APC* mutations, especially those located beyond codon 1,400. CHRPE is linked to mutations located between codon 311 and codon 1,465, and the presence of DTs is related to mutations at the 3′ end of the *APC* gene, in general downstream codon 1,400 (1,445–2,011). The presence of gastric and duodenal polyps have been related to mutations at the 3′ end, before codon 1,395, but also exon 4 and codons 564–1,493.[26] Other genotype–phenotype correlations have been observed with limited evidence.[29] Almost 95% of the
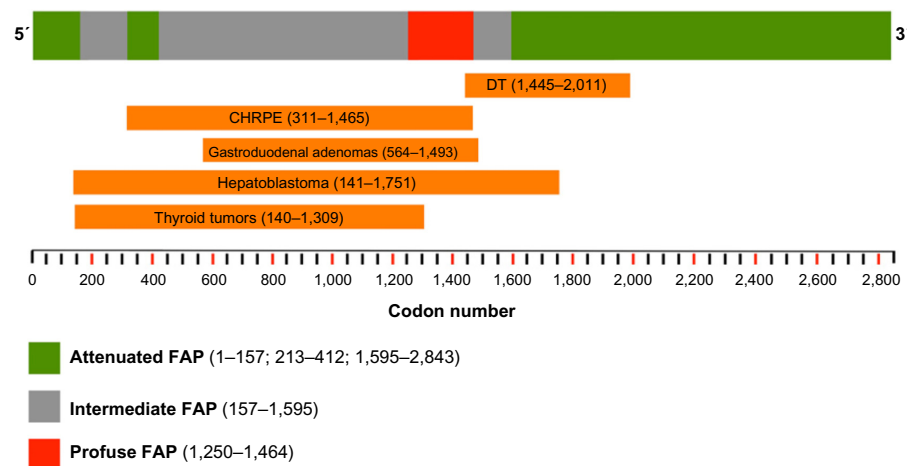
**Figure 2** Genotype–phenotype correlation for the *APC* gene.
**Abbreviations:** DT, desmoid tumors; CHRPE, congenital hypertrophy of the retinal pigment epithelium; FAP, familial adenomatous polyposis.

mutations in hepatoblastoma patients are located on the 5′ to mid region of the *APC* gene between codons 141 and 1,751. Thyroid tumors have been related to mutations between codons 140 and 1,309 (Figure 2).[26,35]

Although genotype–phenotype association is observed, there is a considerable variability among individuals, even among family members, suggesting the influence of environmental factors and/or the effect of modifier genes.[41,42]

## Genetic testing algorithm

Prior to gene testing, affected individuals must receive genetic counseling, so that they understand the pros and cons of cancer genetic testing. Patients must be able to determine whether such testing is acceptable emotionally and take into account other potential issues (such as confidentiality). Once genetic counseling is properly done, if the causative mutation is detected, then presymptomatic diagnosis can be offered to at-risk relatives of the index case. Mid-adolescence is the right time to perform genetic testing, when the diagnosis begins to gain clinical importance in terms of cancer prevention. If germline pathogenic mutation is not found, gene testing cannot be offered to family members, and clinical diagnosis and surveillance is mandatory for all first-degree relatives.

Several methods for *APC* gene testing have been used. Direct sequencing of all 15 coding exons of the *APC* gene is considered the gold standard for mutation detection. However, other approaches have been used. In the past, several clinical laboratories used the RNA-based protein truncation test (PTT). The method is based on the size analysis of products resulting from in vitro transcription and translation, which has a sensitivity ranging from 70% to 90%. However, the PTT

approach has disadvantages, including assay artifacts and an inability to detect nontruncating mutations. Other methods include scanning methods (such as conformation strand gel electrophoresis), followed by sequencing of aberrant fragments. However, none of these methods has the detection sensitivity of direct sequencing, which is a standard method in most clinical laboratories for detecting point mutations and small insertions or deletions, which account for >85% of the *APC* mutations. The remaining 10%–15% of mutations are gross deletions and duplications, which can be detected by multiplex ligation-dependent probe amplification (MLPA), Southern blot, or real-time quantitative PCR analysis.[43–45]

Current guidelines recommend that FAP testing should be performed using full sequencing of the *APC* gene, and if no mutation is detected, then testing for large gene rearrangements should be completed.[14]

## Clinical management
### Colorectal adenomas and CRC

The goal of colorectal neoplasia management in FAP patients is to prevent CRC.[13] This management includes both endoscopic polypectomy and surgery. In families with classic FAP, flexible sigmoidoscopy is an adequate technique because of the almost universal distribution of adenomas, including the rectum. The age at which screening should start depends on the risk of malignant transformation of the colorectal adenomas. In FAP patients, the risk of developing CRC before age 20 is very low; however, up to 1.5% of CRC occur between 11 and 20 years of age.[34] Accordingly, sigmoidoscopy screening should be carried out every 2 years, starting at age 12–14 years, and be continued lifelong in mutations carriers. Once adenomas are detected, total

colonoscopy should be carried out annually until colectomy is planned (Table 2).[34]

In AFAP cases, since adenomas can be localized in the right colon, colonoscopy is recommended instead of sigmoidoscopy. In this setting, screening should be carried out every 2 years until polyposis is diagnosed, starting at the age of 18–20 years. Once adenomas are detected, colonoscopy should be carried out annually.[34]

Surgical removal of the colon at a premalignant stage is a key to prevent the morbidity and mortality associated with advanced CRC. In classic FAP, prophylactic colectomy is usually recommended, when polyposis is profuse or "worrisome" polyps are identified (ie, >1 cm, ulcerated, high grade dysplasia). Most patients with classic FAP undergo surgery between the age of 15 and 25 years. The treatment of AFAP is commonly endoscopic, and only if this is not possible, surgery is performed in a similar manner as in classical FAP.

Surgical options include both proctocolectomy with ileal pouch-anal anastomosis (IPAA) and total colectomy with ileorectal anastomosis (IRA). Compared with IPAA, IRA is relatively simple, with a lower complication rate and usually good bowel function after surgery. For IPAA, more extensive surgery is needed (including pelvic dissection), causing reduction of fertility and worse bowel function.[46] The choice of the surgical technique mainly depends on the age at diagnosis, desmoids, fertility, and the severity of rectal polyposis (>15–20 polyps), as well as patient decision after receiving comprehensive information on the benefits and risks of each approach.[34] Some authors have proposed to use the evidence of genotype–phenotype association in guiding the surgical treatment of patients with a relatively spared rectum.[26,34,47] An IPAA may be recommended in patients with a severe genotype because such patients are at increased risk of developing severe rectal polyposis that will require a secondary proctectomy if IRA is performed.

After surgery, endoscopic follow-up is recommended for those patients with rectal remnant, due to the risk of developing rectal cancer (up to 30% of the cases). Many studies have shown that adenomas and occasionally even adenocarcinomas have been found in the ileo-anal pouch after restorative proctocolectomy.[13,34] Therefore, the surveillance of the pouch and the transitional anal zone is essential.

## Gastroduodenal polyps

In general, screening for extracolonic manifestations should start when colorectal polyposis is diagnosed or at the age of 25–30 years. Gastroduodenal endoscopy using both front and side-view scopes (in order to correctly visualize the Vater's ampulla) should be performed every 5 years until adenomas are detected.[34]

In current practice, given the relative rarity of gastric adenocarcinoma, upper gastrointestinal endoscopic surveillance is driven by the greater risk of duodenal cancer. The stomach is visualized as part of this surveillance, but

**Table 2** Management recommendations for FAP

| Syndrome | Cancer risk | Screening technique | Initiation and periodicity |
|---|---|---|---|
| *APC*-FAP[32,87] | Colorectal | Classic FAP: | |
| | | Sigmoidoscopy | Initiation at 12–14 years |
| | | | Every 2 years |
| | | Colonoscopy | Initiation when adenomas are found at sigmoidoscopy. Every year until colectomy planned |
| | | Attenuated FAP: | |
| | | Colonoscopy | Initiation at 18–20 years, every 2 years |
| | | | If adenomas found → annual colonoscopy and polypectomy if manageable endoscopically |
| | Duodenum | Upper endoscopy (frontal and side-view scopes) | Starting when colorectal polyposis is diagnosed or at 25–30 years |
| | | | Every 5 years |
| | | | If adenomas detected → periodicity depends on the Spigelman stage |
| | Thyroid | Cervical palpation and/or ultrasonography | Starting at 25–30 years, annually |
| | Desmoids tumors | CT or MRI | Individualize (positive family history for desmoids, abdominal surgery) |
| *MUTYH* associated polyposis[32,87] | Colorectal | Colonoscopy | Starting at 18–20 years, every 2 years |
| | | | If adenomas found → annual colonoscopy and polypectomy if manageable endoscopically |
| | Duodenum | Upper endoscopy (frontal and side-view scopes) | Starting when colorectal polyposis is diagnosed or at 25–30 years |
| | | | Every 5 years |
| | | | If adenomas detected → periodicity depends on the Spigelman stage |

**Abbreviations:** FAP, familial adenomatous polyposis; CT, computed tomography; MRI, magnetic resonance imaging.

biopsy or polypectomy is undertaken only for large or unusual looking lesions, especially in the antrum.[30,31]

To standardize the management of duodenal polyps in FAP, Spigelman et al developed a classification system based on four prognostic variables (Table 3): number of polyps, size, histology, and degree of dysplasia.[32,48] Stage I (4 points) indicates mild disease, whereas stages III–IV (>6 points) imply severe duodenal polyposis, with a significant risk of duodenal cancer (7%–36%).[49] Approximately 80% of the patients have stage I–III disease, and 10%–20% have stage IV disease. Current evidence indicates that duodenal inspection with chromoendoscopy or narrow-band imaging increase the detection of duodenal adenomas but without a considerable change in Spigelman stages.[50,51]

The management of patients with multiple larger adenomas (Spigelman stage III or greater) is challenging, and should be centralized in expert centers. The recurrence rate of adenoma development after endoscopic treatment is high (>50%), and treatment is associated with a high complication rate (perforation, hemorrhage, and pancreatitis).[52] Because it is not feasible to remove all adenomas, the usual approach is to remove only large adenomas (>1 cm) or adenomas with high-grade dysplasia, with the aim of delaying/avoiding surgery. In Spigelman IV cases, surgery is often necessary, including duodenotomy with polypectomy, pancreas-sparing duodenectomy, and duodenal-pancreatectomy.[33,52]

## Management of other tumors

Given the increased risk for thyroid cancer, there is expert consensus that thyroid palpation and/or annual cervical ultrasonography should be performed, starting at the age of 25–30 years.[34]

The development of DT is mainly related to a positive family history, abdominal surgery, and the site of the mutation, and can occur inside the abdomen or in the abdominal wall. DT can be diagnosed by computed tomography (CT) scanning or magnetic resonance imaging (MRI). The options for treatment include pharmacological treatment (nonsteroidal anti-inflammatory drugs [NSAIDs] and/or antiestrogens),

chemotherapy, surgical excision, or radiotherapy.[34] The evidence for the efficacy of these treatments is poor and is based on small studies. However, because of the high recurrence rate of DT, surgical resection of intra-abdominal tumors should be delayed unless complications appear. Experts recommend as the first line of treatment in patients with large or growing DT sulindac with tamoxifen, and when patients with intra-abdominal tumors do not respond to this treatment, chemotherapy or radiation is indicated. Abdominal wall DT and mesenteric DT should be considered differently. For the treatment for abdominal wall DT, surgery is usually used as a first-line treatment. However, for mesenteric DT, the optimal management strategy should be individualized, taking into consideration the extent of disease, morbidity, and potential benefit versus risk of the different treatment modalities.[34]

The incidence of other less common extraintestinal malignancies (pancreatic, brain, adrenal, among others) is so low that the use of additional costly imaging studies is not currently recommended. However, surveillance tests should be considered in patients with a strong family history of any of these specific extraintestinal manifestations and in those presenting with symptoms that could be attributed to these tumors.

## Chemoprevention

Chemoprevention using NSAIDs has been proposed in FAP patients. The first drug that was shown to be effective in FAP was sulindac.[53] Long-term use of this drug reduced the number of colorectal adenomas by >50% in the colon as well as in the rectum of patients after colectomy, but not in duodenal polyposis. However, sulindac does not prevent the development of adenomas in FAP.[34] Selective COX-2 inhibitor (cyclooxygenase-2) celecoxib, associated with fewer gastrointestinal side effects than sulindac, was found to reduce the number of colorectal adenomas by 28%,[54] and also reduced the number of duodenal adenomas.[52,55] However, cardiovascular effects (myocardial infarction or stroke) have been described in long-term users of another selective COX-2 inhibitor (rofecoxib), and therefore the role of these drugs remain controversial, and should be considered only in selected patients without cardiovascular risk factors.[34]

Although NSAIDs (sulindac, celecoxib) do not replace surgical treatment for colonic FAP, they may play a role in postponing surgery in patients with colonic polyposis or patients with rectal polyposis after colectomy. Regarding duodenal polyposis, the use of celecoxib might be justifiable for patients with severe duodenal polyposis (Spigelman stage III or IV), because the endoscopic and

**Table 3** Spigelman classification

| Findings at duodenoscopy | 1 point | 2 points | 3 points |
|---|---|---|---|
| Number of adenomas | 1–4 | 5–20 | >20 |
| Size (mm) | 1–4 | 5–10 | >10 |
| Histology | Tubular | Tubulovillous | Villous |
| Dysplasia | Mild | Moderate | Severe |

**Notes:** Staging according to score: stage 0: 0 points; stage I: 4 points; stage II: 5–6 points; stage III: 7–8 points; stage IV: 9–12 points. Data from Spigelman et al.[48]

surgical treatment options in such cases are associated with significant complications. Though celecoxib is registered for the treatment of FAP in several countries, some specialists are reluctant to prescribe it because of the cardiovascular effects, and hence this drug is rarely used.[34]

## MAP

MAP (OMIM #608456) is an autosomal-recessive inherited disorder caused by biallelic germline mutations in the *MUTYH* gene. It was first described in 2002 by Al-Tassan et al in a British family with three affected members and recessive inheritance of multiple colorectal adenomas and carcinoma.[3] Patients with MAP show a great variability in clinical features, but usually present with an attenuated polyposis phenotype, showing fewer than 100 adenomas. Some patients develop extracolonic manifestations indistinguishable from that of FAP patients.

### *MUTYH* gene

The *MUTYH* gene is located on chromosome 1p34.3–1p32.1, and contains 16 exons that encode a 535 aminoacid protein (Figure 1B).[56] The *MUTYH* gene encodes a member of the base excision repair (BER) system. This system is composed of three enzymes (MUTYH, OGG1, and MTH1) that contribute to protect cells against the mutagenic effects of aerobic metabolism, specifically the oxidation of a guanine, leading to the formation of 8-oxo-7, 8-dihydro-2′-deoxyguanosine (8-oxoG). MUTYH acts together with MTH1 and OGG1 to prevent somatic mutations induced by 8-oxoG and its high affinity for adenine (A) instead of cytosine. Specifically, MUTYH is responsible for the removal of adenines mispaired with 8-oxoG.[57–59] In the absence of a functional copy of MUTYH due to biallelic mutations, when an oxo-G:A mismatch is present in the DNA template, a G:C to T:A transversion occurs in the subsequent round of replication. For this reason, somatic G:C to T:A transversions in genes such as *APC* or *KRAS* frequently occur in *MUTYH*-associated adenomas and tumors.[3,60] One such transversion in the *KRAS* gene (c.34G>T in codon 12) is frequently encountered (64%) in patients with MAP CRC.[61] Therefore, the analysis of somatic *KRAS* has been recommended as a prescreening test to identify CRC patients eligible for *MUTYH* germline molecular genetic testing. Since MAP patients can present with conventional adenomas as well as serrated polyps (hyperplastic polyps, sessile serrated adenomas), the existence of two distinct pathways has been suggested, one leading to conventional adenomas with *APC* and/or *KRAS* mutations, and one separate non-*APC* route leading to hyperplastic polyps and sessile serrated adenomas with *KRAS* mutations.[62,63]

## Mutational landscape

More than 300 unique sequence variants have been identified in this gene, including more than 80 pathogenic mutations (http://www.lovd.nl/mutyh).[64] The majority of them are missense substitutions followed by a minority of splice site or truncation mutations.[39] Although infrequent, gross genomic deletions, frameshift, and nonsense mutations have also been reported.[14,57,60] Mutations have been described in almost all exons (except exons 1 and 2). The predominance of missense mutations is based mainly on the two hotspot mutations, p.Y179C (c.536A>G;p.Tyr179Cys, previously known as p.Y165C) in exon 7 and p.G396D (c.1187G>A;p. Gly396Asp, previously known as p.G382D) in exon 13, that represent around 70%–80% of all mutations in populations of European origin (Table 4).[65]

An increasing number of publications on *MUTYH* have unraveled the ethnic and geographic differences in the mutation frequency of this gene. As mentioned earlier, among European populations, the two missense mutations p.Y179C and p.G396D are by far the most common disease-causing variants. Moreover, different variants have a larger role in other populations, pointing to ethnic and geographic differences, such as p.Y104X in Pakistani patients and p.E480X in

**Table 4** *MUTYH* germline mutations

| Mutation (coding region)[a] | Mutation (protein) | Population | Reference |
|---|---|---|---|
| c.536A>G | p.Y179C | Caucasian | 2 |
| c.1187G>A | p.G396D | | |
| c.1147del | p.Ala385ProfsX23 | Northern European | 63 |
| c.1214C>T | p.P405L | Dutch | 88 |
| c.312C>A | p.Y104X | Pakistani | 89 |
| c.1438G>T | p.E480X | Indian | 89 |
| c.733C>T | p.R245C | Japanese | 90,91 |
| c.857G>A | p.G286E | | |
| c.1118C>T | p.A373V | | |
| c.1437delGGA | p.E480X | Italian | 92 |
| c.1118C>T | p.A373V | Korean | 93 |
| c.799C>T | p.Q267X | | |
| c.1361A>C | p.Q454P | | |
| c.857G>A | p.G286E | | |
| c.1227_1228dup | p.E410GfsX43 | Tunisian | 94 |
| c.1437_1439del | p.E480del | Portuguese | 95 |
| | | Spanish | 71,96 |

**Notes:** [a]Annotated according to the longest possible (hypothetical) coding sequence, NM 001128425.1. Due to the choice of the longest MUTYH-transcript as a reference, nucleotide and aminoacid numbering after nucleotide position 157 (aminoacid 53) may differ by up to 42 nucleotides (14 aminoacids).

Indian patients.[66] Other specific mutations have been reported in the Japanese and Southern Europe populations (Table 4).

Several studies have examined the frequency of the two common missense mutations (p.Y179C and p.G396D), and approximately 1%–2% of the general population (of European origin) is predicted to be a carrier.[67–72]

## Phenotypes

The clinical spectrum of *MUTYH* germline mutations is heterogeneous and can include a wide range of phenotypes (Table 1).

### Attenuated and classic adenomatous polyposis

Most biallelic *MUTYH* mutation carriers have between ten and a few hundred polyps, and very few patients develop more than 500 polyps. Biallelic mutations were initially identified in nearly one-third of cases with *APC*-negative AFAP with more than 15 adenomas and in about 10% of cases with *APC*-negative classical FAP, especially in those cases where there is an evident recessive pattern of inheritance.[73] A recent study found biallelic *MUTYH* mutations in 2/119 (2%, 95% CI 0.2%–6%) patients with >1,000 adenomas, 94/1,338 (7%, 95% CI 6%–8%) patients with 100–999 adenomas, 233/3,253 (7%, 95% CI 6%–8%) patients with 20–99 adenomas, and 37/970 (4%, 95% CI 3%–5%) patients with 10–19 adenomas.[74]

### Serrated polyposis syndrome and patients with multiples polyps

Serrated polyps and adenomas are a common finding in patients with MAP. A minority of MAP patients fulfill the WHO criteria for serrated polyposis syndrome (defined when a patient fulfills at least one of the following criteria: 1) at least five serrated polyps proximal to the sigmoid colon, two of which are greater than 10 mm in diameter; 2) any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; and 3) more than 20 serrated polyps of any size distributed throughout the colon),[75] usually in the setting of a synchronous adenomatous polyposis.[62,76] In a recent study centered on patients diagnosed with at least ten polyps of any histology (including adenomatous and serrated polyps), 6.7% (27/405) patients were found to be *MUTYH* biallelic carriers.[76]

### CRC without polyposis

In population-based CRC studies, where patients were recruited on the basis of the diagnosis of CRC, biallelic *MUTYH* mutations were found in 0.3%–2.0% of the population.[60,71] In several population-based studies, up to a third of proven biallelic *MUTYH* mutation carriers did not have a polyposis phenotype.[67–72] Accordingly, biallelic *MUTYH* mutations are not always associated with a polyposis phenotype; therefore, biallelic *MUTYH* mutations should be considered also in early onset CRC patients (≤50 years old), especially if the Lynch syndrome has been ruled out. However, atypical phenotypes have been described.[77] In a recent study that analyzed the *MUTYH* gene in 85 cases with suspected Lynch syndrome with tumors showing mismatch repair deficiency without detectable germline mutation, one biallelic (p.Y179C) carrier was identified that developed CRC, urothelial carcinoma, and a sebaceous gland carcinoma.[78] In this particular patient, sequencing of the tumor revealed two somatic mutations in the mismatch repair system, thus explaining the phenotype.

### Heterozygous *MUTYH* mutations and CRC risk

The risk of CRC in individuals with monoallelic (heterozygous) mutations has been the focus of an intense debate. Several meta-analyses have been performed, with ORs (odds ratios) or RRs (relative ratios) between 1.11 and 1.27, most of them showing no statistical differences.[79–84] The most recent systematic review has shown that monoallelic mutation carrier frequency was greater for cases ascertained due to a family history (3.3%) than for controls (1.4%; *P*=0.02), suggesting that monoallelic carriers with a family history of CRC may be at a greater risk.

### Extracolonic manifestations

Since oxidative stress is present in different tissues, it can be expected that a defective *MUTYH* gene leads to neoplasms in other organs. Vogt et al recently described the spectrum of extracolonic features of a large cohort of MAP patients (276 patients with MAP). In this study, duodenal polyposis occurs in 17% of cases with a lifetime risk of duodenal cancer of 4% and a 38% lifetime risk of any extraintestinal cancer.[85] The incidence of extraintestinal malignancies among cases was almost twice that of the general population with a significant increase in the incidence of ovarian, bladder, and skin cancers and a trend of increased risk of breast cancer.[85] The median age at diagnosis for the different extraintestinal malignancies varied between 51 and 61 years.

Other manifestations also seen in FAP patients have been reported in a small number of MAP patients: gastric FGP, lipomas, CHRPE, epidermoid cyst, DT, and thyroid

carcinoma.[60] Overall, the incidence of FAP-related manifestations in MAP patients is lower than in FAP patients.

## Genotype–phenotype correlation

As in the *APC* gene, genotype–phenotype associations have been described for the common *MUTYH* mutations. Some studies have observed that in accordance with the functionality assays that show a greater reduction in MUTYH glycosylase activity for p.Y179C as compared to p.G396D, patients with biallelic Y179C mutations are associated with a more aggressive phenotype (ie, earlier onset and a greater number of polyps) compared to biallelic G396D mutations.[65,71,76,86] A recent study reported that the p.G396D variant is associated with the development of serrated polyps in MAP patients.[76]

## Genetic testing algorithm

Biallelic *MUTYH* mutations should be suspected in patients with an attenuated form of adenomatous polyposis or classical FAP with a recessive pattern of inheritance. It should also be considered in CRC patients diagnosed before the age of 50 years, and in patients with multiple colonic polyps (>10, including both adenomatous and serrated ones) (Table 1).

Once an individual is found to carry biallelic *MUTYH* mutations, presymptomatic testing can be offered to first-degree relatives, especially to siblings, who have a 25% risk of carrying biallelic mutations. The risk of MAP in the children of MAP patients depends on the status of their reproductive partner.

Germline analysis usually comprises the two most common mutations (p.G396D and p.Y179C).[14] Full-gene sequencing is recommended in: 1) individuals who are found to carry one of the two common mutations; 2) individuals whose ethnic ancestry is not Caucasian; and 3) individuals with Caucasian ancestry with a suggestive clinical presentation and a family history found to be negative for the common mutations. Since large deletions or duplications have been exceptionally reported in the *MUTYH* gene, there is no need for applying methods to analyze these mutations.[14,87]

## Clinical management

The suggested surveillance protocol for MAP patients is similar to that for patients with AFAP (Table 2).[34] Individuals should undergo total colonoscopy every 2 years, starting at age 18–20 years and continuing lifelong. Colorectal polyps management is similar to that proposed for patients with AFAP. Because of the usual attenuated phenotype, in some patients it is possible to remove these polyps endoscopically.

If surgery is required, decisions should be made as in AFAP.

Upper endoscopy starting at age of 25–30 years is recommended, following the same strategy described for AFAP. There is no evidence of the usefulness of any chemopreventive measure in this condition.

Currently, there is no evidence that justifies the screening for extraintestinal manifestations in patients with MAP.

Although still under debate, CRC screening in monoallelic mutation carriers is recommended for first-degree relatives of a patient with sporadic CRC.[29]

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## Disclosure

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