American Journal of Gastroenterology
© 2006 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2006.00375.x

CME

# Familial Adenomatous Polyposis

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**Familial adenomatous polyposis (FAP) is an autosomal-dominant colorectal cancer syndrome, caused by a germline mutation in the adenomatous polyposis coli (APC) gene, on chromosome 5q21. It is characterized by hundreds of adenomatous colorectal polyps, with an almost inevitable progression to colorectal cancer at an average age of 35 to 40 yr. Associated features include upper gastrointestinal tract polyps, congenital hypertrophy of the retinal pigment epithelium, desmoid tumors, and other extracolonic malignancies. Gardner syndrome is more of a historical subdivision of FAP, characterized by osteomas, dental anomalies, epidermal cysts, and soft tissue tumors. Other specified variants include Turcot syndrome (associated with central nervous system malignancies) and hereditary desmoid disease. Several genotype–phenotype correlations have been observed. Attenuated FAP is a phenotypically distinct entity, presenting with fewer than 100 adenomas. Multiple colorectal adenomas can also be caused by mutations in the human MutY homologue (MYH) gene, in an autosomal recessive condition referred to as MYH associated polyposis (MAP). Endoscopic screening of FAP probands and relatives is advocated as early as the ages of 10–12 yr, with the objective of reducing the occurrence of colorectal cancer. Colectomy remains the optimal prophylactic treatment, while the choice of procedure (subtotal *vs* proctocolectomy) is still controversial. Along with identifying better chemopreventive agents, optimizing screening of extracolonic cancers and applying new radiological and endoscopic technology to the diagnosis and management of extracolonic features are the major challenges for the future.**

(Am J Gastroenterol 2006;101:385–398)

## INTRODUCTION

Familial adenomatous polyposis (FAP) is an inherited colorectal cancer syndrome characterized by the early onset of hundreds to thousands of adenomas throughout the large bowel. Left untreated, there is a nearly 100% progression to colorectal cancer (CRC) by the age of 35–40 yr (1, 2), as well as a heightened risk of various other malignancies. CRC can be prevented by the timely implementation of rigid screening programs, and certain medico-surgical interventions.

## METHODS

A literature search was performed from 1980 to August 2005, using the computerized PubMed database, looking for English publications regarding "familial adenomatous polyposis," "attenuated familial adenomatous polyposis," and "MYH associated polyposis." Original articles and case reports discussing genetics, clinical features, genotype–phenotype correlations, screening, and prophylaxis were reviewed. Relevant articles (before or after 1980) were also extracted manually from the references of retrieved publications.

## GENETICS

Familial adenomatous polyposis (FAP) is a highly penetrant autosomal-dominant disorder, caused by a germline mutation in the adenomatous polyposis coli (APC) gene, located on chromosome 5q21. APC is a tumor suppressor gene, first localized in 1987, and cloned in 1991 following mutation analyses in unrelated families with FAP (3–5). It has an 8,538 bp open reading frame, and consists of 15 transcribed exons (6–8) (Fig. 1). This gene is expressed in a variety of fetal and adult tissues, including mammary and colorectal epithelium (6). It encodes for a 312-kDa protein, 2,843 amino acids long (6).

Inactivation of the APC gene product constitutes the initial step in the development of CRC in FAP. APC's major function is that of a scaffolding protein, affecting cell adhesion and migration. It is part of a protein complex, modulated by the Wnt signaling pathway, which regulates the phosphorylation and degradation of $\beta$-catenin (9, 10). $\beta$-catenin is an intracellular protein that binds to the cell adhesion molecule E-cadherin and links E-cadherin to the actin cytoskeleton (6). The phosphorylation of $\beta$-catenin attracts ubiquitin ligases, leading to its destruction at the proteasome (9, 10). When APC is mutated, $\beta$-catenin accumulates in the cytoplasm and binds to the Tcf family of transcription factors, altering the expression of various genes affecting the proliferation, differentiation, migration, and apoptosis of cells, namely those encoding cyclin D1, the proto-oncogene *c-myc*, the metalloproteinase matrilysin, as well as ephrins and capsases (9, 10). APC also plays a role in controlling the cell cycle, by inhibiting the progression of cells from the $G_0/G_1$ to the S

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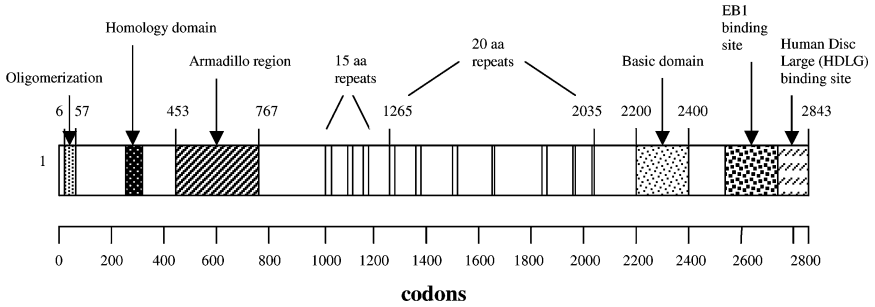


**Figure 1.** APC cDNA (below) and important protein motifs (above). Adapted from Van Es *et al*. (6), Fearnhead *et al*. (7), and Foulkes (8).

phase, helping to suppress tumorigenesis (10). Furthermore, APC stabilizes microtubules, thus promoting chromosomal stability (9). Inactivation of APC can lead to defects in mitotic spindles and chromosomal missegregation, with the resulting aneuploidy leading to cancer (9).

Over 700 different disease-causing APC mutations have been reported to date, but the most common germline mutation involves the introduction of a premature stop codon, either by a nonsense mutation (30%), frameshift mutation (68%), or large deletion (2%), leading to truncation of the protein product in the C-terminal region (11). Most of these germline mutations are clustered at the 5′ end of exon 15, otherwise referred to as the *mutation cluster region* (12). The two most frequently mutated codons are at positions 1061 and 1309 (11). Correlations have been observed between sites of mutations and variations in the phenotype, as will be discussed later. An updated database of APC gene mutations is available online at http://www.cancer-genetics.org.

Despite genetic testing, 20–30% of classical FAP patients have no detectable APC germline mutation by routine screening methods. One possibility is the presence of a nontruncating missense mutation that could be missed by protein truncation testing (PTT), previously used as a first-line screening tool. Heinimann *et al*. found that 12.9% of APC mutation carriers are missed by standard PTT (13). Using SNP assay and direct DNA sequencing, they identified four possibly pathogenic germline missense mutations: R99W and E1317Q in the coding region, A290T within the APC promoter, and A8822G in the 3′UTR end of the gene (13). However, validation of these candidate disease-associated mutations was not performed. Nowadays, PTT has been largely replaced as the first-line genetic test by other mutation-finding techniques, particularly DNA sequencing (currently the standard screening tool in most North American centers), and newer diagnostic methods. Monoallelic mutation analysis (MAMA) is a more sensitive second-line technique, whereby the two APC alleles can be examined independently. Using this method, Laken *et al*. demonstrated significantly reduced expression in one APC allele 7 of 9 FAP patients with no identified truncating APC mutation (14). The authors concluded that APC mutations can be identified in >95% of FAP patients when MAMA is combined with standard genetic testing (14). A modified version of this technique is now called "conversion analysis," and has also been used to identify mutations in mismatch repair genes that have been difficult to detect by other means (15). Multiplex ligation-dependent probe amplification (MLPA) is yet another test that quantifies all APC exon copy numbers. It has been useful in identifying a deletion of the entire APC gene in a patient with classical FAP, as well as large deletions involving several exons of the gene, often missed by conventional tests (16).

The APC missense polymorphism I1307K, resulting from a T-to-A transversion, has also been indirectly linked to colorectal adenoma and carcinoma, by rendering the gene susceptible to somatic mutations. This variant allele has been identified in 6% of Ashkenazi Jewish controls and 10% of Ashkenazi CRC patients (17). Apart from a modest increase in risk of CRC, I1307K has also been linked to a heightened risk of breast cancer among Ashkenazi Jews (18), although the latter association remains controversial. Another gene that is possibly linked with APC mutation-negative FAP in Ashkenazi Jewish families is *CRAC1* (colorectal adenoma and carcinoma gene), located on chromosome 15q14-q22 (19). This gene has also recently been implicated in the hereditary mixed polyposis syndrome in a large Ashkenazi family, characterized by the development of various different colorectal tumors (including juvenile, hyperplastic, adenomatous polyps, as well as CRC). It is inherited as an autosomal-dominant trait (20).

Although microsatellite instability (MSI) is found in about 6% of tissue specimens from APC mutation-negative polyposis patients, the inconsistency of MSI in different tumors from the same patient suggests a somatic inactivation of hMLH1 by promoter hypermethylation, rather than a germline mutation (13). Hence, mismatch repair (MMR) gene deficiency is unlikely to be a cause of APC mutation-negative polyposis. Recently, biallelic mutations in MYH have been deemed responsible for up to 7.5% of APC-negative classic FAP (21), although MYH mutations are more frequently associated with a milder phenotype, as will be discussed later.

## EPIDEMIOLOGY

The birth frequency of FAP in Northern European populations is estimated at roughly 1 in 13,000 to 1 in 18,000 live births (1, 22), and is responsible for less than 1% of all CRC cases (23). In the Swedish Polyposis Registry, the median age

of probands with CRC at diagnosis was 42 yr, compared to 34 yr for those without CRC, while asymptomatic relatives were diagnosed at a median age of 22 yr (22). In the Polyposis Registry of Japan, the mean age of diagnosis of FAP in patients without CRC was 28 yr, compared to 33 yr for those with early cancer (*in situ* or submucosal) and 40 yr for advanced cancer (24). The cumulative risk of CRC exceeded 50% by the age of 42 yr in women, and 44 yr in men (24). In the Danish and Finnish registries, 66–69% of symptomatic probands, *versus* only 2–7% of call-up patients (relatives recruited from pedigrees) had CRC at the time of diagnosis of FAP (25, 26).

## CLINICAL PRESENTATION

### *Lower Gastrointestinal Tract Polyps and Cancer*

The hallmark of FAP is the development of hundreds of adenomatous polyps in the colon and rectum usually in adolescence, with an almost inevitable progression to CRC by the age of 35–40 yr, significantly younger than sporadic cancers. A total of 70–80% of tumors occur on the left side of the colon (22).

### *Upper Gastrointestinal Tract Polyps and Cancer*

Upper gastrointestinal polyps (gastric and duodenal adenomas) are present in nearly 90% of FAP patients by the age of 70 yr, with a median age of diagnosis of 38 yr, based on a prospective study from Nordic and Dutch polyposis registries (27). Interestingly, 12% of duodenal polyps discovered during the initial upper endoscopies in this study were microadenomas, diagnosed from random biopsies without visible lesions (27). Roughly two-thirds of duodenal adenomas occur in the papilla or periampullary region (28). Advanced duodenal adenomas confer an increased risk of small bowel cancer, which is the third leading cause of death in FAP patients (8.2%), apart from metastatic CRC (58.2%) and desmoid tumors (10.9%) (29). The cumulative risk of developing advanced (Spigelman's stage IV) duodenal polyposis is estimated to be 43% at the age of 60 yr and 50% at the age of 70 yr, using side-viewing and forward upper endoscopy, with systematic biopsies of the duodenal papilla (30). The mean age of duodenal cancer diagnosis ranges between 47 and 51 yr according to Dutch and Danish polyposis registries, with a cumulative risk of 3–4% by the age of 70 yr (31). In the prospective Nordic study mentioned above, the cumulative incidence rate was as high as 4.5% at the age of 57 yr (27). One retrospective study of 180 Swedish FAP patients found an unusually elevated cumulative risk of periampullary adenocarcinoma of 10% by the age of 60 yr (32). This stresses the importance of routine upper endoscopic surveillance, and the added value of random biopsies even in the absence of visible lesions.

FAP patients are also at an increased risk for fundic gland polyps (FGPs) in the stomach, with an estimated incidence of 26–61% (27, 33–36), compared with a 0.8–1.9% incidence in the general population (37, 38). FGPs are indeed the most common type of gastric polyp to occur in FAP patients. In contrast to sporadic FGPs, FAP-related FGPs are more numerous, tend to occur at a younger age, with more equal gender distribution (39). *Helicobacter pylori* and its associated atrophic gastritis seem to have the same protective effect against the development of FAP-related FGPs as they do in sporadic FGPs (40). Although FGPs in the general population are typically benign lesions, up to 25% of those in FAP patients show foveolar dysplasia (41), and cases of gastric carcinoma associated with diffuse FGP have also been reported (42–45). In a study of 41 FGPs from 17 FAP patients, 51% of polyps demonstrated an inactivating somatic APC gene alteration, whereas there were no such APC gene mutations in 13 sporadic FGPs used for comparison (46). There was no significant difference in mutation rate among FGPs with or without dysplasia (46). These second-hit somatic APC gene alterations, superimposed on germline APC mutations, could account for the neoplastic potential of FGPs in FAP, which appear to be not only clinically, but also pathologically distinct from sporadic lesions. In fact, sporadic FGPs have recently been shown to harbor a high frequency of somatic mutations in exon 3 of the $\beta$-catenin gene, not identified in FAP-associated FGPs (47), reinforcing the difference in initial mutational events (despite similarity in the altered pathways) causing sporadic *versus* syndromic FGPs.

### *Congenital Hypertrophy of the Retinal Pigment Epithelium*

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) refers to the presence of characteristic pigmented fundus lesions that are thought to occur in roughly 70–80% of patients with FAP (48–50). These ophthalmic manifestations are usually present at birth, largely preceding the development of intestinal polyposis, and are asymptomatic with no malignant potential. They are specific to FAP, as opposed to other hereditary or sporadic colonic cancers (51, 52). The diagnostic criteria with the highest specificity/sensitivity for CHRPE include the detection of four small pigmented lesions, or two lesions of which one is large (>25% of disc surface), using bilateral lens fundoscopic examination (53). The presence of multiple bilateral lesions appears to be a highly specific marker for FAP (95–100% specificity) (54). CHRPE positivity has been associated with increased severity of FAP in probands (namely earlier age of polyposis development and upper gastrointestinal involvement), and correlates with DNA test positivity in undiagnosed kindred belonging to FAP families that are CHRPE-positive (48). This makes ophthalmological examination an attractive noninvasive and early diagnostic test for at-risk family members, aside from genetic analysis. CHRPE lesions can also help predict the mutation site, since they are restricted to a specific mutation subgroup along the APC gene (55) (see section "genotype–phenotype correlations" for more details).

### *Desmoid Tumors*

Desmoid tumors are rare, locally invasive fibromatoses that are a major cause of morbidity, and the second leading cause of death in FAP patients (29). They occur rarely in the general population, where they have been linked to somatic mutations of $\beta$-catenin (56), or associated with estrogens. The overall prevalence of desmoid disease in FAP is 15% (57), with a relative risk of ~850 times that of the general population (58). The majority of tumors occurs within the abdomen (50%), usually involving small bowel mesentery, or in the abdominal wall (48%), with few arising in the trunk or limbs (59). Most tumors are solitary (58%), although the number of tumors per individual can range from 1 to 10 (59). Although most abdominal wall tumors are asymptomatic, intraabdominal tumors can cause abdominal pain, or can be complicated by bowel obstruction or perforation, ureteric obstruction, intestinal hemorrhage, even enterocutaneous fistula (59). The average age of diagnosis is 32 yr (59). Traditionally, desmoids have been linked to trauma, particularly abdominal surgery such as prophylactic colectomy. In a Canadian retrospective study, 80% of desmoids developed postcolectomy, after an average of 4.6 yr (60). Females have twice the odds of developing desmoids compared to males (57, 61). Family history, presence of osteomas, and germline mutations after codon 1399 have also been identified as independent risk factors for desmoid occurrence (57, 61). To this day, treatment remains a challenge. Surgical excision carries risks of bleeding and short bowel syndrome, with recurrence rates as high as 45% (62). Nonsteroidal antiinflammatories (usually sulindac) and antiestrogens have been used, but less than a third of the tumors stabilize or regress (59, 62). Results from the use of cytotoxic chemotherapy and radiotherapy have also been disappointing.

### *Thyroid Cancer*

Another malignancy associated with FAP is thyroid cancer, with an estimated incidence of 1–2% (63, 64). The average age of diagnosis is 25 to 33 yr, with an overwhelming predominance of females (17:1) (63–65). The most common histological type of thyroid cancer in these patients is papillary (>75%), with an unusual cribriform pattern (63–67). Most tumors are multicentric, unilateral (64–66), with one North American series reporting a strong predilection for the left lobe (64). They tend to be well circumscribed, nonaggressive, with a low metastatic potential and 10-yr mortality (63–65, 67). Aside from recommended regular physical examinations of the thyroid gland, there is ongoing debate about the need for additional radiological screening, due to the rarity and excellent long-term prognosis of these tumors.

### *Hepatoblastomas*

Hepatoblastomas are rapidly progressive embryonal liver tumors, usually affecting children under the age of 2.5 yr, with a male:female ratio of 2.3:1 (68). Several reports, since 1983, have made the link between these lethal tumors and a family history of FAP (69–74). Indeed, the incidence of hepatoblastoma among children of FAP patients is 1 in 235, compared to 1 in 100,000 in the general population (75). As with sporadic hepatoblastomas, boys within an FAP kindred are particularly at risk (72).

**Table 1.** Extracolonic Cancer Risks in FAP

| Malignancy | Relative Risk | Absolute Lifetime Risk (%) |
|---|---|---|
| Desmoid | 852.0 | 15.0 |
| Duodenum | 330.8 | 3.0–5.0 |
| Thyroid | 7.6 | 2.0 |
| Brain | 7.0 | 2.0 |
| Ampullary | 123.7 | 1.7 |
| Pancreas | 4.5 | 1.7 |
| Hepatoblastoma | 847.0 | 1.6 |
| Gastric | – | 0.6* |

*Note.* Adapted from Giardiello *et al*. (78), Jagelman *et al*. (76), Sturt *et al*. (57), Lynch *et al*. (58), Bülow *et al*. (27).
*The Leeds Castle Polyposis Group.

### *Other Extracolonic Malignancies*

Although rare, five cases of jejunal and one case of ileal adenocarcinoma were reported by Jagelman *et al*. among 1,255 patients with FAP (76). Other extraintestinal cancers associated with FAP include adrenal, pancreatic, and biliary tract malignancies. Patients from the Johns Hopkins Registry had a relative risk of pancreatic adenocarcinoma of 4.46 compared to the general population, with an absolute risk of 21.4 cases per 100,000 person-years (77). Table 1 summarizes the different extracolonic malignancies with their relative and lifetime risks (27, 57, 58, 76, 78).

## SPECIFIED VARIANTS OF FAP

### *Gardner Syndrome*

Gardner syndrome is more of a historically coined variant of FAP rather than a truly distinct subtype of the disease. It is characterized by the association of gastrointestinal polyposis with osteomas, as well as multiple skin and soft tissue tumors (79–81), including desmoids and thyroid tumors. Although most FAP patients can be found to have at least subtle findings of Gardner syndrome on thorough investigation, the term is usually used by health professionals to refer to patients and families where the aforementioned extraintestinal features are especially prominent. Osteomas typically occur in the mandible, but can also present in the skull and long bones (82). Benign and painless, they usually precede a clinical or radiological diagnosis of intestinal polyposis (82). Epidermal cysts are the most common skin manifestation of Gardner syndrome, typically occurring at an earlier age and at multiple sites, including the face, scalp, and extremities (82). Other cutaneous features of the syndrome include lipomas, fibromas, and leiomyomas. Dental abnormalities, such as supernumerary and impacted teeth, are seen in 22–30%

of FAP patients on panoramic radiographs, and constitute yet another feature of Gardner syndrome (83–85).

### *Turcot Syndrome*

Turcot syndrome, formally described in 1959, refers to the occurrence of a primary central nervous system (CNS) tumor, in conjunction with colorectal polyposis (86). Turcot syndrome has been linked to FAP, as well as the hereditary nonpolyposis colorectal cancer syndrome (HNPCC), attributable to mutations in mismatch repair genes. In families with germline APC mutations, the most common CNS tumor is medulloblastoma, although anaplastic astrocytomas and ependymomas have also been described (87). This contrasts with HNPCC, where the major associated CNS tumor seems to be glioblastoma (87). Strict neurological evaluation has been recommended for FAP families with a member affected by a CNS tumor, due to evidence of familial clustering (87). No guidelines exist, however, and there are no studies so far to determine whether such an intervention could improve survival.

### *Hereditary Desmoid Disease*

In 1996, Eccles *et al*. proposed the existence of yet another variant of FAP, termed "hereditary desmoid disease" (HDD). The authors described a family with multiple desmoid tumors inherited across three generations, but occurring at sites unusual for FAP-related desmoid disease (paraspinal muscles, breast, occiput, arms, and lower limbs) (88). Affected kindred also lacked the colonic features of FAP, except for one patient who had a palpable rectal mass, and another who had <50 adenomatous polyps documented by colonoscopy (88). Like FAP, HDD was inherited in an autosomal-dominant fashion, with 100% penetrance. All affected family members were found to have truncating frameshift mutations at codon 1924 of the APC gene, located in the 3′ half of exon 15 (88).

## GENOTYPE–PHENOTYPE CORRELATIONS

Several genotype–phenotype correlations have been consistently observed (Fig. 2). As regards aggressivity of the disease, mutations at codon 1309 have been typically associated with a more severe clinical phenotype. Patients with mutations at this site tend to develop bowel symptoms more than 10 yr earlier (mean, 19.8 yr) than those with mutations at other sites (89), and have significantly more colorectal polyps (approximately 4,000) at the time of colectomy compared with matched FAP controls (90). Also, mutations at codon 1309 are associated with an earlier age of CRC development (mean, 35 yr) (84).

As regards extracolonic manifestations, mutations from codons 976 to 1067 are associated with a three- to four-fold increased risk for developing duodenal adenomas, while those spanning between codons 543 and 1309 are associated with a high risk of CHRPE (84). In fact, CHRPE lesions are hardly ever present with mutations before exon 9, but are systematically present with mutations past this exon (55). Mutations beyond codon 1309 are linked to a six-fold increased risk of desmoid tumors (84), with the majority of those mutations concentrated between codons 1445 and 1580 (89, 91). Patients with papillary thyroid cancer often have mutations between codons 140 and 1309, the majority of which are concentrated in the CHRPE-associated area on exon 15 (92). Mutations beyond codon 1444 are associated with a two-fold increased risk of osteomas (84, 93).

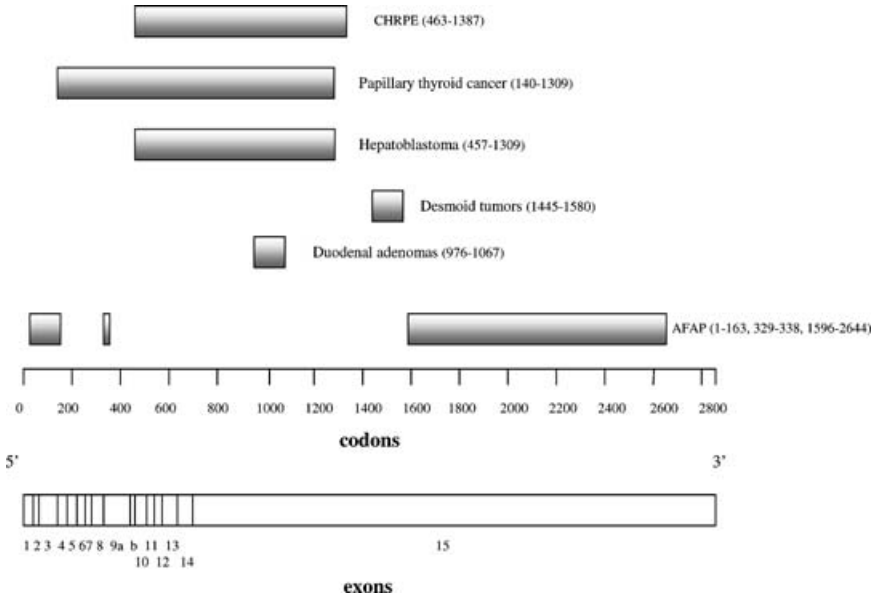


**Figure 2.** APC cDNA (below) and extracolonic genotype–phenotype correlations (above). Except for CHRPE (congenital hypertrophy of the retinal pigment epithelium), most lesions can occur with mutations anywhere along the APC gene, but are more likely in the locations illustrated. AFAP = attenuated FAP. Adapted from Fearnhead *et al*. (7), Foulkes (8), Bertario *et al*. (84), and Cetta *et al*. (92).

Apart from mutation site, variations in phenotype have also been potentially attributed to environmental factors, as well as interdependence of first and second hits, consistent with Knudson's two-hit hypothesis. Moreover, the discovery of a modifier locus (Mom1) on chromosome 4 of the mouse polyposis model (94) has led to the identification of a possible modifier gene on human chromosome 1p35–36, which may also be implicated in the clinical heterogeneity of FAP (95,96). Variations in the *N*-acetyltransferase loci NAT1 and NAT2, located on chromosome 8p22, have also been shown to affect the severity of disease (97). These modifier genes are not in clinical use at this point in time. In most cases, the family history is the best guide as to the likely phenotypic expression of APC mutations.

## MULTIPLE COLORECTAL ADENOMA SYNDROMES

### *Attenuated FAP*

Attenuated familial adenomatous polyposis (AFAP) is a phenotypically distinct variant of FAP, characterized by the presence of fewer than 100 adenomas, a more proximal colonic location of polyps, and delayed age of CRC onset (15 yr later than patients with classic FAP). The cumulative risk of CRC by the age of 80 yr is estimated to be 69%, and 75% of tumors occur in the proximal colon (98). Patients often have no family history of polyps or CRC, and lack extracolonic features, apart from FGPs which are quite common, and duodenal adenomas (99).

AFAP arises from mutations in the extreme proximal or distal portions of the APC gene, specifically truncating frameshift mutations at the 3′ end of the gene (100–104), and nonsense/frameshift mutations at exons 3, 4, and 5 (101, 105). Also reported as a cause of AFAP are nonsense mutations at exon 9 (100, 101).

### *APC Gene Polymorphisms*

Only a minority of patients with "multiple colorectal adenomas" (usually defined as the presence of 3–100 colonic adenomas) harbor an identifiable APC germline mutation, which has made genetic diagnosis challenging. In a British study of 164 unrelated patients with multiple colorectal adenomas, only 8.5% carried germline APC variants, with possible pathogenic effects (100). The most common variant was the missense polymorphism E1317Q, carried by 4.3% of patients (relative risk 11.17, $p < 0.001$), while 1.8% of the patients (all Ashkenazi) carried the I1307K APC variant, discussed earlier (100). Reports concerning the pathogenicity of the E1317Q variant are so far contradictory and controversial. Frayling *et al*. found an E1317Q variant to be present in 2 of 134 multiple adenoma patients, 2 of 30 CRC patients, but in none of 80 controls (106). In another study, the odds ratio of E1317Q in multiple adenoma patients *versus* controls was 2.0, but did not reach statistical significance ($p = 0.4$) (107). More recent studies have shown no difference in the prevalence of this variant between patients with multiple colorectal adenomas and controls (108–110). This variant was also absent in 194 Swedish CRC patients, with sporadic or familial tumors (111).

### *MYH Associated Polyposis*

More recently, an autosomal recessive type of oligopolyposis has also been recognized, involving the human MutY homologue (MYH, or more accurately *MUTYH*) gene, referred to as MYH associated polyposis (MAP). MYH, located on the short arm of chromosome 1, is a base excision repair gene preventing mutations from products of oxidative damage, particularly the oxidized guanine lesion 8-oxodG (112). Biallelic mutations in MYH were first associated with polyposis after the study of a family with multiple colorectal adenomas/carcinomas, who lacked inherited mutations in APC (113). Since then, other patients with multiple adenomas have also been found to be homozygous or compound heterozygous carriers of MYH mutations. Y165C and G382D missense mutations account for the majority (>80%) of disease-causing alleles in Caucasians, whereas E466X nonsense mutation has been identified in Indian families, and Y90X in Pakistani families (114). A mutation in exon 14 of the MYH gene, 1395delGGA, has also recently been identified in three Italian patients with colorectal polyposis (115). In a British study of multiple colorectal adenoma patients, 29% of those with 15–100 adenomas had biallelic pathogenic MYH mutations, in comparison to 7.5% of patients with APC mutation-negative classic polyposis (>100 adenomas) (116). Other studies have noted similar frequencies of MYH alterations in multiple colorectal adenoma patients, ranging from 23% to 36% (114, 117). No unaffected carrier of biallelic MYH mutations has been identified to date, suggesting a high penetrance for this condition (118). In the largest prospective cohort study to date, including 2,239 CRC cases and 1,845 controls from across Scotland, G382D/G382D homozygotes and Y165C/G382D compound heterozygotes had a 93-fold excess risk of CRC (95% CI 42–213) compared to wild-type individuals, while all G382D/G382D homozygote carriers had developed CRC by the age of 65 years (119). The implications of a single MYH-mutated allele remain unclear, but the risk for CRC is unlikely to be more than 50% increased. In Sieber's study of multiple adenoma patients, 6 patients (3.8%) were heterozygotes for an MYH mutation, and had 3–12 (median of 4) adenomas in the colon, as opposed to 18–100 adenomas in homozygous carriers (116). In a Canadian case-control study comparing 1,238 CRC patients and 1,255 healthy controls, 2.34% of case patients *versus* 1.67% of control subjects were heterozygous for either the Y165C or G382D mutation, suggesting a possible weakly penetrant autosomal-dominant inheritance pattern of increased CRC risk associated with monoallelic germline MYH mutations (120). Carriers of either single mutation had a combined OR of 1.4 for CRC, although this did not reach statistical significance (95% CI 0.8–2.5) (120). In the Scottish cohort study mentioned above, there was a 1.68-fold excess risk of CRC (95% CI 1.07–2.95) for heterozygote carriers aged >55 yr,

while the risk for heterozygotes of all ages did not reach statistical significance (119). Further studies are needed before more accurate estimates of risk can be quoted.

## SCREENING

Screening of patients and family members, with timely treatment of affected individuals, has led to a 55% reduction in the occurrence of CRC at diagnosis of FAP, and an improvement in cumulative survival for all FAP patients (121, 122). The American Gastroenterological Association recommends an annual sigmoidoscopy, beginning at the age of 10–12 yr, for patients with a genetic diagnosis of FAP, or at-risk family members who have not undergone genetic testing (123). Most authors also recommend front and/or side-viewing endoscopies of the stomach, duodenum, and periampullary region, every 6 months to 4 yr depending on the polyp burden (27, 35, 36, 124). Some even advocate the systematic use of 0.5% indigo carmine dye, and routine biopsy of the duodenal papilla, even in the absence of macroscopic lesions (30). As far as thyroid cancer is concerned, most would agree that it is reasonable to include a simple thyroid palpation in the routine physical exam (63), while others would go as far as recommending routine thyroid ultrasonography (77). Some experts recommend screening for hepatoblastomas in children of FAP parents by use of routine alpha-fetoprotein levels and imaging of the liver (72, 125), but no standard guidelines exist. Proposed algorithms for screening probands and unaffected first-degree relatives are presented in Figure 3A and 3B, respectively.

## PROPHYLAXIS

Colectomy is the recommended treatment to reduce the risk of colorectal cancer in FAP patients with adenomatosis. In children and adolescents, surgery can usually be safely postponed for several years, while continuing with annual colonoscopies, until an appropriate psychological age is reached where colectomy can be accepted (usually late teens to early twenties). Surgical options include a subtotal colectomy with ileorectal anastomosis, a total proctocolectomy with a continent ileostomy, or a proctocolectomy with ileoanal pouch.

Subtotal colectomy with ileorectal anastomosis (IRA), although simpler and traditionally associated with less perioperative complications and better functional results, has become a less attractive option due to an ongoing CRC risk associated with residual rectal mucosa. The estimated cumulative risk of rectal cancer with this limited procedure is 10% at the age of 50 yr, reaching up to 29% by the age of 60 yr (126). Meanwhile, others have argued that the risk of dying from rectal cancer after an IRA is only 2% after a 15-yr follow-up, making it an acceptable primary treatment option for FAP patients (127). Laparoscopic colectomy with IRA has also proven to be a safe and minimally invasive treatment option for selected FAP patients (128). Those undergoing any form of subtotal colectomy should continue close endoscopic surveillance of the remaining rectum approximately every 6 months, for recurrent adenomas or cancer (126).

Proctocolectomy with an ileal pouch–anal anastomosis (IPAA) has emerged as the surgical treatment of choice, allowing for complete resection of vulnerable colorectal mucosa, while preserving transanal defecation. Although IPAA has been associated with a higher rate of postoperative complications, the functional results of IRA and IPAA appear to be similar, as far as the frequency of bowel movements and daytime soiling are concerned (129). Incontinence occurs in roughly 5.9% of FAP patients with an IPAA, and the average number of bowel movements is 5–6 per 24-h period (129, 130). Pouch failure can occur in 7.7% of FAP patients over a 2–10-yr follow-up period, mostly due to ischemia and late-onset pelvic sepsis (131). Pouchitis occurs in only 11% of FAP patients, compared to 53.8% in patients with underlying ulcerative colitis (130). Concerns have been raised about a marked reduction in female fertility following IPAA, as noted in ulcerative colitis patients (132, 133). Pelvic adhesions, disrupting the normal anatomic relationships between the fallopian tubes and ovaries, may be the cause. In a recent study by Olsen *et al*., the fecundity of women with FAP after IPAA dropped to 46% compared to the preoperative level ($p = 0.001$), while there was no observed change in fecundity before and after IRA (133). Still, the fertility rate of women after IPAA was greater for those with FAP compared to ulcerative colitis (134).

IPAA patients remain at risk for ileal polyps. The risk of developing adenomas within the ileal pouch 5, 10, and 15 yr after proctocolectomy is roughly 7%, 35%, and 75%, respectively (135). Others have estimated an incidence of 53% to as high as 83%, 10–20 yr postsurgery (136, 137). The risk of developing anastomotic adenomas is significantly lower in patients undergoing a mucosectomy with hand-sewn anastomosis, compared with the simpler, more traditional stapled anastomosis (138). Although IPAA significantly decreases the residual risk of rectal cancer that accompanies an IRA, there have been four cases of invasive adenocarcinoma at the ileoanal anastomosis (139–142), one case of adenocarcinoma within the ileal pouch (143), and two cases of adenocarcinoma within the anal transitional zone (144) reported in the literature. Continued endoscopic surveillance of the ileoanal anastomosis is probably warranted, although no formal guidelines exist.

Medical interventions for CRC prevention have also been proposed, although at this point in time they are not effective enough to be considered a reasonable alternative to surgery. Sulindac, a nonsteroidal antiinflammatory drug, has been proven to cause regression of colorectal adenomas in FAP patients, by the induction of apoptosis (145). Most studies, however, have shown incomplete polyp regression, and over short follow-up periods ($\leq$1 yr) (146–150). Long-term benefits of sulindac therapy for FAP patients having had IRA are inconsistent, ranging from no difference (151), to a 72% decrease in baseline polyp number (152). COX-2 inhibitors

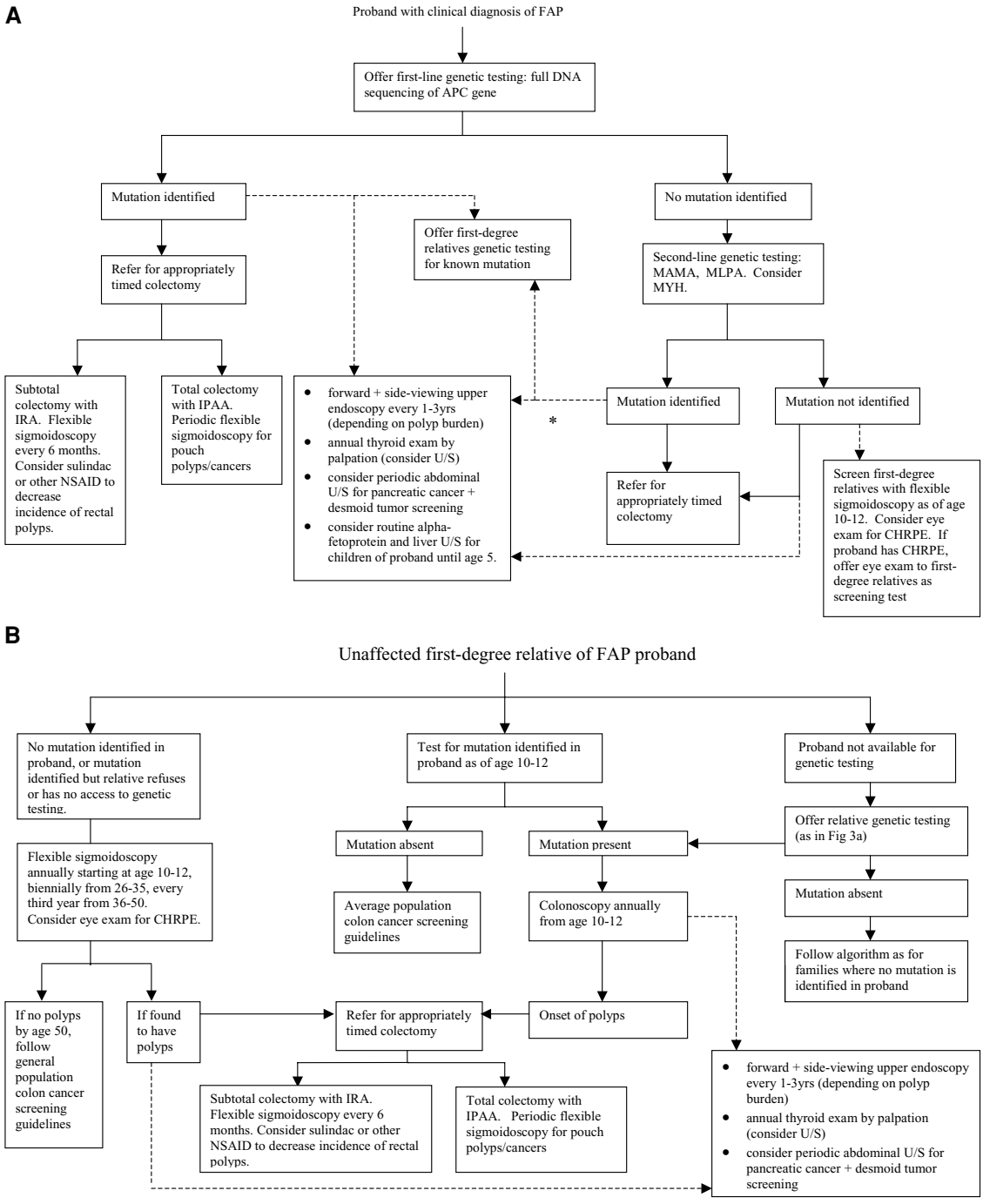


**Figure 3.** (*A*) Algorithm for proband with clinical diagnosis of FAP. *Extracolonic cancer screening is not yet established for MYH mutation carriers. (*B*) Algorithm for first-degree relatives of FAP proband. CHRPE = congenital hypertrophy of the retinal pigment epithelium, IPAA = ileal pouch-anal anastomosis, IRA = ileorectal anastomosis, MAMA = monoallelic mutation analysis, MLPA = multiplex ligation-dependant probe amplification, NSAID = nonsteroidal antiinflammatory drug, U/S = ultrasound.

have also been investigated. Celecoxib was proven to significantly decrease duodenal polyposis after 6 months of high-dose treatment (400 mg twice daily) (153). Rofecoxib was also shown to reduce the rate of colorectal polyp formation in eight patients with FAP (154). Recent reports, however, of increased cardiovascular and thrombotic events with COX-2 inhibitors in adenoma chemoprevention trials are cause for concern (155, 156), and make the use of these drugs for this indication much less appealing.

Although surgical prophylactic measures have favorably changed the natural history of FAP with regards to CRC risk, management of duodenal adenomatosis remains a challenge. There are several endoscopic options available, including snare polypectomy, thermal ablation (using

monopolar/bipolar cautery or argon plasma), and laser coagulation. Unfortunately, the multiplicity of lesions, their often sessile or flat configuration, and the risk of scarring and stricturing of the ampulla as a result of repeated excisions and diathermy limit their usefulness. Photodynamic therapy (PDT) is a method used to induce localized necrosis using an endoscopic light after the administration of a photosensitizing agent. There is still very little experience in using PDT to treat duodenal polyps in FAP, and one pilot study has shown only limited responses, with reduction in adenoma size but no complete eradication (157). A more radical approach for isolated extraductal ampullary lesions involves endoscopic snare papillectomy with or without pancreatic stent placement. This technique seems to be well tolerated, with an 8–15% complication rate (including pancreatitis, bleeding, and perforation); however, adenomas have been shown to recur (158, 159).

The high prevalence of FAP-associated duodenal adenomas, the difficulty in early detection of duodenal cancer, the limitations of local ablative techniques, and the grim prognosis of invasive tumors raise the question of preventive surgery for severe or progressive duodenal adenomatosis. However, the optimal timing and technique remain unclear, and conclusive evidence of improved prognosis with early surgical treatment is still lacking.

Most experts agree that prophylactic surgery should be considered for Spigelman stage III–IV polyps (villous changes, severe dysplasia), rapidly growing lesions, periampullary adenomas in patients over 35–40 yr of age, particularly if there is a family history of duodenal cancer (160). Surgical options include pylorus-preserving pancreaticoduodenectomy (PPPDR), pancreas-sparing duodenectomy, duodenotomy with surgical polypectomy, and ampullectomy (161). Duodenotomy with polypectomy is the least preferred, as it has been associated with up to 100% recurrence of adenomas within 6–36 months (162). There are few follow-up data on the use of pancreas-sparing duodenectomy, and concern that cancer may develop in the area of mucosa surrounding the ampulla that is left behind. PPPDR is the preferred procedure in most centers. Notwithstanding, there is a reported morbidity and mortality rate in the range of 40% and 4.5%, respectively (163). Outcomes of PPPDR may be worse in FAP patients due to adhesions and desmoplastic changes related to previous surgery, notably colectomy.

## GENETIC COUNSELING

Genetic counseling is essential in the management of FAP patients and families, and in most centers constitutes a prerequisite for genetic testing. Not only do individuals need to understand the clinical aspects and implications of FAP, they must be made aware of the risks, benefits, and limitations of genetic testing in order to make an informed decision, and be prepared to cope with the eventual results. The American Society of Clinical Oncology (ASCO) advocates that genetic testing only be done in the setting of pre- and posttest counseling, to address the clinical, psychological, and ethical issues that are raised during the process (164). In a nationwide study of 177 American patients being tested for APC gene mutations, only 18.6% received pretest counseling, while only 16.9% provided informed consent (165). The authors found that nearly 20% of tests were ordered for indications considered unconventional, resulting in a low rate of positive results (2.3%) in this subgroup of individuals (165). Also, it was estimated that as many a third of patients tested would have received misleading answers, owing to the inability of many physicians interviewed to correctly interpret the test results, particularly where false negatives were concerned (165). The use of consistent pre- and post-genetic counseling would likely have avoided many of these problems. Ideally, genetic counseling sessions should be face-to-face, with a professional who could collect the necessary data to construct a three-generation pedigree, educate the patient and family as to the medical aspects of the disease, the inheritance pattern, and the recommended screening guidelines, explore the psychosocial aspects of testing, obtain informed consent, disclose the results and address the risks and management, as well as be available to answer further questions and assure follow-up when this is required (166, 167).

## SUMMARY

FAP is an autosomal-dominant syndrome, most commonly caused by a truncating mutation in the APC gene at chromosome 5q21. It is characterized by the early onset of numerous colonic adenomas, with an almost inevitable progression to CRC. Other features include gastroduodenal polyps, desmoid tumors, and extraintestinal manifestations including CHRPE, osteomas, and other malignancies. Genotype–phenotype correlations have been observed. An attenuated form of FAP exists, characterized by the development of $<100$ colorectal adenomas, and a delayed CRC onset. MYH-associated polyposis is an distinct autosomal recessive condition, caused by mutations in the MYH gene, which should figure in the differential diagnosis of anyone with multiple colorectal adenomas, particularly in the absence of an identifiable APC mutation. Strict endoscopic surveillance is recommended for all FAP patients and at-risk family members. The optimal treatment remains prophylactic colectomy, while continued surveillance of the rectal remnant or ileoanal anastomosis seems warranted because of ongoing risks of adenomas and carcinomas within residual mucosa.

Although heightened awareness, endoscopic surveillance, and the establishment of polyposis registries have successfully decreased the incidence and mortality from CRC, the challenge now lies in determining the optimal screening and therapeutic modalities for associated extracolonic malignancies that are consequently becoming more prominent. The emergence of capsule endoscopy raises the question of its utility in detecting small bowel polyps and cancers in the

context of FAP, as in other hereditary polyposis syndromes. With the progress of endoscopy, techniques such as ampullectomy with or without thermal ablation are being evaluated as an alternative to surgery for the management of periampullary adenomas or malignancies confined to the papilla. Ultimately, the aim is to decrease morbidity, and strive for longevity and an acceptable quality of life for those affected.

## ACKNOWLEDGMENTS

We wish to thank the two anonymous referees for their helpful comments.

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*Received July 11, 2005; accepted September 12, 2005.*

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