Identification of an Adenomatous Polyposis Coli Mutation Associated with Attenuated Familial Adenomatous Polyposis

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The author has no conflicts of interest to disclose.

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Case Study

D.R. is a healthy 42-year-old male who presented to the High Risk Familial Cancer Clinic because his father had been recently diagnosed with attenuated familial adenomatous polyposis. His father, L. R., age 65 years with a history of hypertension and heart failure, had visited his primary care practitioner (PCP) complaining of fatigue. His PCP obtained a complete blood cell count and examined his stool for occult blood. L.R. was found to have microcytic anemia (hemoglobin of 8.6/dL, hematocrit of 25.8%, mean corpuscular volume of 76 fL) and guaiac-positive stools; his PCP referred him for a colonoscopy. Although L.R. was 65 years old, this was his first colonoscopy. Over 100 polyps with variable pathology were identified throughout the colon and rectum, including hyperplastic polyps and tubular and tubulovillous adenomas. The largest tubulovillous adenoma was 1 cm. L.R. was referred for genetic counseling and, after informed consent was obtained, underwent testing for familial adenomatous polyposis. The test results showed a deleterious mutation in the adenomatous polyposis coli gene (exon 4:c.426_427delAT). L.R. underwent a total proctocolectomy with ileal pouch anal anastomosis. After receiving genetic counseling, D.R. received site-specific testing for the genetic mutation identified in his father and subsequently tested positive for the same mutation. Of note, D.R. has three children, ages 10, 12, and 14. All three children tested positive for the same mutation (see pedigree in Figure 1).

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Hereditary colorectal cancer syndromes can be divided into polyposis and nonpolyposis groups. Despite the implications of the term "nonpolyposis," this syndrome is associated with polyps, though they are usually fewer in number. Advanced practitioners may use the presence of 10 or more polyps as a rough estimate when considering genetic testing for a polyposis syndrome (Hampel, 2009). Histologic characteristics of polyps will also identify types of polyps and help to differentiate between hamartomatous and adenomatous polyposis syndromes.

Hamartomas are defined as overgrowths of cells and tissues native to the anatomic location in which they occur (Odze & Hornick, 2009). In the gastrointestinal tract, hamartomas typically incorporate both stroma and

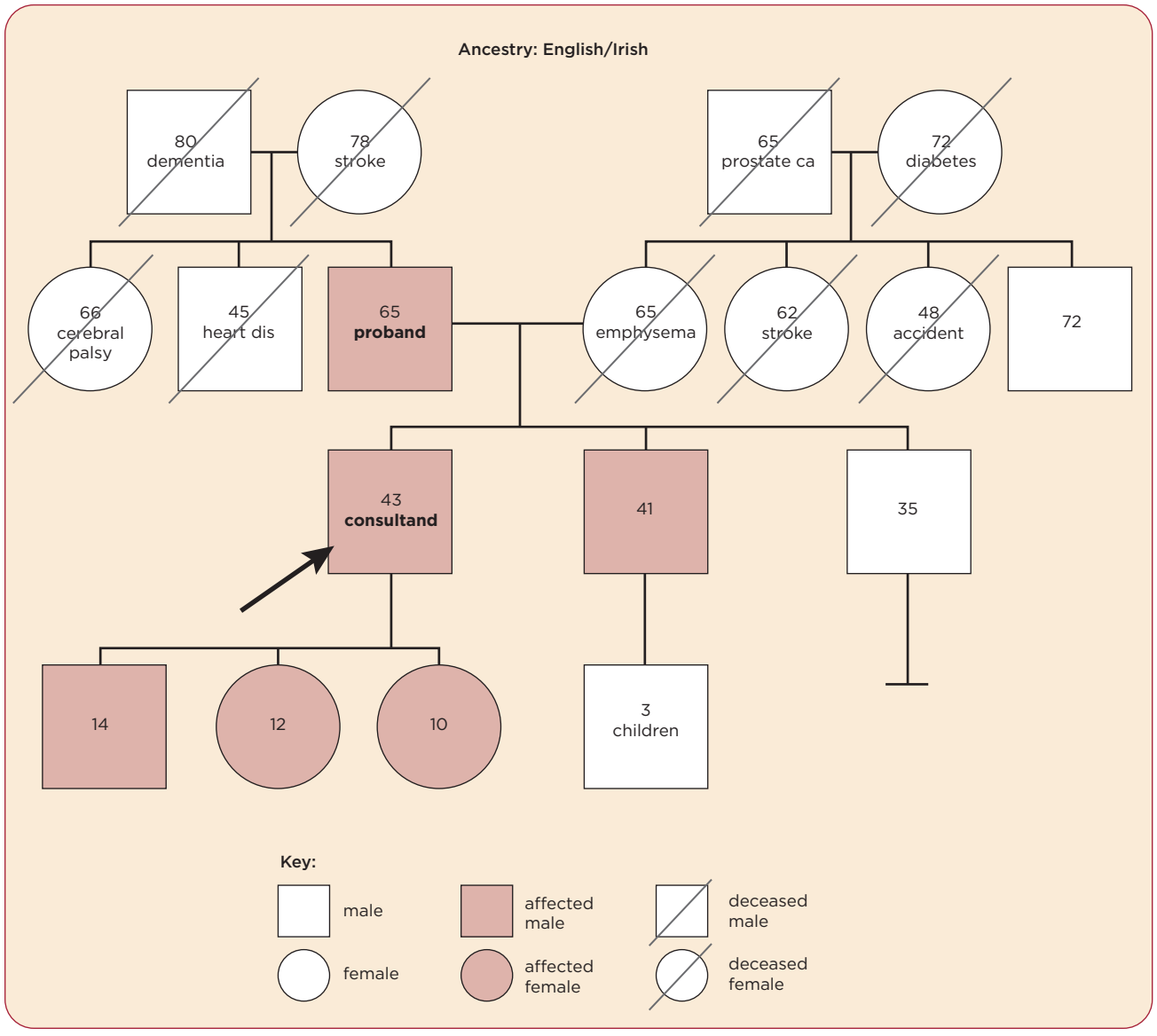

Figure 1. Pedigree showing family members affected with adenomatous polyposis coli mutation associated with attenuated familial adenomatous polyposis. The *proband* is the person initiating the genetic workup. The *consultand* is the individual presenting for genetic counseling.

epithelial components (Odze & Hornick, 2009). Hamartomatous polyps represent non-neoplastic overgrowths of both stromal and epithelial elements, with no dysplastic features observed in the epithelium. This is in contrast to adenomatous polyps, which may include dysplastic features such as may be noted in villous adenomas. The syndromes associated with hamartomatous polyposis are juvenile polyposis syndrome; Peutz-Jeghers syndrome; hyperplastic polyposis syndrome; and the phosphatase and tensin homolog (PTEN) hamartomatous tumor syndrome (PHTS), which consists of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (Genetics Home Reference, 2010). Within the adenomatous polyposis syndromes are familial adenomatous polyposis (FAP) and its variants: attenuated FAP (AFAP), Gardner syndrome, Turcot syndrome; and *MUTYH*-associated polyposis (MAP; also referred to as *MYH*-associated polyposis).

All of the adenomatous polyposis syndromes (with the exception of MAP) represent colon cancer predisposition syndromes associated with a mutation in the adenomatous polyposis coli (*APC*) gene (Table 1). However, these syndromes may present in different manners and with varying de-

Table 1. Polyposis syndromes

Polyposis syndromes	Specific polyposis syndromes	Genetic mutations
Hamartomatous polyposis syndromes	Juvenile polyposis syndrome	*BMPR1A* or *SMAD4* gene
	Peutz-Jeghers syndrome	*STK11* gene (also known as *LKB1*)
	Hyperplastic polyposis syndrome	Gene(s) have not been identified
	Phosphatase and tensin homolog (PTEN) hamartomatous tumor syndromes • Cowden syndrome • Bannayan-Riley-Ruvalcaba syndrome	*PTEN* gene
Adenomatous polyposis syndromes	Familial adenomatous polyposis • Attenuated familial adenomatous polyposis • Turcot syndrome • Gardner syndrome	*APC* gene
	Human MutY homolog (MUTYH)-associated polyposis	*MUTYH* gene
Mixed polyposis syndromes	Hereditary mixed polyposis syndrome	Gene(s) have not been identified

Note: Based on information from Groden et al., 1991; Howe et al., 1998; Howe et al., 2001; Hemminki et al., 1998; Al-Tassan et al., 2002; Burt & Jasperson, 2008; and Hampel, 2009.

grees of risks of cancer. Some of these differences are summarized in the following paragraphs.

FAP. Hundreds to thousands of precancerous colonic polyps develop, beginning on average at 16 years (range, 7–36 years). By age 35, 95% of individuals with FAP have polyps. Without colectomy, the development of colon cancer is inevitable, with the mean age of colon cancer diagnosis in untreated individuals at age 39 years (range, 34–43 years). Extracolonic manifestations may be present and include polyps of the gastric fundus and duodenum, osteomas, dental anomalies (especially supernumerary teeth and/or odontomas), congenital hypertrophy of the retinal pigment epithelium, soft-tissue tumors (specifically epidermoid cysts and fibromas), desmoid tumors, and associated cancers (Burt & Jasperson, 2008).

AFAP. A significant risk for colon cancer exists with AFAP, but there are also fewer colonic polyps (average of 30), more proximally located polyps, and diagnosis of colon cancer at a later age. Because AFAP is characterized by the presence of fewer adenomas and a later onset of disease, it is generally considered to be a "milder" form of FAP, and management may be substantially different. In addition, AFAP is associated with a more limited expression of extracolonic features (Galiatsatos & Foulkes, 2006). Exact standards regarding the criteria for attenuated FAP do not exist; however, Nielsen et al. (2007) have proposed the following:

a. No family member with more than 100 polyps before age 30 years
AND
a. At least two individuals with 10–99 adenomas diagnosed after age 30 years
OR
b. One individual with 10–99 adenomas diagnosed after age 30 years and a first-degree relative with colorectal cancer with a few adenomas

Although this definition accounts for the variability in colonic phenotype seen in AFAP (e.g., one individual may have ≥ 100 polyps at a later age, whereas most have < 100 polyps), it does not account for the *APC* mutation status of an individual. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Colorectal Cancer Screening (version 1.2010) have also noted that individuals with ≥ 100 polyps occurring at older ages (35–40 years or older) may have AFAP (NCCN, 2010).

Gardner syndrome. This condition is characterized by colonic polyposis typical of FAP along with osteomas and soft-tissue tumors (Burt & Jasperson, 2008).

Table 2. Estimates of cancer risks in *APC* mutation carriers

Site	Type of cancer	Lifetime risk of cancer
Colon-FAP	Adenocarcinoma	~100% lifetime
Colon-AFAP	Adenocarcinoma	69% by age 80
Small bowel: duodenum or periampullary	Carcinoma	4%–12%
Small bowel: distal to the duodenum	Carcinoma	Rare
Thyroid	Papillary thyroid carcinoma	1%–2%
Pancreas	Adenocarcinoma	~2%
CNS	Usually medulloblastoma	< 1%
Liver	Hepatoblastoma	1.6% in children < 5 years
Gastric	Adenocarcinoma	0.6%
Bile ducts	Adenocarcinoma	Low but increased

Note: APC = adenomatous polyposis coli; FAP = familial adenomatous polyposis; AFAP = attenuated FAP. Based on information from Burt & Jasperson, 2008; NCCN, 2010.

Turcot syndrome. Colonic polyposis develops, as do central nervous system tumors, primarily medulloblastoma (Burt & Jasperson, 2008).

Differences in phenotype may relate to the location of the mutation within the *APC* gene. In addition, variability in disease presentation between and within families with *APC* mutations is common.

D.R. and his father L.R. were both identified as having a deleterious mutation in *APC*, a tumor suppressor gene. L.R. has over 100 identified polyps, whereas D.R. has very mild polyposis, with fewer than 10 polyps detected over 5 years of surveillance.

Risks

FAP accounts for about 1% of colorectal cancers (Fletcher & Ramsey, 2009). A highly penetrant genetic mutation associated with this syndrome confers a 100% risk of developing colon cancer by age 50 if the colon is not removed (NCCN, 2010). Approximately 8% of families with FAP display AFAP, which is considered a rare condition (Nielsen et al., 2007). However, clinical recognition of AFAP remains a challenge; in some cases, an individual may present with few colonic adenomas, making it difficult to clinically distinguish such an individual from a patient with sporadic polyps. For this reason, AFAP may be underdiagnosed.

The risk of colorectal cancer rises sharply after age 40 years in an individual known to have a mutation associated with AFAP, and by age 80, the risk of colorectal cancer is 69% (Neklason et al., 2008). The average age of colon cancer diagnosis in individuals with AFAP is 50–55 years, which is 10–15 years later than in those with classic FAP but earlier than in those with sporadically occurring colon cancer (Giardiello et al., 1997). Additional cancers and extracolonic manifestations are also associated with FAP and AFAP (Table 2).

Testing/Results

Clinical genetic testing is considered standard care for FAP/AFAP patients because of the high penetrance of the *APC* gene and the documented value of prophylactic colectomy in cancer risk reduction (NCCN, 2010). The risk reduction of colorectal cancer post surgery will be dependent on the amount of rectum remaining, with an 88%–95% risk reduction (Vasen et al., 2001; Aziz et al., 2006) if the rectum is preserved. Testing for FAP/AFAP is performed through evaluation of the *APC* or *MYH* genes in blood.

This syndrome (FAP/AFAP), when inherited in an autosomal-dominant fashion, is caused by mutations in the *APC* gene located on chromosome 5q21 (Galiatsatos & Foulkes, 2006). The *APC* gene encodes a protein that plays a major role in tumor suppression by antagonizing the Wnt signaling pathway (Online Mendelian Inheritance in Man, 2010). The normal APC protein promotes apoptosis in colonic tissue, whereas mutations of the *APC* gene result in a truncated/nonfunctional protein. Loss of *APC* function prevents apoptosis and allows beta catenin, a protein, to accumulate intracellularly and to stimulate cell growth, with

subsequent development of adenomas (Wehbi et al., 2009). This rapid growth along with other genetic events contributes to cancer progression, as occurs in FAP.

Approximately 75%–80% of individuals with *APC*-associated polyposis conditions have an affected parent, whereas 15%–20% of cases are *de novo* without clinical or genetic evidence of FAP in the parents (Burt & Jasperson, 2008; Aretz et al., 2004). In addition, 20% of individuals with an apparent *de novo APC* mutation have somatic mosaicism (Hes et al., 2007). A mutation that occurs during embryonic development after fertilization may result in a person being mosaic, with some cells normal and some cells carrying the mutation. In mosaicism, therefore, one person carries more than one genetic cell line, in contrast to most mutations, which are autosomal dominant (e.g., *APC* gene mutation) and occur at fertilization. Autosomal-dominant mutations are present in all cells of the body (Holm, 2009).

More recently, the MutY human homolog (*MYH*) gene has been identified and may be associated with an autosomal-recessive pattern of inheritance through bi-allelic mutations (Al-Tassan et al., 2002). MYH is an excision repair protein that can become dysfunctional, resulting in G:C (guanine:cytosine) to T:A (thymine:adenine) transversion during DNA replication. *MYH* mutations are thought to cause cancer because of somatic accumulation of these transversions, resulting in a phenotype of multiple adenomatous polyps followed by cancer (de la Chapelle, 2004; NCCN, 2010). When polyposis is present in a single person with a negative family history, consider testing for a *de novo APC* mutation; if negative, follow with testing for *MYH* or, if a positive family history for a sibling with polyposis exists, consider recessive inheritance and test for *MYH* first (NCCN, 2010).

L.R. (father) originally underwent full-gene sequencing of the *APC* gene with the identification of a deleterious mutation. Most mutations in *APC* are nonsense or frameshift mutations that cause premature truncation of the APC protein (Burt & Jasperson, 2008), which means that the protein is nonfunctional, thus leading to an altered phenotype (clinical findings associated with FAP/AFAP). The likelihood of detecting an *APC* mutation is highly dependent on the severity of colonic polyposis. Individuals who have classic FAP are much more likely to have an identified *APC* mutation than an individual with a less severe colonic phenotype (i.e., < 100 polyps; Sieber et al., 2002; Aretz et al., 2005). Fewer than 30% of individuals with attenuated FAP are expected to have an identifiable *APC* mutation (Lefevre et al., 2006). The inability of testing to detect an *APC* mutation may be due to the presence of undetectable mutations, other genes, MYH-associated polyposis, or other syndromes.

Mutations involving the *APC* gene are considered to be autosomal dominant, which means that all first-degree relatives (parents, siblings, and children) have a 50% likelihood of having this same mutation. Therefore, counseling and testing of all at-risk relatives are advised, as they will improve diagnostic certainty and reduce the need for costly screening procedures in those at-risk family members who have not inherited the disease. In addition, knowing the location of the *APC* mutation can be helpful in determining extracolonic cancer risks in affected individuals. Because a mutation had been identified in L. R., his son D.R. underwent testing for the same mutation. D.R. tested positive, as did all three of his children. D. R.'s brother also tested positive, whereas all three of his children tested negative. A third brother was negative for this mutation.

Surveillance

Surveillance measures for *APC* mutation carriers are critically important (see Table 3). The consultand (the individual presenting for genetic counseling), D.R. is undergoing surveillance with an annual colonoscopy along with an esophagogastroduodenoscopy (EGD) every 2 years. Although this screening represents a higher level of monitoring than the NCCN Guidelines (NCCN, 2010) discuss, with the exception of colon cancer, screening recommendations are generally based on expert opinion rather than evidence. The screening for D.R. began at age 42; he is currently 47. Because AFAP patients have a tendency to develop adenomas in the proximal colon, colonoscopy is preferred to sigmoidoscopy as a screening approach. Surveillance is important both before surgery (e.g., colectomy or proctocolectomy) as well as postoperatively. Thus, post-proctocolectomy surgical surveillance must be instituted with regard to any retained rectum and should include ongoing evaluation of the upper gastrointestinal tract.

Table 3. Surveillance measures for individuals with FAP/AFAP

Screening measure	FAP	AFAP
Colonoscopy	Beginning at age 10–12 years; repeat every 1–2 years (colonoscopy or sigmoidoscopy); colonoscopy once polyps detected	Beginning at age 18–20 years; repeat every 2–3 years
EGD including side-viewing examination[a]	Beginning at age 25; repeat every 1–3 years[a]	Beginning at age 25; repeat every 1–3 years[a]
Abdominal ultrasonography and serum alpha-fetoprotein evaluation for screening for hepatoblastoma	Infancy to age 5 years; interval unknown, however, recommendation at least every 3–6 months[b]	Nonapplicable
Palpation of thyroid with consideration of ultrasonography and fine-needle aspiration for thyroid nodules[c]	Annual starting in late teenage years	Annual
Physical examination with evaluation for extraintestinal manifestations	Annual	Annual

Note: Other than screening measures for identification of colon cancer, recommendations are based on expert opinion rather than evidence (NCCN, 2010). FAP = familial adenomatous polyposis; AFAP = attenuated FAP; EGD = esophagogastroduodenoscopy. [a]Side-viewing examination of the duodenal papilla should occur. Adenomatous tissue is commonly found at the papilla, even if no polyps are visualized, so biopsy of the papilla is recommended if it seems enlarged or dense lesions are noted (Giardiello et al., 2001; NCCN, 2010). The utility of video capsule endoscopy (VCE) in screening for small bowel lesions in FAP is unclear (Wong et al., 2006). The frequency of EGD is dependent on the severity of duodenal adenomas. [b]From Hirschman et al., 2004; Aretz et al., 2007; NCCN, 2010. [c]From Herraiz et al., 2007.

Thus far, D.R. has had only hyperplastic polyps or tubular adenomas ≤ 5 mm, which have been identified and removed. He has had a total of six hyperplastic polyps and three tubular adenomas detected in 5 years of annual colonoscopies. His EGDs have been negative.

Since D.R.'s youngest brother tested negative for the known mutation in this family, his colon cancer surveillance measures would be based on those of the general population. This brother did undergo a colonoscopy to assess for polyps, which was negative; he will not undergo another one until he is 50. D.R.'s other brother, who also had an identified mutation, had three children who tested negative for this mutation. Those children should undergo normal colon cancer screening measures beginning at age 50.

Management

As outlined in the preceding paragraphs, the management of FAP/AFAP involves diligent surveillance with appropriate screening measures. In general, colectomy is advised when more than 20–30 adenomas or multiple adenomas with advanced histology have occurred (Burt & Jasperson, 2008). However, the timing of prophylactic surgery (proctocolectomy or colectomy) may depend on several aspects of care. In classic FAP, surgery may be performed at the outset of polyposis, or its timing may be based on the severity of the familial phenotype and genotype, the extent of polyposis at diagnosis, and individual considerations (NCCN, 2010). Annual colonoscopy will remain essential if surgery is not performed. Individuals should be managed by physicians or centers with expertise in FAP, and that management should be individualized to account for genotype, phenotype, and personal considerations (e.g., patient wishes, fertility considerations, compliance with regimen).

The treatment of patients with AFAP will vary based on the patient's age and adenoma burden. Colectomy should be considered when the number of polyps exceeds 20, the polyps are larger than 1 cm, or advanced histology (high-grade dysplasia, villous architecture) is evident (NCCN, 2010). Early colectomy should be considered in patients with a personal history of AFAP if there is a family history of colorectal cancer under age 40 or if the individual is not compliant with surveillance (NCCN, 2010). About one third of patients with AFAP will not need colectomy but can be managed safely with interval colonoscopy and polypectomy (Burt et al., 2004).

Table 4. Surgical management

Surgical approach	Indications: genotype	Indications: phenotype	Procedure/ anatomic changes	Ostomy	Considerations/ care
Total abdominal colectomy with ileorectal anastomosis (TAC/IRA)	Site of *APC* mutation associated with mild form of FAP; mutations found at extreme ends of gene and in alternatively spliced part of exon 9[a]	No polyps/very few polyps in rectum	Small intestine attached to upper portion of rectum; colon removed, all or most of rectum retained	No	Good bowel function should be preserved; antidiarrheal medication may be needed for fecal frequency/ urgency; no risk of bladder or sexual function problems
Total procto-colectomy with ileal pouch anal anastomosis (TPC/IPAA)	*APC* gene mutation associated with intermediate (mutations in parts of gene not associated with mild or severe expression) or severe expression of disease (between codons 1250 and 1464, especially mutation at codon 1309)[a]	Many polyps in the rectum; increased risk of desmoid tumors	Pouch developed from ileum and joined to anus; colon and most of rectum removed	Temporary loop ileostomy; taken down after 8–10 weeks	Bowel function may be unpredictable; small risk of bladder and sexual dysfunction; fertility in women significantly reduced as compared with TAC/IRA
Total procto-colectomy with ileostomy (TPC/EI)	*APC* mutation between codons 1250 and 1464, especially mutation at codon 1309, associated with a severe form of FAP[a]	Patients with low, locally advanced rectal cancer; those who cannot have an ileal pouch due to desmoid tumors; those with a poorly functioning ileal pouch, or those with contraindication for IPAA	Removes entire colon and rectum	Permanent ileostomy	Risk of bladder or sexual dysfunction; fears associated with permanent stoma; risks of electrolyte and fluid loss

Note: APC = adenomatous polyposis coli; FAP = familial adenomatous polyposis. [a]From Nieuwenhuis & Vasen, 2007; NCCN, 2010.

The possible surgical procedures for management of FAP/AFAP include:

- Total abdominal colectomy with ileorectal anastomosis (TAC/IRA)
- Total proctocolectomy with ileal pouch anal anastomosis (TPC/IPAA)
- Total proctocolectomy with end ileostomy (TPC/EI)

The choice of surgical procedure will depend on the individual and familial phenotype. Factors affecting this decision include a review of the rectal polyp burden and the presence of colon or rectal cancer at diagnosis. For individuals with a classic FAP phenotype, proctocolectomy is the procedure of choice, as the risks of developing rectal cancer are negligible (Table 4).

L.R. (father) underwent a total proctocolectomy with ileal pouch anal anastomosis. This procedure should be considered for patients with attenuated FAP with phenotypes such as his, which resulted in carpeting of the colon and rectum. This operation has certain advantages: 1) the risks of developing rectal cancer are minimal, and 2) a permanent stoma is not needed. L.R. continues to undergo surveillance of the ileal pouch annually. He also undergoes EGD every 2 years, which has remained negative for any cancers.

The role of nonsteroidal anti-inflammatory drugs (NSAIDs) as chemoprevention to reduce the incidence and recurrence of colorectal adenomas

in FAP has been debated. NSAIDs, especially sulindac, have been found to decrease the number of polyps requiring ablation in the remaining rectum of individuals with FAP who have had a colectomy with IRA (Cruz-Correa, Hylind, Romans, Booker, & Giardiello, 2002). However, a randomized, double-blind, placebo-controlled study by Giardiello et al. (2002) found that sulindac did not prevent the development of adenomas in individuals with FAP. Therefore, the use of chemoprevention with NSAIDs is not believed to be effective as primary treatment for FAP, though it could be considered following initial prophylactic surgery for both classic and attenuated FAP to reduce the rectal polyp burden (NCCN, 2010).

Summary

This case illustrates an atypical presentation of AFAP, which began as a *de novo* mutation in the proband, L.R. He was asymptomatic until presenting with anemia and fatigue; he underwent colonoscopy that revealed > 100 polyps lining the colon and rectum. Pathologic examination of the removed colon did not reveal malignant cells. Testing revealed a deleterious mutation in the *APC* gene. Although we do not have a previous colonoscopic evaluation to know the age at which L.R. began to develop polyps, he was diagnosed as having AFAP because of his age at presentation and based on criteria delineated by Nielsen et al. (2007) and NCCN (2010). He underwent a TPC/IPAA and continues to undergo surveillance, with no subsequent cancers found.

The consultand (son) also tested positive for this deleterious mutation in the *APC* gene. He continues to undergo surveillance measures and after 5 years has never had more than one or two polyps identified annually. All three of his children, beginning at age 10, undergo annual colonoscopies, and no polyps have been detected. Of note, some of the surveillance measures for this family exceed the NCCN recommendations. This approach is per family request and individual consideration.

The advanced practitioner who is following a patient with a FAP/AFAP should ensure that the patient understands the importance of surveillance measures and will adhere to the proposed screening regimen. Surveillance of FAP/AFAP patients leads to a reduction in colorectal cancer and colorectal cancer-associated mortality. The establishment of registries of FAP families worldwide has encouraged participation in surveillance programs and has significantly reduced death from colorectal cancer (Vasen et al., 2008).

Although the role of prophylactic surgery cannot be disputed, the timing for this intervention may depend on the patient's genotype and phenotype along with other personal considerations. The patient should make the final decision after being fully informed about the pros and cons of the surgical options. The importance of surveillance measures post surgery must be reinforced.

Because of improved surveillance and surgical options, the prognosis of FAP patients appears to be determined increasingly by extracolonic features of FAP, especially duodenal cancer and desmoid tumors (Vasen et al., 2008). Thus, clinical trials that focus on improvements in the pharmacologic, surveillance, or surgical management of these tumors should be encouraged.

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