Inherited Colon and Rectal Cancer: Surgical Perspectives

Part 3—Familial Adenomatous Polyposis and the Polyposis Syndromes: One Gene, Many Manifestations

THE ALPHABET SOUP
of Genetics and Diagnosis Explained

By Jordan R.H. Hoffman and Gary H. Hoffman, MD

In Parts 1 and 2 of this series, we looked at the genetics, diagnosis and treatment of hereditary nonpolyposis colorectal cancer (HNPCC).

In Part 3, we examine familial adenomatous polyposis (FAP), other polyposis syndromes and the damage caused by these inherited diseases. Emphasis is placed on the genetics of the disease and how knowledge of the mutational pattern can help the clinician secure a diagnosis, and begin treatment. Look-alike diseases, those looking like FAP but arising from a mutation on a different gene, also will be considered.

Genotype to Phenotype: From Genetics to Appearance

FAP, an inherited disorder, is responsible for 1% of all colorectal malignancies. Caused by a mutation in a single gene, the adenomatosis polyposis coli (*APC*) gene, FAP can lead to a radical change in the structure and functioning of the body.

How can a seemingly small change in the genotype so drastically alter the phenotype in such a lethal manner? The answer is in the genetic realm where proteins are produced. The APC protein is made up of 2,843 amino acids. A mutant gene produces an abnormal protein that leads to disease.

A nucleotide is formed by the combination of a five-carbon sugar, one or more phosphates and one of the purine or pyrimidine nucleobases guanine, adenine, cytosine or thymine. A trinucleotide sequence, also known as a triplet or codon, codes for and produces a specific amino acid using processes called transcription and translation. A long sequence of codons with start and stop codons defines a single gene, which codes for many amino acids. These amino acids bond together to form a protein.

Proteins participate in every process within the cell. Proteins are the building blocks of enzymes and also make up the structural or mechanical elements of cells and tissues. Proteins play integral roles in cellular signaling, cellular division and cell death, or apoptosis. Each protein is considered to be the protein product of its parent gene.

The gene is a long-term storage area for the genetic code, or DNA, and all of the genes form a set of blueprints used by the body to control cellular structure and functioning. Many genes reside on a linear stretch of DNA and the entire length of these genes plus the intervening, non-coding portions form a chromosome. Humans have 46 chromosomes (the common fruit fly has eight and goldfish have 104). Human chromosome 5 has between 900 and 1,300 genes. One of these is the *APC* gene.

In both FAP and sporadic colorectal cancers (CRCs), a mutation of the *APC* gene is one of the earliest events leading to polyp formation, and subsequent malignant degeneration. This is known as the adenoma–carcinoma sequence.[1] Six hundred mutations have been discovered in the *APC* gene. A mutation in any one of the 600 *APC* codons can lead to disease through the production of a defective, malfunctioning, truncated APC protein product. The ubiquitous APC protein belongs to the family of suppressor proteins and is commonly found in the cell cytoplasm. It interacts with several other cytoplasmic proteins, including β-catenin. β-catenin may be responsible for transmitting the contact inhibition signal that causes cells to stop dividing once an epithelial layer is complete. Normally, the APC protein binds to, and downregulates β-catenin through destruction of the β-catenin. Because of truncation, or shortening, of the now malfunctioning APC protein, β-catenin may enter the nucleus and actually stimulate cell proliferation. This begins a neoplastic cascade and malignant transformation through unchecked cellular division. The result of this is polyp and tumor growth. The APC protein is highly concentrated in colonic mucosa.[2]

Different mutant codons within the *APC* gene may code for different forms of FAP or attenuated familial adenomatous polyposis (AFAP), and also code for the development of extracolonic tumors. In other words, the mutation at the genotype level is translated into a somatic mutation, deformity or neoplasm at the phenotype level. For example, "mutations between codons 1301 and 2011 are associated with a sixfold increase in desmoid tumors relative to the low-risk region. Codons 1250-1464 are associated with severe polyposis and earlier onset cancer. Duodenal adenoma risk and extracolonic manifestations are highest between codons 976 and 1067."[3]

Mutations associated with AFAP are located on either end of this large *APC* gene (Figure).[4] Mutations found in the *APC* gene of patients with FAP or AFAP are similar to those found in patients with *sporadic* CRC. However, in contrast to sporadic colorectal carcinoma, the *APC* mutation in inherited disease is present at birth.[5]

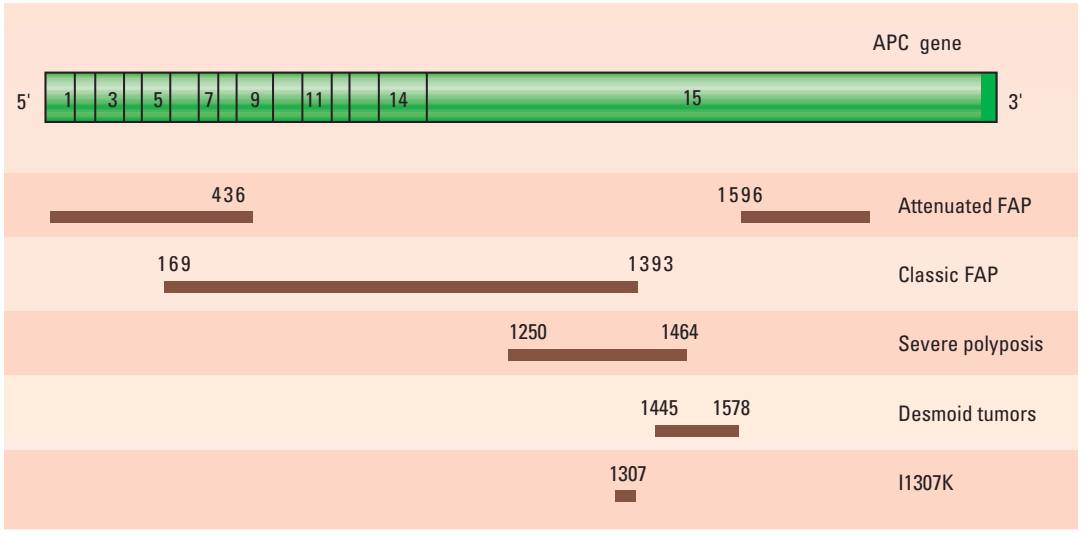

FIGURE. GENOTYPE-PHENOTYPE CORRELATION ON THE APC GENE.

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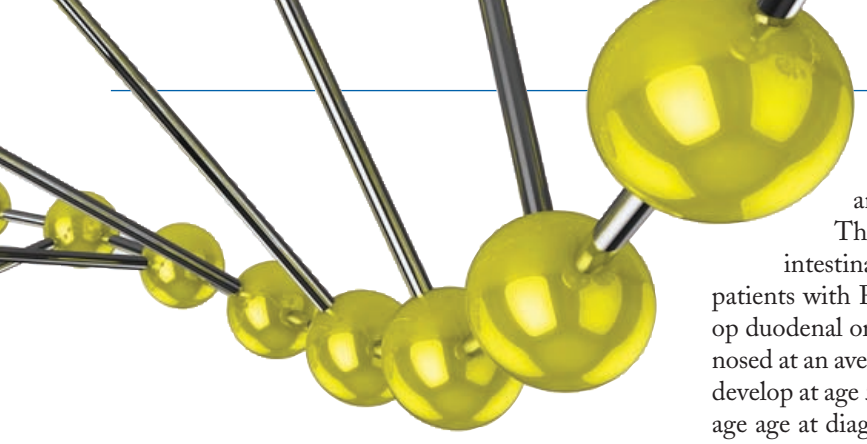
From Phenotype to Diagnosis: The Many Faces of FAP

FAP is a rare autosomal dominant disorder characterized by the pancolonic formation of hundreds or thousands of polyps that develop at an early age. It is associated with at least eight other malignancies. The *APC* gene mutation has a high penetrance rate, meaning that individuals with the mutated gene (the genotype) will almost surely develop polyps (the phenotype).

In the average, untreated patient, the natural history of the disease is as follows[6]:

- Age of appearance of adenomas: 23 years
- Age of onset of symptoms: 33 years
- Age of diagnosis of adenomas: 36 years
- Age of diagnosis of carcinomas: 39 years (65 years in the general population)



- Age of death from carcinomas: 42 years (71 years in the general population)

Of patients who present with symptoms of FAP, 65% already have a colorectal carcinoma. **There is an almost 100% risk for developing colon cancer if patients with FAP remain untreated. Therefore, early diagnosis and treatment are of paramount importance.**

Eighty percent of patients will have a family history of FAP or AFAP, with a known, precisely located mutation, heightening diagnostic suspicion and making the diagnosis of FAP straightforward. However, 20% of patients will have a *de novo* mutation in an unknown gene location. In patients who are unaware of their disease, symptoms generally begin when the polyposis is complete, at an average age of 33 years.

Rectal bleeding and diarrhea are the most common presentations. As the symptoms call attention to the need for evaluation, colonoscopy is the surest way to detect the disease. Extracolonic manifestations of disease (see below) also may be discovered on physical examination, calling attention to the diagnosis. The diagnosis is secured with histopathologic confirmation of adenomatous polyps. Affected patients have as few as 100 colonic polyps and may have thousands of polyps carpeting large sections of the colon. Polyp size can range from microscopic to greater than 1 cm; however, most of the polyps are small. The smaller adenomas may require the use of indigo carmine or narrow-band imaging to be discovered.

In contrast to hereditary nonpolyposis CRC (HNPCC), where the disease is predominantly located proximal to the splenic flexure, FAP commonly affects the left side of the colon. Rectal carcinoma occurs in 59% of patients. However, the entire colon must be examined, as rectal sparing has been reported.[7] Of patients with FAP, 24% have a sigmoid malignancy, and the remainder of cases shows more proximal disease.[8]

In FAP, there is a lifetime risk for developing associated desmoid tumors (15%), duodenal cancer (4%), thyroid cancer (2%), brain cancer (2%), ampullary cancer (1.7%), pancreatic cancer (1.7%), hepatoblastoma (1.6%) or gastric cancer (0.6%). Early diagnostic questioning and subsequent evaluation must focus on these areas.[9] Esophagogastroduodenoscopy often may disclose fundic gland polyps that might point the clinician to search in the direction of a defective *APC* gene. Suitable radiographic examinations such as computed tomography scanning or magnetic resonance imaging evaluation might be employed in the search for extracolonic disease.

Clinical Variants of Familial Adenomatous Polyposis

Attenuated Familial Adenomatous Polyposis

AFAP is characterized by the formation of fewer, more proximal polyps developed at a later age.[10,11] Clinically, AFAP has been recognized relatively recently. It may be a variant of FAP, or may be a disease in its own right.

Securing a diagnosis of AFAP is more challenging but must be considered in younger patients with between 10 and 100 proximally located colonic polyps. The polyps often are flat. An upper gastrointestinal (GI) examination must be performed in patients with FAP or AFAP, as 80% to 90% will develop duodenal or periampullary adenomas. They are diagnosed at an average age of 44 years. Carcinomas in AFAP develop at age 56 compared with FAP in which the average age at diagnosis is 10 to 15 years earlier. It is possible that the differential in age of onset of the polyposis and malignant transformation between FAP and AFAP is due to a lack of earlier recognition of AFAP by physicians and patients, rather than being a true difference in the age of onset.[5]

It often is difficult to distinguish between FAP and AFAP based solely on the number of polyps seen on examination. In fact, there is evidence that AFAP and FAP may not be separate diseases, but different manifestations of a single entity. In a single family with a single mutation, the number of colonic polyps in each family member may vary widely. Extracolonic disease is similar in both forms of polyposis.

Genetically, FAP and AFAP are associated with a large number of different *APC* mutations. Clinically, patients with fewer than 100 polyps may have FAP, AFAP or HNPCC. In a single family, patients may present with widely differing clinical manifestations.

"The definition of AFAP, 'multiple, but fewer than 100 synchronous colorectal adenomas, is one that suffers from an arbitrary imposition of a finite number of polyps combined with a spectrum of subtle variations.'"[5]

Even though the polyps in AFAP are predominantly right-sided and the mutation is usually located on either end of the *APC* gene, the underlying disease remains FAP.[5] AFAP simply may be a form of FAP with mild expression.

Turcot Syndrome

Turcot syndrome describes the association of colorectal adenomatous polyposis with central nervous system tumors, specifically, cerebellar medulloblastomas. Sixty-six percent of patients have an *APC* gene mutation and 33% have a mutation in a mismatch repair gene. Mismatch repair genes are commonly associated with hereditary nonpolyposis CRC, and Turcot syndrome may be a disease that has several underlying genetic etiologies.

APC I1307K

There are 360,000 American Ashkenazi Jews who are carriers of a mutant gene located on codon 1307 of the *APC* gene. This represents 5% of the Ashkenazi population. People carrying this mutation, known as *APC I1307K*, are at a 1.7 times greater risk for colorectal neoplasia compared with those who do not have this mutation. Additionally, there are greater numbers of adenomas and CRCs in this group, and a younger age at diagnosis. It is estimated that *APC I1307K* is responsible for up to 4% of all CRCs in Ashkenazi Jews. Although the impact of this mutation is not fully understood at this time, it is thought that genetic testing of this entire population, irrespective of a family history of CRC, followed by appropriate clinical screening and surveillance might benefit the mutation carriers who are expected to develop CRC.[12]

Gardner Syndrome

Gardner syndrome is the association of FAP with epidermoid cysts, osteomas and fibromas (now called desmoid tumors). Colorectal polyposis was later added to the syndrome. Gardner syndrome is thought to be FAP with an extraintestinal feature. As this seems to be the case in most clinical presentations of FAP, Gardner syndrome is no longer considered to be a distinct entity.

MYH Mutations: A Look-Alike, But a Different Gene

MYH-associated polyposis syndrome is a condition resembling FAP on a phenotypic level but results from a mutation on a gene other than the *APC* gene. The *MYH* gene is located on the short arm of chromosome 1. Being inherited in an autosomal recessive manner means that both alleles or both copies of the *MYH* gene must be mutant to cause the phenotypic expression of disease. MYH syndrome is usually associated with a smaller number of colorectal polyps, but some cases have been reported presenting with hundreds of colorectal adenomatous polyps; hence, the inclusion of MYH polyposis in the family of inheritable colonic polyposis syndromes. In patients with clinical disease, in whom no *APC* mutation is identified, a diagnosis of MYH polyposis syndrome should be considered and should be evaluated using gene analysis of a whole blood sample. Although malignant transformation of the polyps does occur, the

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Table. Extracolonic Manifestations Of Familial Adenomatous Polyposis

Ectodermal Origin
Epidermoid cyst
Pilomatrixoma
Tumors of central nervous system
Congenital hypertrophy of the retinal pigment epithelium
Mesodermal Origin
Connective tissue
Fibroma
Fibrosarcoma
Desmoid tumors
Diffuse fibrosis mesenteric retroperitoneum
Excessive intra-abdominal adhesion
Bone
Osteoma
Exostosis
Sclerosis
Dental
Dentigerous cyst
Odontoma
Supernumerary teeth
Unerupted teeth
Lymphoid
Hyperplasia of ileum
Endodermal Origin
Adenomas
Stomach
Duodenal
Hepatopancreatobiliary system
Small intestine
Adrenal gland
Adrenal cortex (adenomas)
Thyroid gland
Carcinomas
Fundic gland polyp
Hepatoblastoma

Adapted from reference 13.

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exact incidence of this transformation is unknown. Treatment and surveillance is as for patients with FAP.

Other Look-Alikes: Rare but Troublesome

Peutz-Jeghers syndrome, juvenile polyposis syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome and metaplastic polyposis all are rare inherited conditions with varying presentations, varying types of polyps and variable degrees of risk for the development of a malignancy. The common phenotypic disorder linking them together is the development of GI polyposis. The polyps become manifest at differing ages and have differing malignant potentials. The key point for the clinician to keep in mind is that the histopathologic features of the polyps must be identified in order to appropriately guide surveillance and treatment. Genetic counseling is an integral part of the care of these patients.

Extracolonic Manifestations Of Familial Adenomatous Polyposis

Endoderm-Derived Disease

FAP affects the entire body and may give rise to extracolonic neoplasms derived from the embryologic endoderm, ectoderm or mesoderm (Table).[13] The etiology of the extracolonic manifestations is not clear and may involve the *APC* gene, other genes or environmental factors. There is inconclusive data that suggest that the codon location of the *APC* mutation may have a phenotypic effect.[14] Death from extracolonic disease in patients with FAP is now more common than death from colorectal carcinoma.[15]

The prevalence of gastric polyps ranges from 34% to 100%. Most are hyperplastic polyps and a few are adenomatous and are located in the antrum. Malignant transformation rarely occurs. There is evidence that the adenomatous polyps are located in areas that have been exposed to bile through reflux.[16-18]

Duodenal polyps are found in more than 90% of patients with FAP. They often are located in the periampullary region. They vary in number, size and morphology. However, they are almost always adenomas. The concern for these patients relates to the potential for malignant transformation of these adenomas. Up to 35% of patients with FAP have been found to have a duodenal or periampullary carcinoma. However, other studies have reported a much lower incidence of carcinoma.[9] After desmoid tumors, periampullary carcinoma is the second-leading cause of death in patients with FAP.[15]

Small intestinal adenomas and carcinomas occur rarely, and the risk for developing a malignant lesion is small.

Mesoderm-Derived Disease

Desmoid tumors arise from benign fibroaponeurotic tissue. They are thought to be true neoplasms as opposed to a fibroblastic reaction. They are locally invasive. Commonly, they cause pressure on surrounding structures and erosions of adjacent tissue. Small bowel obstructions are common and also are the result of local growth. The most common symptom in patients with an intra-abdominal desmoid tumor is a painful mass, with pain being secondary to a small bowel obstruction.

There is an almost 100% risk for developing colon cancer if patients with familial adenomatous polyposis remain untreated. Therefore, early diagnosis and treatment are of paramount importance.

Desmoid tumors have been observed in 14% of patients undergoing laparotomy for FAP.[19] They are even more common in patients undergoing a repeat laparotomy.[20] Growth rates range from indolent to rapid. Although rare, spontaneous regression has been noted. In up to 38% of cases of laparotomy, a desmoid tumor interfered with the planned procedure. Treatment is controversial, empirical and difficult, especially with desmoid involvement with abdominal vessels, the ureters or the mesentery. Because of a high rate of recurrence, it is felt that a conservative approach, including the use of combinations of nonsteroidal anti-inflammatory drugs and/or anti-neoplastic agents is warranted, with operative treatment reserved for patients having life-threatening complications such as local invasion into vital structures.[21] Death as a result of desmoid disease is from local invasion into a vascular structure, sepsis resulting from an enteric fistula or as the result of the attempted therapeutic operation.[22]

Osteomas may occur in any bone, particularly in the facial bones. They are benign, cause symptoms due to local growth and are sometimes identified prior to the diagnosis of FAP. Dental abnormalities such as unerupted or supernumerary teeth, dentigerous cysts or odontomas occur often in FAP and their appearance is diagnostically useful.[21,23]

Ectodermal Disease

Ectodermal lesions associated with a mutated *APC* gene involve the eye, the skin or the brain.

Congenital hypertrophy of retinal pigment epithelium (CHRPE) is considered a marker for FAP, and is restricted to a mutation in codons 463 to 1444. The lesion is a hamartoma, which is a collection of cellular elements normally found at the site, but presenting as a disordered mass of histologically normal tissue. CHRPE is asymptomatic and benign. It is best viewed on indirect ophthalmoscopy through a dilated pupil. As a marker for FAP, it has a 79% sensitivity rate and a 95% specificity rate.[21,24] In other words, patients presenting with CHRPE most likely will have FAP.

Epidermoid cysts are found on the limbs, face and scalp. They may be found in up to 50% of patients with FAP. They rarely are found in children except in FAP, and may appear even prior to the development of colorectal polyps. The association is strong enough that any child with an epidermoid cyst should undergo a sigmoidoscopy after age 14. Histologically, the cyst is made up of a thin layer of squamous cells and may be asymptomatic or may present as a painful nodule.

Although also found in patients with HNPCC, medulloblastomas more often are found in FAP. This association bears the name of Turcot syndrome, after Jacques Turcot, the Canadian surgeon who discovered this new extracolonic manifestation of FAP. Although rare, Turcot syndrome is usually fatal, with death occurring at an average age of 20 years. In two studies, 75% of patients died from the medulloblastoma and 16% died from CRC.[25,26]

Part 4 of this series will evaluate the surveillance and surgical options for patients and family members affected by familial adenomatous polyposis.

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