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. 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.

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.”

Mutations associated with AFAP are located on either end of this large APC gene (Figure). 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.

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:

• 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)
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 at onset of the polypsis 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

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 Esophagastroduodenoscopy 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

<table>
<thead>
<tr>
<th>TABLE. EXTRACOLONIC MANIFESTATIONS OF FAMILIAL ADENOMATOUS POLYPOSIS</th>
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<tbody>
<tr>
<td><strong>Ectodermal Origin</strong></td>
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<tr>
<td>Epidermoid cyst</td>
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<td>Pilomatrixoma</td>
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<td>Tumors of central nervous system</td>
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<td>Congenital hypertrophy of the retinal pigment</td>
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<td><strong>Mesodermal Origin</strong></td>
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<tr>
<td>Connective tissue</td>
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<tr>
<td>Fibroma</td>
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<td>Fibrosarcoma</td>
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<td>Desmoid tumors</td>
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<tr>
<td>Diffuse fibrosis mesenteric retroperitoneum</td>
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<tr>
<td>Excessive intra-abdominal adhesion</td>
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<td>Bone</td>
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<td>Osteoma</td>
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<td>Exostosis</td>
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<td>Scleroderma</td>
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<td><strong>Dental</strong></td>
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<td>Dentigerous cyst</td>
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<td>Odontoma</td>
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<td>Supernumerary teeth</td>
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<td>Unerupted teeth</td>
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<td><strong>Lymphoid</strong></td>
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<tr>
<td><strong>Endodermal Origin</strong></td>
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<tr>
<td>Adenomas</td>
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<td>Stomach</td>
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<td>Duodenal</td>
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<td>Hepatopancreatobiliary system</td>
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<tr>
<td>Small intestine</td>
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<tr>
<td>Adrenal gland</td>
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<td>Adrenal cortex (adenomas)</td>
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<td>Thyroid gland</td>
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<td>Carcinomas</td>
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<td>Fundic gland polypl</td>
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<td>Hepatoblastoma</td>
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Adapted from reference 13.

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 colocolic 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
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, Ban-
nayan-Riley-Ruvalcaba syndrome and metaphastic polyposis all are rare inher-
ited conditions with varying presentations, varying types of polyps and variable degrees of risk for the development of a malignancy. The common phenotyp-
ic disorder linking them together is the diaphanous root of GI polyps. 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 integ-
ral part of the care of these patients.

Extracolonic Manifestations Of Familial Adenomatous Polyposis Endodermal-Derived Disease FAP affects the entire body and may give rise to extracolonic neoplasms derived from the embryologic endoderm, ecto-
derm 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 muta-
tion may have a phenotypic effect.14 Death from extracolonic disease in patients with FAP is now more common than death from colorectal carcinoma.15 Small intestinal adenomas and carcino-
mas occur rarely, and the risk for developing a malignant lesion is small. Mesodermal-Derived Disease Desmoid tumors arise from benign fibroaponeurotic tissue. They are thought to be true neoplasms as opposed to a fibro-
blastic reaction. They are locally invasive. Commonly, they cause pressure on sur-
rounding structures and erosions of adja-
cent 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.

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