

Familial adenomatous polyposis: a review of gastrointestinal manifestations

Catherine E Hagen

Namrata Setia

Gregory Y Lauwers

Abstract

Familial adenomatous polyposis (FAP) is an autosomal dominant cancer predisposition syndrome. Although colonic manifestations including multiple adenomas and subsequent adenocarcinomas are characteristic of this syndrome, benign and malignant involvement of the extracolonic gastrointestinal tract is also seen. The aim of this article is to review the clinical, pathologic and molecular genetics features of familial adenomatous polyposis syndrome in the entire gastrointestinal tract. Detailed characterization of these findings can facilitate appropriate surveillance strategies, treatment and preventative measures by collective efforts between the clinicians, genetic counsellors, and pathologists.

Keywords adenocarcinoma; adenoma; APC gene; beta-catenin; extracolonic; familial adenomatous polyposis; gastrointestinal

Familial adenomatous polyposis (FAP), also known as adenomatous polyposis coli and familial polyposis coli, is the best characterized and most common genetic polyposis syndrome. Accounting for <1% of all colorectal cancers and caused by an autosomal dominant mutation in the APC gene, FAP is estimated to occur at an incidence of 1:7000–10,000.^{1–3} Variants of FAP include Gardner syndrome (FAP with extraintestinal manifestations) and Turcot syndrome (FAP with glioblastoma or medulloblastoma). A subset of patients also display an attenuated version of FAP (AFAP), developing fewer adenomas at a later age of onset. Without treatment, nearly 100% of patients will develop colorectal cancer, and therefore, early diagnosis and surveillance is imperative. In this review, we will particularly underscore the extracolonic gastrointestinal manifestations of FAP and genetic advances in FAP.

Catherine E Hagen MD Assistant Professor, Department of Pathology, Medical College of Wisconsin, Milwaukee, WI, USA. Conflicts of interest: none declared.

Namrata Setia MD Fellow in Gastrointestinal Pathology, Department of Pathology, Massachusetts General Hospital, Boston, MA, USA. Conflicts of interest: none declared.

Gregory Y Lauwers MD Professor, Department of Pathology, Massachusetts General Hospital, Boston, MA, USA. Conflicts of interest: none declared.

Epidemiology of colonic and extracolonic manifestations

Colonic adenomas commonly represent the first manifestations, and are usually detected in the 2nd decade of life with most patients developing adenomas by age 35.⁴ Classic FAP is diagnosed when a patient presents with over 100 adenomatous colorectal polyps. Over time, the adenomas increase in size and number, with patients eventually developing hundreds to thousands of adenomas. As polyps increase in number, so does the risk of cancer, with a mean age of diagnosis at 39 years.⁵ However, cases of colorectal cancer have been reported in teenagers and overall 7% of patients develop cancer by age 21.^{6–8} If left untreated, there is a nearly 100% chance of developing colorectal cancer, with 95% of patients developing cancer by age 50.⁵

Approximately 8% of patients demonstrate an attenuated form of the disease, i.e. AFAP,⁹ developing fewer polyps, usually <100 (median 25), with an average age of onset of 41 years. The diagnostic criteria of AFAP are less established, but the following have been proposed: (1) two patients in a family are diagnosed with 10–99 adenomas at age >30 years or (2) one patient diagnosed with 10–99 adenomas at age >30 and a first-degree relative is diagnosed with colorectal cancer.¹⁰ Others have proposed that the diagnostic criteria include (1) a dominant mode of inheritance and (2) development of <100 colorectal adenomas at age ≥25 years.¹¹ With fewer polyps, these patients are at a slightly lower risk of developing colorectal cancer. The mean age of diagnosis for colorectal cancer is 58 years with a cumulative lifetime risk of 69% by age 80.¹²

Upper gastrointestinal tract manifestations are common in both FAP and AFAP patients. Fundic gland polyps (FGPs) are seen in 50–90% of patients, and 40% may develop dysplasia. True adenomatous polyps can also be seen, but are much less common, and the risk of gastric cancer is <1%. Duodenal adenomas are also seen in up to 90% of FAP patients.^{5,13,14}

Benign extraintestinal manifestations include congenital hypertrophy of retinal pigmented epithelium (75–90%), epidermoid cysts (50%), osteomas (50–90%), desmoid tumours (10%), supernumerary teeth (70–80%), and adrenal adenoma (7–13%). Extraintestinal cancer risks include pancreas (2%), thyroid (1–2%), liver (1–2%), and central nervous system (<1%).^{5,13,14}

Genetics

FAP is typically caused by an autosomal dominant germline mutation of the adenomatous polyposis coli (APC) gene located on chromosome 5q21-22.¹⁵ Despite the majority of FAP patients having an established family history of colorectal polyps and cancer, 25–30% of APC mutations arise de novo.^{3,13} Further studies have revealed that 10–15% of these de novo mutations are actually a result of somatic mosaicism.¹⁶ MUTYH-associated polyposis, discovered in recent years, may account for an additional 10–30% of patients presenting with an FAP phenotype but without APC mutations.^{17–19}

APC is a tumour suppressor gene belonging to the Wnt signalling pathway and responsible for downregulation and degradation of β-catenin. In the absence of APC, β-catenin accumulates in the nucleus, leading to expression of targets and subsequently upregulation of downstream proto-oncogenes.¹³ The coding region of APC is composed of 15 exons and

encodes for a protein containing 2843 amino acids. Several different types of mutations have been reported, currently with over 3800 variants.²⁰ Of these, the most common mutation is a deletion involving codon 1309, found in approximately 10% of patients. Despite the large mutational variation, the majority of the mutations result in the production of a truncated protein. Sixty percent of mutations in the APC gene are found in the centre of the protein, which has been termed the mutational cluster region (MCR). The MCR corresponds to the region of the APC gene responsible for β -catenin downregulation.¹³

Specific APC mutations have been shown to correspond to characteristic phenotypes, although the correlation is not exact. Patients with mutations involving codons 1250–1549, often involving the MCR, are more likely to present at an early age with profuse polyposis (>5000 colorectal polyps) and a decreased median survival. Individuals with mutations involving codons 157–1595, excluding the MCR, typically present with classical FAP, and those with AFAP usually have mutations at the 5' or 3' end of the gene or in the alternatively spliced region of exon 9. Mutation site also has been shown to correlate with extracolonic manifestations. Congenital hypertrophy of the retinal pigment epithelium has been associated with mutations in codons 311–1465, desmoid tumours with mutations in codons 1310–2011, and upper gastrointestinal tract polyps with codons 564–1987.^{21,22} However, the usefulness of the genotype–phenotype correlation to guide surveillance and management strategies is debated, since intra-familial variation is not uncommon (Figure 1).

APC mutations are not only seen in FAP patients, but also occur early in sporadic colorectal carcinogenesis.²³ Interestingly, at least 12 single-nucleotide polymorphisms (SNPs) have been identified in the APC gene, three of which result in amino acid substitutions. Although patients with these SNPs do not have FAP or any of the associated extracolonic manifestations, the SNPs do appear to alter the risk of colorectal neoplasia. Patients with the D1822V variant have a slightly decreased risk of colorectal neoplasia compared to wild type, while patients with the E1317Q variant have a slightly increased risk. The E1307K variant, reported to occur in 6% of Ashkenazi Jews, also results in a significantly higher risk of colorectal neoplasia (about twofold) compared to wild type.²⁴

Diagnosis

Genetic testing may be used to diagnose cases that are clinically challenging or to detect asymptomatic family members at risk. Up to 85% of patients with classic FAP exhibit a mutation, while only 20–30% of AFAP patients will have a mutation detected.²⁵ Multiple different methods can be used individually or in combination, including protein truncation testing (PTT), gene sequencing, and multiplex ligation probe amplification. PTT only looks for an abnormally shortened APC protein in exon 15 and does not detect mutations that do not result in a truncated protein. Given the large size of the APC gene, whole gene sequencing is expensive and labour intensive, and also may miss large insertions or deletions. However, it has the advantage of potentially being predictive of the patient's phenotype. Multiplex ligation probe amplification can be used to detect large deletions or insertions.¹³

Clinical management

In patients with classical FAP, endoscopic screening is recommended starting around age 10. Sigmoidoscopy can be performed initially every two years until adenomas are detected, and then colonoscopy should be performed annually until colectomy is performed. In patients with AFAP, surveillance is recommended to start around age 20. Full colonoscopy is recommended every two years, given the predominance of right-sided adenomas in these patients. Prophylactic colectomy is ultimately required, usually between ages 15–25, either with ileal pouch-anal anastomosis (IPAA) or ileorectal anastomosis (IRA). IRA is a relatively simple procedure compared to IPAA with a low complication rate, but may not be a viable option for patients with numerous rectal adenomas. Endoscopic follow-up is recommended in patients undergoing IRA every 3–6 months, and 6–12 months for patients with IPAA.^{5,8}

There is no consensus on surveillance guidelines for upper gastrointestinal tract disease, but some have recommended endoscopy starting at age 25–30.⁸ Despite the majority of FAP patients developing duodenal adenomas in their lifetime, the cumulative incidence of duodenal cancer is only about 5%.²⁶ However, upper endoscopy can help identify those with severe

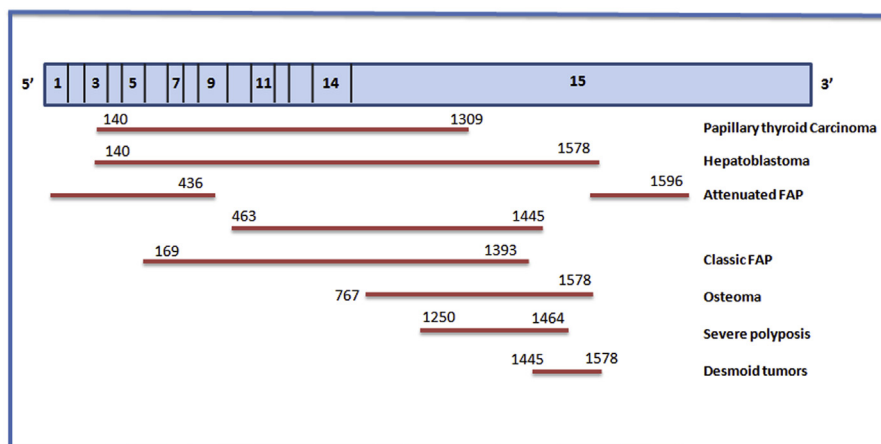


Figure 1 Correlation of phenotype with location of the APC gene mutation.

Download English Version:

<https://daneshyari.com/en/article/6215229>

Download Persian Version:

<https://daneshyari.com/article/6215229>

[Daneshyari.com](https://daneshyari.com)