Spontaneous Mutation in Familial Adenomatous Polyposis

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Rustin RB, Jagelman DG, McGannon E, Fazio VW, Lavery IC, Weakley FL. Spontaneous mutation in familial adenomatous polyposis. Dis Colon Rectum 1990;33:52-55.

A retrospective review of the familial adenomatous polyposis registry at the Cleveland Clinic Foundation revealed an incidence of spontaneous mutation in familial adenomatous polyposis (FAP) of 22 percent of family kindreds. These patients were reviewed retrospectively and compared with the total FAP population followed at The Cleveland Clinic Foundation with respect to the onset of disease, the incidence of carcinoma in the resected colon, and incidence of extracolonic manifestations. Review of the characteristics and presentations of these patients suggested that these individuals may harbor a more severe form of FAP. This may be due, in part, to the delay in diagnosis and, therefore, a higher rate of development of colorectal carcinoma and possibly duodenal adenomas. There is also a demonstrable higher rate of extracolonic manifestations of FAP present in this subset of patients. When selecting the initial type of prophylactic colonic resection the surgeon should bear in mind the increased incidence of extracolonic manifestations of the disease in this group of patients and their potential for complications. [Key words: Familial adenomatous polyposis; Spontaneous mutation]

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FAMILIAL ADENOMATOUS POLYPOSIS (FAP) is characterized as a Mendelian inherited condition, which predisposes the affected individual to a high risk of colonic cancer at an early age. This condition has a variable degree of clinical expression, ranging from the classically described clinical adenomas common to all patients, to numerous and varying extracolonic manifestations.

As of January 1988, the polyposis registry at the Cleveland Clinic Foundation contained 270 living, known, affected patients in 188 identified families. Forty-two individuals have been determined to be "spontaneous mutations." We have defined "spontaneous mutation" as the spontaneous expression of the clinical manifestations of FAP in the absence of antecedent family expression of that abnormality. These patients were studied and compared retrospectively to the classic FAP population.

Patients and Methods

The diagnosis of FAP at the Cleveland Clinic Foundation has been made in 325 individuals overall, and, at this time, 270 live known affected patients are under surveillence. Since the conception of the polyposis registry in 1979, over 5500 individuals within 188 families have been identified (Table 1).

Read at the meeting of the American Society of Colon and Rectal Surgeons, Anaheim, California, June 12 to 17, 1988.

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TABLE 1. *Cleveland Clinic Foundation Familial Polyposis Registry*

Familial polyposis families at Cleveland Clinic Foundation	188
Familial polyposis family members identified	5000
Live known affected patients followed at Cleveland Clinic Foundation	270
Dead known affected patients at Cleveland Clinic Foundation	55
Other known affected patients not seen at Cleveland Clinic Foundation	597

TABLE 2. *Criteria for a Diagnosis of Spontaneous Mutation Familial Adenomatous Polyposis*

No other family history of FAP
Full negative examination of parents and siblings of the affected individual
No other family member in same generation or antecedent generation with the disease
A "strong clinical impression" in the absence of complete information

Diagnostic workup for these patients has included an extensive family history, including premature deaths, tendencies to acquire colonic polyps, and any history of extracolonic malignancies. A complete family tree for at least three generations has been prepared by full-time FAP registry personnel. Further evaluation of individual patients includes thorough history and physical examination, rigid proctosigmoidoscopy with appropriate biopsies, retinoscopy, esophagogastroduodenoscopy. and panorex radiography. All medical records from outside institutions are obtained, when possible, for evaluation. All findings, serial examinations, surgery, and family trees were then entered into a computer for ease of retrievability, review, and comparison with other patients.

If there is no demonstrable antecedent family history of the expression of any manifestation of FAP, the individual is recorded as a "spontaneous mutation." These patients are further subdivided into two groups—"examination documented" and "historically documented" mutations. The criteria for establishing a patient as a documented spontaneous mutation are listed in Table 2. Family members must not exhibit clinical evidence or findings believed to be associated with FAP, in particular no evidence of colorectal adenomas (Table 3). Because of the three-to-four generation span of FAP and occasional difficulties in obtaining medical records, a strong clinical impression is sometimes relied upon. For example, if the parents of an affected individual both died at an age over 65 years of a cause apparently unrelated to FAP, it may be assumed, with a reasonable degree of confidence, that they did not inherit FAP. If examination of siblings and parents of the affected individual was incomplete, but review of medical records revealed no evidence of FAP, the patient was then recorded as a "historical" mutation.

The spontaneous mutations were reviewed retrospectively and compared with the standard FAP population within our registry. Specifically, symptoms on initial presentation, age at prophylactic colectomy, incidence of carcinoma of the resected colon, desmoids, osteomas, atypical retinal pigmentation, gastric and duodenal polyps, and other extracolonic manifestations of FAP were reviewed and compared.

Results

Of the 188 families in the polyposis registry at our institution, 42 individuals (22 percent) were believed to be spontaneous mutations. Of this number, 32 patients were "documented mutations." Only the documented cases were reviewed and compared with the standard FAP population (Table 3). The majority of patients (98 percent) presented initially with bloody diarrhea and some degree of abdominal discomfort. One asymptomatic patient was discovered to have FAP on routine physical examination. The average age at presentation and colectomy was 33 years and the incidence of carcinoma in the resected specimen was 38 percent. The incidence of desmoids was 26 percent, osteomas 24 percent, abnormal retinal pigmentation 77 percent, and subsequent extracolonic neoplasms 22 percent. Twenty-eight of the 32 patients underwent esophagogastroduodenoscopy at the time of initial diagnosis. Gastroduodenal polyps were present in 52 percent of these individuals. Gastric fundic gland polyps were present in 56 percent and duodenal adenomatous polyps were present in 86 percent.

Previous reviews of the overall FAP population at our institution demonstrated a mean age at colectomy of 29 years, incidence of carcinoma in the resected colon

TABLE 3. *Comparison of Spontaneous Mutations with FAP Population at Cleveland Clinic*

	Spontaneous Mutations	Total FAP Population
Mean age at presentation with disease	33 years	27 years
Mean age at colectomy	33 years	29 years
Colon cancer	38%	17%
Desmoids	26%	9%
Osteomas	24%	16%
Retinal pigmentation	65%	77%
Gastric polyps	56%	26%
Duodenal polyps	86%	33%
Extracolonic cancers	22%	9%

TABLE 4. *Spontaneous Mutation in Familial Adenomatous Polyposis*

Spontaneous mutation occurred in 22% of FAP kindreds
There is a delay in diagnosis
There is a higher rate of colorectal carcinoma
There is a higher rate of extracolonic manifestations
They seem to have a more severe form of the disease

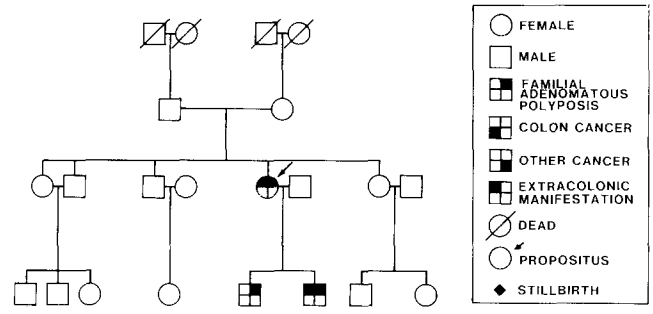

FIG. 1. Familial adenomatous polyposis kindred—spontaneous mutation with two affected offspring.

of 17 percent,[1] desmoid tumors 8.9 percent,[2] abnormal retinal pigmentation 77 percent,[3] and gastroduodenal polyps 46 percent.[4] The incidence of gastric and duodenal polyps in this group was 26 percent and 33 percent, respectively. The incidence of extracolonic neoplasms in the total FAP population in our institution is approximately 9 percent.

Discussion

Familial adenomatous polyposis is a relatively rare, genetically transmitted disorder with a frequency of approximately 1 in 7000 to 1 in 10,000 births.[5] Scientists have identified by linkage analysis a defective gene located on the long arm of chromosome 5 in the region of 522.[6] Much is still unknown regarding factors contributing to the spontaneous expression of FAP. It is known, however, that virtually all individuals with FAP who are untreated will die from cancer of the colon or other associated factors by the age of 50 years and often at a much younger age.

To our knowledge, no previous review of spontaneous mutation in FAP has been undertaken. Because of the relative infrequence of this disorder, an organized polyposis registry with extensively developed family histories is necessary to perform such a collective review. The 42 patients in this series filled our criteria for establisment as spontaneous mutations. Ten of the 42 patients were considered "historically documented" mutations only. In this group, medical records and family history were relied upon more heavily than examination for verification of FAP. The remaining 32 patients were "documented mutations" by examination of the affected individual, all siblings, and parents. If parents or siblings had died at an age greater than 65 years of a non-polyposis-related death, they were considered free of disease (FAP).

The mutation rate of roughly 22 percent approximates other previously written reports.[7] One could theorize that, in every family affected with FAP, a spontaneous mutation was the initiating event at one time or other. However, with the difficulty of obtaining accurate family histories, identification without certainty of every spontaneous mutation is not always possible.

Rectal bleeding, diarrhea, or abdominal discomfort were the presenting symptoms in all but one of the 32 documented spontaneous mutations, at an average age of 33 years. In the total FAP population, most patients presented with similar symptoms at an average age of 27 years. Omnious symptoms such as bloody diarrhea were less common in the total FAP group, because many patients were diagnosed in their teenage years by early screening of affected at-risk individuals. The severity of presenting symptoms is commonly a sign of malignancy, as evidenced by the incidence of malignancy in the resected colons in the mutation patients (38 percent). A previous report of carcinoma in the total FAP population of 17 percent at our institution[1] attests to the earlier detection of the disease in properly screened FAP family members. The choice of operation in the 32 spontaneous mutations were total proctocolectomy and end ileostomy 25 percent (81 patients), total abdominal colectomy and ileorectal anastomosis 72 percent (23 patients), and total proctocolectomy with J-pouch-ileoanal reservoir 3 percent (1 patient). Of the 23 patients who underwent ileorectal anastomosis, only one developed a rectal cancer requiring completion proctectomy. This particular individual had gone eight years without a follow-up examination after his original colectomy despite warnings about lack of compliance with follow-up.

Comparison of extracolonic manifestations of polyposis in the spontaneous mutation patients and total FAP population produced several interesting findings (Table 4). The incidence of desmoids in the mutation group was approximately 26 percent, most occurring after colectomy. A previous review by Jones *et al.*[2] revealed an incidence of 9 percent in our total FAP population. This striking difference in similarly age-matched patients may have significant clinical bearing. In this subset of polyposis patients who demonstrate an apparent increased risk of development

of desmoid tumor, one should consider the consequences of surgical options available such as proctocolectomy with ileoanal reservoir, ileorectal anastomosis, and proctocolectomy with end ileostomy. Desmoid tumors in the polyposis population seem to be principally mesenteric in origin and surgical intervention should be reserved for complications such as bowel or urinary obstruction. Whether the development of desmoid tumors in patients who have undergone an ileoanal reservoir procedure carries a higher risk of reoperation for obstruction or takedown of the pouch is yet to be determined.

The incidence of osteomas was similar in both groups, 24 percent in the mutation group and 16 percent in the total FAP population. Osteomas were diagnosed when clinically evident and by radiographic findings of the mandible on panorex examination. Reports in the medical literature vary widely with incidences as high as 94 percent.[8]

Thirteen mutations underwent retinoscopy with a 77 percent reported incidence of congenital hypertrophy of the retinal pigment epithelium (CHRPE). This is similar to the incidence of 65 percent CHRPE in a review of 150 retinoscopies currently underway at our institution.[3] There is consideration that CHRPE may be of value in screening at-risk patients as a possible clinical marker for FAP in at least some families. Gastric and duodenal polyps have been described previously as a frequent finding in the FAP population. In an earlier review by Sarre *et al.*,[4] prospective endoscopic examination of 100 FAP patients revealed an incidence of gastroduodenal polyps of 46 percent.

Gastric fundic gland polyps were present in 26 percent, and duodenal adenomatous polyps in 33 percent of the total FAP population. The spontaneous mutations exhibited a much higher incidence of gastric fundic gland polyp and duodenal adenomatous polyps, 26 and 86 percent, respectively. The potential for malignant transformation of duodenal adenomatous polyps places affected individuals at a potential risk of developing carcinoma of the duodenum or periampullary area. Age does not appear to affect the appearance of gastric gland polyps, whereas the incidence of duodenal adenomas does increase with age. The difference in rates of duodenal polyps in these two similarly age-matched groups may be indications of a more severe form of FAP in the mutation group of patients, or that without a family history, the spontaneous mutation group was diagnosed at a later age, which is also possible, as duodenal adenomas do increase with age.

The incidence of extracolonic neoplasms in the mutation population reviewed (22 percent), was higher than the overall incidence of 9 percent in the total FAP population at our institution. These malignancies included medulloblastoma, thyroid, ovarian, uterine, ampullary, and duodenal carcinomas. Although sporadic in nature and location, the increased occurrence of these lesions may indicate a tendency toward a more severe form of the disease in the mutation group of FAP patients.

Several conclusions can be reached from this review of patients with spontaneous mutations in FAP (Fig. 1). The incidence of spontaneous mutation occurred in 22 percent of our FAP kindreds. There is a delay in diagnosis due to lack of patient awareness of the disorder. Subsequently, a higher incidence of carcinoma is reported in the resected colons of these individuals. They seem to have a more severe form of the disease as manifested by an increased incidence of extracolonic manifestations, such as desmoids, duodenal adenomatous polyps, and extracolonic neoplasms. Examination of the offspring of these individuals will also provide interesting information regarding the transmission of their disease, possibly in a more severe form.

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