Genetic Testing and Phenotype in a Large Kindred With Attenuated Familial Adenomatous Polyposis

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Background & Aims: An attenuated form of familial adenomatous polyposis has been described, but the phenotype remains poorly understood. Methods: We performed genetic testing on 810 individuals from 2 attenuated familial adenomatous polyposis kindreds harboring an identical germline adenomatous polyposis coli gene mutation. Colonoscopy was performed on mutation-positive persons. Results: The disease-causing mutation was present in 184 individuals. Adenomatous polyps were present in 111 of 120 gene carriers who had colonoscopy at an average age of 41 years. The median number of adenomas was 25 (range, 0–470), with striking variability of polyp numbers and a proximal colonic predominance of polyps. Colorectal cancer occurred in 27 mutation carriers (average age, 58 years; range, 29–81 years), with 75% in the proximal colon. The cumulative risk of colorectal cancer by age 80 was estimated to be 69%. An average of 3.4 recurrent polyps (range, 0–29) were found in the postcolectomy rectal remnant over a mean of 7.8 years (range, 1–34 years), with 1 rectal cancer. Conclusions: This investigation shows that attenuated familial adenomatous polyposis in the kindreds examined shows a much smaller median number of polyps than typical familial adenomatous polyposis, a wide variability in polyp number even at older ages, and a more proximal colonic location of polyps and cancer, yet it is associated with an extremely high risk of colon cancer. The phenotype of attenuated familial adenomatous polyposis mimics typical familial adenomatous polyposis in some cases but in others is difficult to distinguish from sporadic adenomas and colorectal cancer, thus making genetic testing particularly important.

We previously described a large kindred with variable numbers of adenomatous polyps and linkage of the phenotype to the adenomatous polyposis coli (APC) locus. The disease-causing mutation was found to reside in the APC gene. This and several additional kindreds seemed to define an attenuated form of familial adenomatous polyposis (FAP), and all kindreds showed disease-causing mutations in the 5′ end of the APC gene, more proximal than that noted for families with typical FAP. Additional families with an attenuated FAP (AFAP) phenotype have now been described with mutations in the far 5′ part of the gene (5′ to codon 175),3–5 in the 3′ end of the gene (3′ to codon 1596),6–12 and in exon 9.11,13,14 Examination of tumors from AFAP patients showed a low-frequency loss of the mutated allele, leading to the suggestion that the mutated APC allele in AFAP has residual gene activity.15 A phenotype is emerging that, when compared with typical FAP, is characterized by fewer adenomas, more proximal colonic adenomas, later age of onset for colon adenomas and cancer, and a somewhat decreased lifetime cancer risk. Understanding of the phenotype remains incomplete, however, in part because of variable disease expression between the families described.16

We have completed genetic testing and characterization of the colonic phenotype in the large kindred we originally studied (kindred 353) and also in an additional kindred (kindred 439) with an identical germline mutation. The findings allow a precise description of AFAP in 2 families in which all affected persons have the same underlying disease-causing mutation of the APC gene. The study shows the usefulness of DNA-based genetic methods to clinically describe and define a novel premalignant syndrome, define polyp and cancer risk, and use genetic testing to guide prevention efforts.

Abbreviations used in this paper: AFAP, attenuated familial adenomatous polyposis; APC, adenomatous polyposis coli; CRC, colorectal cancer; FAP, familial adenomatous polyposis; GI, gastrointestinal.
Materials and Methods

All aspects of this study were reviewed and approved by the Institutional Review Board of the University of Utah.

Family and Participant Recruitment

Two large kindreds with an identical 2–base pair deletion in exon 4 of the APC gene participated in this study. Kindred 353 structure was established, and the kindred was expanded by application of the Utah Population Database, a family advocate system, and standard genealogy research techniques. The Utah Population Database includes genealogies abstracted from the Utah Family History Library linked to cancer records from the Utah Cancer Registry (a Surveillance Epidemiology and End Results registry) and Utah death and birth certificates. Kindred 439 was identified through referral and was expanded similarly by using a family advocate system. With the family advocate system, family members assisted in constructing pedigree charts and establishing contact with relatives to inform them of the study.

Family members were invited to the Huntsman General Clinical Research Center, where they received education on colon cancer risks and screening approaches for colorectal cancer (CRC) prevention. They were informed about the study and the benefits and risks of participation. A number of the family members lived outside the Salt Lake City study area. Many were able to travel for the investigation (49%), whereas others underwent colonoscopy by participating endoscopists at other sites (51%). Each subject completed a personal medical and family history questionnaire. Cancer and colonic polyp history were confirmed through medical records, the Utah Cancer Registry, and death certificates.

Clinical Assessment and Colonoscopy

Medical history and physical examination were completed for each patient, with attention to evidence of inherited colon cancer conditions. Colonoscopy with polypectomy was performed in the General Clinical Research Center or by participating endoscopists with standard preparation and monitoring.

Genetic Testing Methods

All subjects were offered appropriate genetic counseling. DNA used for genetic testing was extracted from blood and buccal swabs by using standard methods. The germline mutation responsible for AFAP in the 2 kindreds has been previously reported. The mutation is a 2–base pair deletion (nucleotides 426–427) in exon 4 of the APC gene that causes a frame shift resulting in a downstream stop codon and a predicted truncated peptide of 145 amino acids. The 2–base pair deletion creates an AciI restriction site. The region of the APC gene surrounding the mutation was polymerase chain reaction–amplified, followed by digestion with AciI. DNA bands were resolved and visualized by electrophoresis.

Cancer Risk and Survival Analysis

We performed survival analysis with Kaplan–Meier and proportional hazards methods. The following end points were selected: (1) any first cancer, excluding noninvasive (in situ) cancer (47 observed); (2) first gastrointestinal (GI) tract cancer (35 observed); or (3) first invasive CRC (27 observed). Of the 54 cancers reported in Table 1, 5 were described in medical records, but the primary record was not obtained (2 uterine, 1 ovarian, and 2 thyroid). Medical records or death certificates were obtained on all other 49 cancers. For the CRC-free survival analysis, survival was defined as the interval between birth and the first colon cancer diagnosis. Subjects were censored (deleted from the analysis at a certain age) for colectomy or death; all observations were censored after 1999, because records on all subjects were available only through 1999.

Table 1. Cancers Among Affected Family Members (n = 182)

<table>
<thead>
<tr>
<th>Kindred (branch)</th>
<th>Colorectum</th>
<th>Small intestine</th>
<th>Stomach</th>
<th>Liver</th>
<th>Thyroid</th>
<th>Breast</th>
<th>Uterus</th>
<th>Ovary</th>
<th>Prostate</th>
<th>Brain</th>
<th>Melanoma</th>
<th>Pancreas</th>
<th>Esophagus</th>
<th>Total cancers</th>
<th>Total subjects with cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>353(B) (n = 41)</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>353(E) (n = 109)</td>
<td>18</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>439 (n = 32)</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Total (n = 182)</td>
<td>27</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>54</td>
<td>47</td>
</tr>
<tr>
<td>Average age at diagnosis, yr (range)</td>
<td>58 (29–81)</td>
<td>60 (52–63)</td>
<td>47 (45–49)</td>
<td>58 (52–65)</td>
<td>26 (21–33)</td>
<td>52 (42–62)</td>
<td>49 (47–51)</td>
<td>52 (51–52)</td>
<td>67 (64–69)</td>
<td>17</td>
<td>35</td>
<td>49</td>
<td>82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aSmall intestine cancer includes the duodenum.

*Two breast cancers were reported for 1 person in K353(E) at ages 42 and 60; only the age at first diagnosis is included in calculation of average.
Results

Mutation Testing in Kindreds

The entire kindred 353 included more than 4000 members spanning 7 generations. Our research efforts focused on 2 of 5 branches in which the APC mutation was transmitted. These branches were designated "B" and "E" and contained 1707 individuals. Kindred 439 contained 550 individuals. The specific AFAP mutation was present in 43 of 299 tested individuals from K353(B) and was absent in the remaining 256. One hundred four of 416 tested individuals from K353(E) carried the mutation, and 312 did not. In K439, 37 of 95 tested individuals carried the mutation, and 58 did not. Genetic testing was performed on all participating family members, including the offspring of individuals with unknown or mutation-negative status. Thus, the mutation-positive individuals accounted for less than the predicted 50%. Of the 184 mutation-positive individuals, 148 participated in clinical research by either undergoing endoscopy or providing medical records of past procedures (Table 2).

Physical Examination Findings

A thorough physical examination was completed by our staff on 60 mutation-positive participants; detailed attention was given to phenotypic features seen in some classic FAP cases.\(^1\) Only 1 patient with an osteoma was observed, but no congenital hypertrophy of the retinal pigment epithelium, dental abnormalities, sebaceous or epidermoid cysts, or fibromas were observed on physical examination. No desmoid tumors have been diagnosed in any affected individuals, although systematic abdominal imaging was not performed.

Endoscopy Findings

Colonoscopy was completed by our staff on 60 mutation-positive individuals. Medical records of colonoscopy procedures were obtained and abstracted on 88 additional mutation-positive individuals. All examining physicians used strict colonoscopy-reporting guidelines that specified the quality of the examination as well as the size, location, number, and appearance of polyps. Forty-nine of the 88 individuals for whom outside colonoscopy data were obtained had also undergone colectomy. For these subjects, polyp numbers were abstracted from endoscopic procedures performed before surgery, through pathology reports of the removed colon, or both. Quantifiable colonoscopy results were available on 120 mutation carriers (59 procedures by our staff plus 61 abstracted records).

Adenomas were present in 111 of the 120 subjects who had undergone colonoscopy. The median number of adenomas was 25, with a range of 0–470. The median number of adenomas in those who had polyps was 29 (range, 1–470). The average age at the time of the procedure was 41 years, with a range of 16–79 years. The number of adenomas found was highly variable in all age groups. Adenoma number by patient and age is given in Figure 1. All but 30 of the 120 examined individuals had

| Table 2. Genetic Status, Colonoscopy Examination, and CRC History of Research Subjects |
|--------------------------------|-------|-------|-------|
| Genetic status                   |       |       |       |
| Number mutation positive         | 83    | 101   | 184   |
| Number mutation negative         | 299   | 327   | 626   |
| Total number of subjects         | 382   | 428   | 810   |
| Colonoscopy performed in 148 mutation-positive subjects |       |       |
| Number of subjects               | 68    | 80    | 148   |
| Average age at colonoscopy (yr)  | 40    | 44    | 42    |
| Number with colectomy            | 28    | 39    | 67    |
| Average age at colectomy (yr)    | 45    | 47    | 47    |
| Quantifiable colonoscopy results in 120 mutation-positive subjects\(^a\) |       |       |
| Number of subjects               | 56    | 64    | 120   |
| Average age at colonoscopy (yr)  | 39    | 43    | 41    |
| Median number of adenomas        | 34    | 15    | 25    |
| Cancer history in 148 mutation-positive subjects and 34 obligate mutation carriers |       |       |
| Number of subjects               | 87    | 95    | 182   |
| Number of subjects with CRC      | 10    | 17    | 27    |
| Average age at diagnosis (yr)    | 48    | 63    | 58    |

\(^a\)Precise polyp counts available.
fewer than 100 adenomatous polyps. For patients with 10 or fewer adenomas, there was a nearly even distribution of adenomas throughout the colon. In patients with more than 10 adenomas, the distribution of adenomas was predominantly proximal colonic (Table 3).

The median and maximum size of adenomas is given by colonic segment in Table 4. Median and maximum polyp sizes did not differ significantly by colonic location. Polyp size also did not differ by total polyp number. In patients with 1 to 10 total adenomas, the median polyp size was 3 mm (163 examinations). In those with 11 to 50 adenomas, the median size was 2 mm (39 examinations), and in those with >50 adenomas, the median polyp size was 3 mm (31 examinations).

A number of AFAP patients could potentially have been misdiagnosed as having sporadic adenomas had the genetic diagnosis not been known, because they showed a small number of adenomas. Of persons 30 to 79 years of age, 27 of 97 had fewer than 10 adenomas, 21 had fewer than 6 adenomas, and 7 had no polyps. Thus, depending on the number of adenomas one considers consistent with sporadic adenoma, possibly a quarter of AFAP patients could have been misclassified as having sporadic adenoma(s).

Another issue of AFAP that differs from typical FAP is the timing of colectomy. Medical records were available on 148 mutation-positive individuals, inclusive of the 120 who underwent clinical evaluation. Sixty-seven of the 148 had been treated with colectomy, either for cancer or polyposis, and 81 had not yet had colectomy. Of mutation-positive subjects aged 40 years and older, 41 of 88 had not had a colectomy, and of subjects 60 years or older, 12 of 19 had not had colectomy. The oldest person who had not had colectomy was 76. Thus, many patients have not had either cancer or a sufficient number of polyps for managing physicians to deem it necessary to perform colectomy. Surgical intervention may change with better knowledge of the syndrome, but the observed management is nonetheless very different from what one would expect for typical FAP.

Cancers

In addition to the 148 mutation-positive individuals with medical records, death certificates were available on an additional 33 obligate carriers from upper generations. Twenty-seven confirmed invasive CRCs were identified in 27 individuals who carried the disease-causing mutation (Table 1). The average age of diagnosis of the first CRC was 58 years and ranged from 29 to 81 years. Information on the colonic location of the cancer was available in 24 patients with CRC. Eighteen of these (75%) were proximal colonic: cecum, n = 6; ascending, n = 3; hepatic flexure, n = 3; transverse, n = 5; and right colon, n = 1. Distal colonic cancers were found in the following locations: descending, n = 1; sigmoid, n = 1; rectosigmoid, n = 1; and rectum, n = 3. In patients who underwent colon surgery for cancer, synchronous polyp numbers were available in only 9 cases. Three had more than 100 polyps. Three had 3 to 100 polyps. Surprisingly, 3 cases had only 3, 2, and 1 polyp at the time of cancer diagnosis and surgery.

CRC was more common in women (17.9%) than in men (11.6%), but the age of diagnosis was much older in women (63 years, compared with 48 years in men; Table

### Table 3. Colonic Polyp Distribution in Mutation-Positive Subjects

<table>
<thead>
<tr>
<th>Total no. of adenomas</th>
<th>No. subjects</th>
<th>Female-male ratio</th>
<th>Average age, yr (range)</th>
<th>Average % proximal adenomas per patient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9</td>
<td>5:4</td>
<td>36.2 (19–49)</td>
<td>NA</td>
</tr>
<tr>
<td>1–10</td>
<td>35</td>
<td>23:12</td>
<td>36.4 (16–67)</td>
<td>54 (41–66)</td>
</tr>
<tr>
<td>11–50</td>
<td>26</td>
<td>13:13</td>
<td>39.2 (21–76)</td>
<td>73 (64–82)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>17</td>
<td>8:9</td>
<td>48.1 (27–79)</td>
<td>78 (70–85)</td>
</tr>
</tbody>
</table>

NOTE. Patients were stratified into 4 groups based on the total number of adenomas per patient. The sex, age, and average percentage of proximal polyps per patient are shown by group. Detailed records of polyp location and number were available from 87 of the 120 individuals for this analysis.

NA, not applicable; CI, confidence interval.

### Table 4. Median and Maximum Colonic Polyp Size (in mm) by Location

<table>
<thead>
<tr>
<th>Colonic location</th>
<th>Average median size (±SD)</th>
<th>Number of examinations</th>
<th>Average maximum size (±SD)</th>
<th>Number of examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecum</td>
<td>3.3 (±5.9)</td>
<td>75</td>
<td>6.2 (±9.9)</td>
<td>89</td>
</tr>
<tr>
<td>Ascending</td>
<td>2.7 (±1.8)</td>
<td>79</td>
<td>6.7 (±9.0)</td>
<td>101</td>
</tr>
<tr>
<td>Transverse</td>
<td>4.4 (±6.4)</td>
<td>61</td>
<td>6.4 (±7.2)</td>
<td>83</td>
</tr>
<tr>
<td>Descending</td>
<td>3.3 (±2.5)</td>
<td>75</td>
<td>6.3 (±6.8)</td>
<td>97</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>4.4 (±4.6)</td>
<td>111</td>
<td>5.6 (±6.1)</td>
<td>123</td>
</tr>
<tr>
<td>Rectum</td>
<td>4.4 (±4.6)</td>
<td>76</td>
<td>5.3 (±8.2)</td>
<td>82</td>
</tr>
</tbody>
</table>

NOTE. Median and maximum size of polyps were abstracted from a subset of medical records containing accurate location and size. The number of examinations includes multiple records from some participants.
2). However, proportional hazards regression analysis of cancer-free survival showed no significant difference in cancer risk by sex (results not shown).

In addition to invasive colon cancers, there were 7 cases of high-grade dysplasia (carcinoma in situ) in the colonic polyps of 6 individuals (all women); the first diagnosis was at an average age of 37 years, with a range of 31–64 years. Although each of these cases was diagnosed because of a symptomatic presentation, review of the records suggests that the symptoms were almost certainly not related to the lesions. Thus, the lower age of high-grade dysplasia diagnosis compared with the age of cancer diagnosis likely occurred because dysplasia cases were discovered through screening, albeit serendipitous screening.

The 27 non-CRCs in 182 gene carriers (mutation-positive plus obligate carriers) are listed in Table 1. The relationship of any of these to the phenotype is inconclusive, although the occurrence of 6 cancers in the small intestine and 3 specific to the periampullary region of the duodenum raises concern of etiologic association. Of additional concern were 2 gastric cancers at ages 45 and 49, 1 high-grade gastric dysplasia at age 32, and 2 new reports since the initial ascertainment of 1 gastric cancer at age 75 and 1 duodenal cancer at age 72.

Kaplan–Meier curves for CRC-free survival compared with the Utah Population Database population cohort data are given in Figure 2. Lifetime cancer penetrance (estimated as 100% minus the fraction surviving disease free at age 80) was estimated at 74% for any cancer (95% confidence interval, 46%–73%), 68% for GI cancers (95% confidence interval, 46%–81%), and 69% for invasive CRC (95% confidence interval, 41%–84%). The risk of having colectomy by age 80 because of multiple polyps, CRC, or colonic polyps with advanced histology was estimated at 79% (95% confidence interval, 61%–89%). The counterintuitive result that the estimated penetrance is higher for CRC than for GI cancer (of which it is a subset) is due to counting subjects as being at risk for GI cancers (but not for CRC) after colectomy. Because most GI cancers observed in the kindreds were CRC, the lifetime risk of GI cancer was clearly reduced, but not fully eliminated, among those who had had a colectomy.

**Rectal Remnants**

Follow-up data were available on 41 patients with a retained rectum after subtotal colectomy (n = 38) or right hemicolectomy (n = 3). The average duration of follow-up in these patients was 7.8 years (±8.2 SD; range, 1–34 years), with a median follow-up of 4.0 years. The number of proctoscopic examinations varied from 1 to 14 in the 41 patients, with an average of 2.9 (±2.7 SD) examinations and a median of 2. The average cumulative number of polyps in the rectum over this follow-up period was 3.4 (±5.9 SD; range, 1–29), with a median of 1. Eighteen patients had no polyps in the retained rectum during follow-up, with an average follow-up of 6.6 years (±7.9 SD; range, 1–28 years), with a median of 3.5 years. There were only 3 patients with a cumulative total of more than 10 polyps, and they had an average follow-up period of 11.3 years (±3.8 SD; range, 7–14 years). The number of adenomas present at the time of colectomy did not differ between those with no polyps at follow-up and those with more than 10 polyps; several patients in both groups had more than 100 polyps at the time of colectomy. One patient developed invasive rectal carcinoma 34 years after subtotal colectomy with ileorectal anastomosis for in situ carcinoma at the splenic flexure. There had been only 4 recurrent adenomas found in 8 proctoscopic examinations over the 34 years.

**Discussion**

The clinical characteristics of these 2 kindreds, in view of their size and genetic diagnosis, allow a highly precise definition of the colonic polyp and cancer risk of the syndrome of AFAP in the kindreds studied. The phenotype first seemed related to FAP when we found...
linkage in kindred 353 to the APC gene. Identification of the disease-causing mutation in the APC gene has subsequently allowed us to make precise genetic diagnoses of kindred members, accurate clarification of the phenotype, and genetically directed colon cancer surveillance.

The median number of colonic adenomas was 29, with wide variability, even at older ages, and adenomas showed a more proximal colonic distribution. This colonic phenotype differs substantially from typical FAP, for which there are an average of 1000 colonic adenomas that are evenly distributed throughout the colon. The large kindred sizes in this study and availability of many patients in all age groups allow precise definition of the phenotype and confirm that the variability of adenoma expression is a true phenotypic characteristic of AFAP in these kindreds and not an effect of age or differing phenotypes in separate families. Extracolonic findings such as osteoma, desmoids, and soft tissue tumors were unusual in these 2 kindreds. Other studies have likewise shown some extraintestinal lesions when proximal or 5' mutations account for AFAP, but they seem to be relatively few compared with families in which distal or 3' mutations of the APC gene give risk for the attenuated syndrome.

Both a strength and a limitation of this study is that observations come from a large number of AFAP patients with an identical APC mutation. This is a strength because all phenotypic descriptions, particularly the wide variability of polyp number, can be concluded to be true features of the syndrome in these kindreds and not an artifact from observing persons with different underlying mutations. At the same time, one must ask whether the observations in these large kindreds with identical disease mutations are relevant to other families with AFAP. We suggest that the observations are likely quite germane to the overall phenotype of AFAP because the major phenotypic characteristics of the kindreds in this study are consistent with other AFAP descriptions. Nonetheless, caution is prudent until the findings of this study are confirmed by findings in similarly large numbers of AFAP patients from kindreds with different mutations.

The colon cancer occurrence in these kindreds was delayed by 15 years compared with classic FAP, and the colon cancer risk was 69%, compared with nearly 100%. The risk for advanced lesions (cancer together with high-grade dysplasia), however, approached 80%. The cancer risk and adenoma distribution indicate that screening in those with or at risk for AFAP should be performed with complete colonoscopy, starting in the late teens and continuing yearly.

Colectomy is performed in virtually all patients with typical FAP, often in the mid to late teens and often with mucosal resection of the rectum. The lower cancer risk and the decreased number of adenomas in AFAP have allowed us to manage a number of patients by interval colonoscopy and polypectomy. Forty-one mutation carriers older than 40 years have not required colectomy, and 12 older than 60 years still have intact colons. The oldest person with an intact colon is 76 years of age. This is markedly different from typical FAP, in which almost all patients with regular follow-up would most likely have undergone colectomy by age 40 years. Although somewhat arbitrary, we generally consider colectomy in AFAP patients when polyps are difficult to control colonoscopically, meaning 20 polyps or more or when 1 or more polyps show advanced characteristics, including size larger than 1 cm or advanced histology.

When profuse polyposis or advanced histology has led to colectomy, subtotal colectomy with ileorectal anastomosis has almost always been performed because of the relative rectal sparing from adenomas and the low rate of polyp recurrence in the rectum, an approach also supported by other studies. Because polyp recurrence in the rectum seems to be much less than in typical FAP, examination of the rectum every 1 to 2 years with polyp removal seems adequate for most patients. A small number of patients who show more numerous polyps may need follow-up every 6 months or yearly. Unfortunately, the number of adenomas at the time of surgery does not predict rectal polyp recurrence rates. Follow-up intervals after surgery must therefore be individualized on the basis of rectal examinations after surgery. There was 1 rectal cancer during follow-up of those with a rectal remnant, but that was in a 69-year-old patient, 34 years after colectomy. In this patient, there had been only 4 small polyps found in 8 examinations over the 34 years, emphasizing that there is some risk, albeit small, of rectal cancer that is not necessarily predicted by a high number of recurrent adenomas.

Additional issues requiring further definition in AFAP include the risk of extracolonic malignancies, especially gastric and duodenal cancer, and the expression of upper GI polyps. In the present kindreds, the incidence of upper GI cancers was similar to that of typical FAP. Screening recommendations for the upper GI tract of patients with AFAP should therefore be similar to those for typical FAP.

Possibly the most important issue with AFAP is that many affected persons are difficult to distinguish from
persons with sporadic adenomatous polyps or colon cancer without genetic testing, as indicated by the number of persons with few polyps, even at older ages. Yet a precise diagnosis of AFAP is necessary in view of cancer risk.

The present recommendation is that genetic testing for APC gene mutations (and possible AFAP) should be performed for persons with 20 or more colonic adenomas. Fifty-seven of 120 patients with AFAP in this study had fewer than 20 adenomas, many of them at older ages, and thus would have fallen outside the present guidelines. In addition, 27 of these 57 did not even have a first-degree relative with 20 or more adenomas. Present guidelines should thus be re-evaluated, although final guidelines will also depend on determining the fraction of AFAP diagnoses among all persons with multiple adenomas.

The existence of AFAP shows that a moderately penetrant genetic predisposition may give rise to inherited colon cancers at older ages compared with the well-recognized inherited syndromes of colon cancer. Genetic epidemiology studies indicate that moderately penetrant inheritance may account for up to one third of colon cancer cases. When the clinical syndrome of FAP or AFAP is apparent, genetic testing should include APC gene evaluation, and if that is negative and the family seems to show recessive segregation, MYH genetic testing should be considered. There are likely yet-to-be-defined gene mutations that may also be important for the identification of persons who should have more aggressive colon cancer screening.

The wide variability of adenoma number in AFAP also suggests that environmental and/or genetic modifiers affect the underlying inherited susceptibility of this condition. Large kindreds may provide a unique opportunity to specify factors that modify the basic genetic defect of this condition. Such modifying factors could also be important in understanding cancer susceptibility in the broader population.

Chemoprevention is an attractive approach that is already indicated as an adjunct to the standard management of FAP. In view of the lower polyp burden in AFAP, chemoprevention has the potential of delaying colectomy in a number of patients and possibly even decreasing the fraction of AFAP patients who need to undergo colectomy. Patients with more adenomas in the retained rectum could also benefit from chemoprevention, similar to patients with typical FAP. Dietary intervention might likewise be more effective in the less aggressive inherited polyp susceptibility of AFAP compared with typical FAP. Thus, it would be of considerable interest to perform chemopreventive and dietary preventive studies in AFAP cohorts.

This investigation has verified the wide variability of adenoma numbers in AFAP by observing this phenotype in a large number of subjects of all ages who had an identical mutation. It has also shown a more proximal distribution of colonic adenomas and allowed a precise estimate of colon cancer risk and age of cancer diagnosis in AFAP. This study has also shown how clinical genetic testing can be used both to define and to precisely clarify the phenotype of a moderately penetrant inherited condition and then to use test results to guide screening for cancer prevention in the persons and families at risk.

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