Variable phenotype of familial adenomatous polyposis in pedigrees with 3' mutation in the APC gene

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Abstract

Background—Germline mutation in the adenomatous polyposis coli (APC) gene on chromosome 5 causes familial adenomatous polyposis. “Attenuated” phenotype has been reported with mutation in the 5' end of the gene (5' to codon 158), but genotype-phenotype relations at the 3' end (3' to codon 1596) have not been described fully.

Aims—To describe and compare colorectal and extracolonic phenotypes in a case series of families with mutation in the 3' end of the APC gene.

Methods—Thirty one at risk or affected members from four families with a mutation in the APC gene located at codon 1979 or 2644 were evaluated.

Results—Variable intradigree colorectal phenotype was observed, some members at older age had oligopolyposis (fewer than one hundred colorectal adenomas) whereas other members had classic polyposis at young age. Colorectal cancer was diagnosed at older mean age (50 (7) years) in the four families than in classic FAP pedigrees (39 (14) years). Extracolonic lesions characteristic of FAP occurred with 3' APC mutations, but variability in intradigree and interdibegree extracolonic phenotype and dissociation of severity of extracolonic manifestations from number of colorectal polyps was noted.

Conclusions—Families with 3' mutations of the APC gene exhibit variable intradigree phenotype similar to the heterogeneity noted in families with proximal 5' mutations. Genotyping of FAP and oligopolyposis pedigrees can guide appropriate surveillance of the upper and lower gastrointestinal tract in affected members.

Keywords: familial adenomatous polyposis; attenuated adenomatous polyposis coli; adenomatous polyposis coli gene mutation; extracolonic lesions

Familial adenomatous polyposis (FAP) is an autosomal dominant disease classically characterised by the development of hundreds of adenomatous colorectal polyps, usually in the teenage years.1 Most families who are not treated with colectomy develop colorectal cancer by the sixth decade of life.2 Germline mutations in the adenomatous polyposis coli (APC) gene, located on the long arm of chromosome 5 in band q21, cause FAP.3 The APC gene has 15 exons and encodes a predicted gene product of 2843 amino acids with a molecular weight of about 312 000 daltons. Both frameshift and point mutations of the APC gene occur in FAP and are generally distributed in the 5' half of the coding region.

Genotype-phenotype correlation studies have reported that mutations in the extreme 5' end of the APC gene are associated with a less severe phenotype of FAP,4–6 termed attenuated adenomatous polyposis coli (AAPC) by Spirio et al in 1992.7 The clinical characteristics of the attenuated variant include fewer than 100 colorectal adenomas (oligopolyposis) at presentation but notable phenotypic variation within pedigrees, and a delayed onset of colorectal cancer which occurs on average 12 years later than in classic FAP.4–6 Further evaluation revealed that APC mutations 5' to codon 158 (proximal 5' mutations) predict the attenuated phenotype, while mutations 3' to codon 167 are associated with classic FAP.8

Recently, several pedigrees with mutations in the distal 3' portion of the APC 9 gene have also been reported to have an attenuated phenotype.6–9 These pedigrees have mutations of the APC gene 3' to codon 1596, while mutations of codons 1444 to 1578 have been associated with classic polyposis and multiple extracolonic manifestations.6 7 9 We performed a detailed evaluation of the phenotype of four families with mutations that occurred in codon 1979 or 2644 and compared them to other reports of families with distal 3' mutations. The implications for clinical management of patients in these pedigrees are addressed.

Methods

At the time of this study, The Johns Hopkins Polyposis Registry contained 340 pedigrees with FAP. After informed consent was obtained, at least one member with FAP from 112 available pedigrees was evaluated for mutation of the APC gene. The APC gene was analysed using DNA and/or RNA from peripheral blood leucocytes by in vitro synthesised protein (IVSP) assay and/or cloning and sequencing the entire coding region of the gene, as described previously.10–12 Only two of the registry families were found to carry a mutation 3' to codon 1596 (families 1 and 4). Two additional families with mutation in this region (families 2 and 3) are included. Family 2 is reported in collaboration with Indiana University Medical...
Center, Indianapolis, Indiana, and family 3
with the University of Colorado Cancer
Center, Denver, Colorado.

The records of the members from these four
families with mutation in the 3' region of the
APC gene were reviewed in detail. The age at
diagnosis of FAP, number of polyps at first
examination of the colon, age at diagnosis of
colorectal cancer, and extracolonic manifesta-
tions were evaluated in the members of each
pedigree. The diagnosis of FAP in family
members was verified by clinical and patho-
logical criteria. The age of colorectal cancer
diagnosis in these 3' pedigrees was compared
with that of FAP families from the Johns Hop-
kins Polyposis Registry with mutations 5' to
codon 1596.

Results
Families 1–3 had a four base pair deletion
(ACAA) at codon 1979, which resulted in a
detectable truncated protein by IVSP assay.

There were no evidence of a founder effect for
these three families. Family 4 had a four base
pair deletion (TTAT) at codon 2644 which did
not produce a truncated protein by IVSP assay.

The pedigrees are shown in fig 1 and
summarised in tables 1 and 2. In the three
families which had multiple affected members
(families 1, 2, and 4), heterogeneity in the
colorectal phenotype within each family was
noted (table 1). Gene test results were available
for multiple members in families 1 and 2.

There were seven gene positive people ranging
in age from 22 to 46, each with fewer than
seven adenomas on colonic examination, rep-
resenting oligopolyposis. By contrast, there
were five people with polyposis (greater than
100 polyps) diagnosed between 25 and 74
years of age in these same pedigrees. For
example, in family 2, subjects III:2 and III:3
(fig 1) had profuse polyposis necessitating
collectomy at ages 25 and 28.

Extracolonic manifestations characteristic of
FAP (table 1) also showed intrafamilial varia-
tion and did not correlate with phenotypic
expression of colorectal polyposis. Individual
II-6 in family 1 had only four colorectal adeno-
amas at age 44, but she had multiple fundic
gland retention polyps of the stomach. Similar-
ly, subjects II-5, III-3, and III-4 were all
affected with skin lesions, despite the presence
of very few if any colorectal polyps. In family 2,

<table>
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<th>Subject no</th>
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<th>Sex</th>
<th>Gene status</th>
<th>Examination type</th>
<th>Age at examination</th>
<th>Number of colon polyps</th>
<th>Colon cancer (Y/N)</th>
<th>Age at cancer diagnosis</th>
<th>Extracolonic manifestations</th>
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<td>48</td>
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<td>N/A</td>
<td>Osteomas, fibrosarcoma, lipoma, desmoids, duodenal polyps*</td>
</tr>
</tbody>
</table>

*Upper endoscopy performed.
NK, not known; N/A, not applicable.
individual III:1 had sebaceous cysts but only three colorectal adenomas at age 33. The great variety of extracolonic manifestations contrasted with the lack of typical colonic polyposis. Also, despite identical mutations of codon 1979 in families 1–3, interfamilial variability in the severity of extracolonic manifestations was evident (tables 1 and 2).

Four cases of colorectal cancer with known age of cancer diagnosis were noted at 46, 46, 48, and 60 years of age in families 1, 2, and 4. The average age at diagnosis of colorectal cancer (50 (SD 7) years) contrasted with the younger age of colorectal cancer diagnosis (39 (14) years) in classic FAP families in the Johns Hopkins Polyposis Registry.15 29 Two patients in whom colorectal polyp number was known had polyposis (more than 100 adenomas) at the time of cancer diagnosis (polyp number in patient I:2 in family 2 and patient III:1 in family 4 could not be quantitated). None of the patients with fewer than 100 adenomas developed colorectal cancer.

**Discussion**

We found that mutation in the 3' end of the APC gene was associated with intrapedigree variability of both colonic and extracolonic manifestations.
phenotype, as evidenced by families 1, 2, and 4 which had multiple affected members available for study. Intrapedigree variability of colorectal phenotype has been noted by other investigators in subjects presumed to be genotypically affected, as reviewed in table 1. Similar variability is also seen in the colorectal phenotype of all pedigrees described to date with mutations 5' to codon 158.15 Analogous to the boundary for phenotypic manifestations of mutations at the 5' end of the APC gene, a boundary at the 3' end of the gene at codon 1596 separates families with variable intrapedigree phenotype from classic FAP phenotype.

The evolution of colorectal cancer seemed to parallel expression of colorectal polyposis in our study. The two individuals with colorectal cancer and information about the number of polyps both had classic polyposis. An older mean age at diagnosis of colorectal cancer (50 (7) years) was noted in these four patients in families 1, 2, and 4 compared with classic FAP pedigrees.9 This is consistent with the delayed development of colorectal cancer observed in AAPP families with proximal 5' mutations. Nevertheless, the cumulative risk of colorectal cancer seems to reach 100% in attenuated adenomatous polyposis caused by 5' mutation of the APC gene,15 and 3' families may follow a similar course.16 Extracolonic manifestations characteristic of FAP also showed intrafamilial variation and did not correlate with phenotypic expression of colorectal polyposis. The great variety of extracolonic manifestations in family members contrasted with the frequent occurrence of oligopolyposis. This phenomenon has also been described by others.21 Specifically, Eccles et al20 reported a family (with a 2 bp insertion at codon 1204 of the APC gene) with hereditary desmoid disease and the presence of other extracolonic manifestations including osteomas, fibromas, and epidermoid cysts, but only one member with colorectal polyps.

Although the four families included in our series were the only ones known to us with mutations 3' to codon 1596, each pedigree included at least one member with classic polyposis (more than 100 polyps) who led to APC gene testing of the family. Our study results are, therefore, biased by selection on the basis of classic disease phenotype. Individuals with oligopolyposis in the absence of a family history of classic disease could also have mutation in the 3' or 5' region of the APC gene but would not have been tested.

Recognition that an attenuated colorectal phenotype can occur in some patients with germ line mutations of the APC gene makes routine genotyping of families with multiple adenomas important for clinical management. Colonoscopic rather than sigmoidoscopic screening of at risk members to evaluate the entire colon is appropriate when mutations involve the proximal or distal end of the APC gene because of the occurrence of oligopolyposis. Also, gene positive members of families with variable intrapedigree phenotype should consider surveillance with oesophagastroduodenoscopy even before the development of colorectal cancer observed in several study subjects had upper gastrointestinal polyposis rather than colorectal polyposis. Finally, because of the possibility of a 3' or 5' APC mutation, this study argues that APC gene testing should be considered for patients with small numbers of adenomas (10 or more) if they present at young age (less than 40 years), with extracolonic lesions characteristic of FAP, or with a family history of adenomas and/or cancer.

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1924 of the APC gene.


