Fundic Gland Polyps in Familial Adenomatous Polyposis

Neoplasms with Frequent Somatic Adenomatous Polyposis Coli Gene Alterations

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Fundic gland polyps (FGPs) are the most common gastric polyps in patients with familial adenomatous polyposis (FAP). FGPs have traditionally been regarded as nonneoplastic, possibly hamartomatous lesions, but the pathogenesis of FGPs in both FAP and sporadic patients remains unclear. FGPs in FAP can show foveolar dysplasia, and rarely invasive gastric adenocarcinoma has been reported in patients with FAP and fundic gland polyposis. Using direct gene sequencing and allelic loss assays at 5q, we analyzed somatic adenomatous polyposis coli (APC) gene alterations in 41 FAP-associated FGPs (20 with foveolar dysplasia, six indefinite for dysplasia, and 15 nondysplastic) and 13 sporadic FGPs. The foveolar epithelium and dilated fundic glands of the polyps were separately microdissected and analyzed in 25 of 41 FAP-associated FGPs and 13 of 13 sporadic FGPs. Somatic APC gene alterations were identified frequently (21 of 41 cases, 51%) in FAP-associated FGPs. Both the foveolar epithelium and the dilated fundic gland epithelium comprising the FGPs were shown to carry the same somatic APC gene alteration in 24 (96%) of 25 cases. Furthermore, there was no difference in the frequency of somatic APC gene alterations between FGPs with foveolar dysplasia (10 of 20, 50%), indefinite for dysplasia (four of six, 67%), and nondysplastic (seven of 15, 47%) in FAP patients ($P = 0.697$). In contrast, FGPs from non-FAP patients showed infrequent (one of 13, 8%) APC gene alterations ($P = 0.008$). These results show that FGPs in FAP patients are pathogenetically distinct from sporadic FGPs. Somatic, second-hit APC gene alterations, which precede morphological dyspla-

sia in many FAP-associated FGPs, indicate that FGPs arising in the setting of FAP are neoplastic lesions. (Am J Pathol 2000, 157:747-754)

Fundic gland polyps (FGPs) are the most common gastric polyps in both familial adenomatous polyposis (FAP) and sporadic patients.¹ FGPs are reported to occur in 12.5 to 84% of patients with FAP,²⁻¹³ whereas sporadic FGPs are identified in 0.8 to 1.9% of non-FAP patients undergoing upper gastrointestinal endoscopy.^{14,15} In addition to increased prevalence in patients with FAP, FAP-associated FGPs tend to be more numerous, occur at a younger age, and have a more equal gender distribution than sporadic FGPs.¹⁴⁻¹⁷

Histopathologically, FGPs are characterized by cystically dilated and irregularly budded fundic glands in a background of otherwise normal gastric mucosa.^{18,19} The pathogenesis of FGPs remains uncertain. FGPs have generally been regarded as nonneoplastic lesions, either hamartomatous or hyperplastic/functional in nature.^{16,19,20} Although some studies have reported no differences in the histology between sporadic FGPs and FGPs in patients with FAP,¹⁸⁻²⁰ others have disputed this. In contrast to sporadic FGPs, FGPs in patients with FAP frequently show foveolar dysplasia,^{8,21-23} including a 25% prevalence of low-grade dysplasia in FAP-associated FGPs.²¹ In addition, neoplastic progression of FGPs in FAP patients has occasionally been reported, including the development of a large dysplastic gastric polyp with an activating codon 12 K-ras gene mutation in one patient²⁴ and three cases of infiltrating gastric adenocarcinoma^{23,25,26} arising in association with fundic gland polyposis.

The molecular pathogenesis of other polypoid lesions in the upper and lower gastrointestinal tract in FAP patients has been well characterized.²⁷⁻²⁹ Most adenomas

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of the colorectum, duodenum, and stomach in patients with FAP can be demonstrated to have bi-allelic inactivation of the adenomatous polyposis coli (APC) gene on chromosome 5q21-q22. These neoplasms typically harbor a somatic alteration of one allele of the APC gene locus (typically either truncating mutation or allelic loss) coupled with an inactivating germline APC gene mutation in the other allele. Although the exact cellular functions of the APC protein are not fully known, there is data indicating that it has a role in directing cell migration, particularly in enterocyte migration from the crypt to villus in the small intestine.³⁰

The molecular pathogenesis of foveolar dysplasia in FGPs from FAP patients has not been elucidated. One previous study identified somatic (second-hit) mutations of the APC gene in three (27%) of 11 FAP-associated FGPs, suggesting that at least some FGPs involve the APC pathway typically seen in the adenoma-carcinoma sequence.²⁹ However, the histological features of the FGPs, particularly the presence of foveolar dysplasia, were not reported in that study. To better elucidate the molecular pathogenesis of FGPs, we investigated somatic APC gene alterations in dysplastic and nondysplastic FGPs from FAP patients and in sporadic FGPs. To assess whether somatic alterations in other genes associated with gastrointestinal neoplasia contribute to foveolar dysplasia in FGPs, we additionally evaluated *K-ras* gene mutations in dysplastic and nondysplastic FAP-associated FGPs.

Materials and Methods

Case Selection

The study population consisted of 17 patients with FAP or attenuated FAP who had upper gastrointestinal endoscopy with gastric biopsies at The Johns Hopkins University Hospital between 1991 and 1999. Information concerning germline APC gene mutations in these individuals, obtained from The Johns Hopkins Hereditary Colorectal Cancer Registry, is shown in Table 1. A total of 41 FGPs from these patients was analyzed. FGPs were separated into three categories based on examination of hematoxylin and eosin (H&E)-stained histological sections according to previously published criteria:²¹ 1) no dysplasia of the foveolar epithelium (15 FGPs), 2) epithelial changes indefinite for dysplasia (six FGPs), and 3) foveolar epithelial dysplasia (20 FGPs: 19 with low-grade dysplasia and one with high-grade dysplasia). Six gastric body adenomas from these patients were also included in the study. For comparison, 13 sporadic FGPs from 13 patients without FAP were also analyzed.

DNA Extraction

Microdissection of H&E-stained slides for DNA extraction was performed from formalin-fixed, paraffin-embedded specimens. Among the 41 FAP-associated FGPs, separate microdissection of the dilated fundic glands of the polyp and the overlying foveolar epithelium was accom-

plished in 25 cases. In 11 cases, only the foveolar epithelium could be microdissected because of contamination of the dilated glands by mucous neck cells; in four cases only the dilated glands could be microdissected because of denudation of the foveolar epithelium; and in one case both the foveolar and glandular epithelium of the polyp were included together. In all 13 sporadic FGPs, foveolar epithelium and underlying glands were microdissected and analyzed separately. Genomic DNA was extracted as described previously.³¹ Corresponding control DNA was extracted from nonneoplastic gastric or duodenal epithelium.

Mutational Analysis of the APC Gene

Two sets of oligonucleotide primers (C1: 5'-GGCAT-TATAAGCCCCAGTGA-3' and C2: 5'-AAATGGCTCATC-GAGGCTCA-3' for codons 1417 to 1516; D1: 5'-ACTC-CAGATGGATTTTCTTG-3' and D2: 5'-GGCTGGCTTTT-TTGCTTTAC-3' for codons 1497 to 1596) were used to amplify the mutation cluster region of the APC gene for gastroduodenal polyps.^{29,32} Polymerase chain reaction (PCR) was performed under standard conditions in a 50 μ l volume using PCR Master (Boehringer Mannheim, Mannheim, Germany) and 1 μ mol/L of both 5' and 3' oligonucleotides with 40 cycles (94°C for 1 minute, 58°C for 1 minute, and 72°C for 2 minutes). PCR products were purified using shrimp alkaline phosphatase and exonuclease I (Amersham, Buckinghamshire, United Kingdom). Purified PCR products were sequenced directly with SequiTherm Excel II DNA Sequencing Kit (Epicentre, Madison, WI) with the same primers used for DNA amplification. Oligonucleotides were end-labeled with [γ -³²P]-ATP (DuPont-New England Nuclear Research Products, Boston, MA) using T4 polynucleotide kinase (New England Biolabs, Beverly, MA). All mutations were verified in both the sense and anti-sense directions.

Allelic Loss on 5q

Loss of heterozygosity (LOH) on 5q was assessed by microsatellite assays using PCR amplification of three microsatellite markers (D5S299, D5S346, and D5S82) as previously described.³³ Briefly, assays were performed in 96-well plates with 38 cycles (95°C for 30 seconds, 55°C for 30 seconds, and 72°C for 1 minute) using PCR Master in a 10 μ l volume, 10 ng of both 5' and 3' oligonucleotides (200 μ mol/L), and ~50 ng of genomic DNA in each well. The 5' oligonucleotide was end-labeled with [γ -³²P]-ATP using T4 polynucleotide kinase. LOH was considered to be present when there was disappearance or at least a 50% reduction in the intensity of a heterozygous band as compared with nonneoplastic control mucosa in at least one informative marker.

Mutational Analysis of the K-ras Gene

Sequencing of the *K-ras* gene was performed in 39 FAP-associated FGPs and 13 sporadic FGPs. One set of

Table 1. Germline and Somatic APC Gene Alterations in FAP Patients

Patient	Germline mutation	Type of gastric polyp	Histology	Somatic APC alteration
1	1055FS (del 5 bp)	FGP	LGD	1554-1556FS (ins 1bp)
		FGP	LGD	Not detected
		FGP	ND	Not detected
		Adenoma	LGD	Not detected
2	1309FS (del 5 bp)	Adenoma	LGD	Not detected
		FGP	LGD	1554-1556FS (ins 1bp)
3	N/A	FGP	LGD	Not detected
4	1309FS (del 5 bp)	FGP	Indef	Not detected
		FGP	LGD	Not detected
5	1309FS (del 5 bp)	FGP	ND	1554-1556FS (ins 1bp)
		FGP	ND	Not detected
		FGP	ND	1554-1556FS (ins 1bp)
6	1055FS (del 5 bp)	FGP	ND	1554-1556FS (ins 1bp)
		FGP	Indef	1554-1556FS (ins 1bp)
		FGP	LGD	1554-1556FS (ins 1bp)
		FGP	LGD	Not detected
		FGP	LGD	R1450X
		Adenoma	Indef	Not detected
7	Not detected	LGD	LGD	R1450X
		FGP	LGD	Not detected
		FGP	ND	Not detected
8	N/A	Adenoma	LGD	Not detected
		FGP	LGD	Not detected
9	N/A	FGP	LGD	1554-1556FS (ins 1bp)
10	Q541X	Adenoma	LGD	LOH
11	1546FS (del 5 bp)	FGP	LGD	Not detected
		FGP	LGD	LOH
		FGP	LGD	LOH
12	1059FS (ins 2 bp)	Indef	LOH	LOH
		FGP	LGD	1554-1556FS (ins 1bp)
		FGP	ND	Not detected
13	K1030X	FGP	LGD	Not detected
		FGP	ND	Not detected
		FGP	ND	Not detected
		Adenoma	ND	Not detected
14	Not detected	LGD	LGD	LOH
		FGP	LGD	Not detected
		FGP	LGD	LOH
		FGP	LGD	LOH
		FGP	LGD	Not detected
15	Segment 3 (codons 1099–1693)	FGP	LGD	LOH
		FGP	ND	1554-1556FS (ins 1bp)
		FGP	ND	1554-1556FS (ins 1bp)
		FGP	Indef	R1450X
16	N/A	ND	Not detected	Not detected
		FGP	ND	Not detected
		FGP	ND	1554-1556FS (ins 1bp)
17	Segment 2/3 (codons 686–1693)	FGP	Indef	1554-1556FS (ins 1bp)

All patients met clinical criteria for FAP or attenuated FAP. Somatic APC alterations represent either allelic loss (LOH) or mutation detected by direct sequencing. Location of somatic mutation is shown by codon of APC gene (FS, frameshift). All patients were informative for allelic loss at one or more markers. N/A, not available; FGP, fundic gland polyp; LGD, low-grade foveolar dysplasia; ND, nondysplastic; indef, indefinite for dysplasia; HGD, high-grade foveolar dysplasia.

oligonucleotide primers (sense: 5'-GAG-AAT-TCA-TGA-CTG-AAT-ATA-AAC-TTG-T-3' and anti-sense: 5'-TCG-AAT-TCC-TCT-ATT-GTT-GGA-TCA-TAT-TCG-3') was used to amplify a region in exon 1 of K-ras spanning codons 12 and 13. PCR reaction was performed under standard conditions in a 50- μ l volume using PCR Master and 1 μ mol/L of both 5' and 3' oligonucleotides with 40 cycles (94°C for 1 minute, 50°C for 1 minute, and 72°C for 1 minute). PCR products were purified using shrimp alkaline phosphatase and exonuclease I. Purified PCR products were sequenced directly with the SequiTherm

Excel II DNA Sequencing Kit using an internal primer (5'-ATT-CGT-CCA-CAA-AAT-GAT-3').

Statistical Analysis

Fisher's exact test was used to compare differences in frequencies of somatic APC gene alterations (mutation or allelic loss) between FAP-associated and sporadic FGPs. The log likelihood ratio test was used to compare somatic APC gene alteration frequencies among FAP-associated FGPs which were negative, indefinite, and positive for

Figure 1. Histopathological appearance of FAP-associated FGPs. Polyps are composed of cystically dilated fundic glands lined by attenuated parietal cells and chief cells (**left column**). Dysplasia is assessed by grading the surface and foveolar epithelium as nondysplastic, indefinite for dysplasia, or dysplastic (**right column**). FGPs with foveolar dysplasia demonstrate nuclear enlargement, hyperchromatism, and stratification. Those graded as indefinite for dysplasia have milder nuclear hyperchromatism and stratification which are insufficient for classification as low-grade dysplasia.

foveolar dysplasia. A *P* value of <0.05 was considered statistically significant.

Results

Somatic APC Gene Alterations in FAP-Associated FGPs

A high frequency of somatic APC alterations (APC gene mutation by direct sequencing or allelic loss at 5q) was present in FGPs from FAP patients. Twelve (75%) of 16 FAP patients with FGPs demonstrated an inactivating somatic APC gene alteration in at least one FGP. Overall, 21 (51%) of 41 FGPs from patients with FAP demonstrated somatic APC gene alterations. Somatic APC alterations were detected in three (50%) of six FAP-asso-

ciated gastric body tubular adenomas, a rate similar to that detected in FAP-associated FGPs. Somatic APC gene mutations were of two types: insertion of base A into a 6-base poly(A) tract spanning codons 1554 to 1556 in 13 FGPs, and CGA→TGA (stop) mutation at codon 1450 in two FGPs and one adenoma. 5q LOH was present in an additional six FGPs and two adenomas. Notably, these two different pathways for somatic APC gene inactivation, truncating mutation or allelic loss, were never demonstrated to occur in the same patient; all patients from whom multiple polyps were analyzed showed exclusively either LOH or APC gene mutations in their polyps. (A summary of the specific APC gene alterations in FGPs and gastric adenomas is presented in Table 1.)

There were no significant differences between somatic APC alteration rates among FGPs with dysplasia, indefi-

Figure 2. Somatic APC gene mutations in FAP-associated FGPs. **a:** Representative DNA sequencing autoradiograph of a CGA→TGA (stop) mutation (arrow) at codon 1450, present in both the foveolar epithelium and the epithelium of the dilated fundic glands from an FGP graded as indefinite for dysplasia (patient 15). **b:** Insertion A into a 6 base poly(A) tract (bracket) spanning codons 1554–1556 in both the foveolar epithelium and the dilated fundic glands from an FGP with low-grade dysplasia (patient 2). Corresponding mutations are not present in the normal, nonpolypoid mucosa.

nite for dysplasia, and no dysplasia. Specifically, we detected somatic APC gene alterations in seven (47%) of 15 nondysplastic FGPs, four (67%) of six FGPs indefinite for dysplasia, and 10 (50%) of 20 dysplastic FGPs ($P = 0.697$, log likelihood ratio test) (Figures 1 to 3 and Table 2). There was high concordance for genetic alterations in the foveolar epithelium and the underlying dilated fundic glands of the FGPs. Among the 25 FGPs in which the foveolar epithelium and underlying fundic glands were microdissected and analyzed separately, 24 (96%) of 25 showed concordance in APC gene mutation/5q LOH status. In the one discordant case, a somatic APC gene mutation (insertion of A in codons 1554 to 1556) was detected in the foveolar epithelium but not in the under-

Figure 3. Allelic loss on chromosome 5q in FAP-associated FGPs. Loss of heterozygosity (arrows) with the D5S299 and D5S82 markers in both the foveolar epithelium (D₂) and dilated fundic glands (F₂) from an FGP with low-grade dysplasia (patient 14), but not in an FGP with high-grade dysplasia (D₁) or in the nonpolypoid mucosa (N) from the same patient.

lying glands of an FGP with low-grade dysplasia (patient 1, Table 1), possibly secondary to contamination by inflammatory cells or admixed nonneoplastic fundic glands. Analysis of control normal DNA from each FAP patient demonstrated no somatic APC mutation in nonpolypoid mucosa.

We were able to detect the known germline APC mutation in control mucosa from only one patient, a 5-bp deletion spanning codons 1544 to 1546 (patient 11, Table 1). In this patient, sequencing of control mucosa demonstrated the mutant and wild-type alleles in equal intensities, whereas three separate FGPs which had LOH at 5q also showed a relative decrease in the intensity of the wild-type allele on sequencing, confirming that the allelic losses were of the wild-type allele (data not shown).

Somatic APC Gene Alterations in Sporadic FGPs

No APC gene mutations were identified in the same sequenced regions among 13 sporadic FGPs, and LOH on 5q was present in only one sporadic FGP (8%). In this case, allelic loss was identified with both the D5S299 and D5S346 markers (D5S82 was noninformative) in the foveolar epithelium but not in the underlying dilated fundic glands of the polyp. The frequency of somatic APC alterations in FAP-associated FGPs was therefore significantly higher than in sporadic FGPs (51% versus 8%; $P = 0.008$; Fisher's exact test) (Table 2).

K-ras Gene Mutations in FGPs

A K-ras gene mutation was detected in only one (2.6%) of 39 FAP-associated FGPs, an FGP showing low-grade foveolar dysplasia with a GGT→GTT mutation in codon 12 (Figure 4). No K-ras gene mutations were detected in any of the sporadic FGPs.

Discussion

Accumulating evidence indicates that FAP-associated FGPs are clinically and pathologically distinct from spo-

Table 2. Frequency of Somatic APC Gene Alterations in FAP-Associated and Sporadic FGPs

Type of FGP	Number	Somatic APC gene alterations		
		Mutation (%)	Allelic loss (%)	Total (%)
FAP-associated	41	15 (37)	6 (15)	21 (51)*
Negative for dysplasia	15	7 (47)	0 (0)	7 (47) [†]
Indefinite for dysplasia	6	3 (50)	1 (17)	4 (67) [†]
Dysplastic	20	5 (25)	5 (25)	10 (50) [†]
Sporadic	13	0 (0)	1 (8)	1 (8)*

*FAP-associated FGPs were significantly more likely to show somatic APC alterations (gene mutation by direct sequencing or LOH) than were sporadic FGPs ($P = 0.008$, Fisher's exact test).

[†]There was no difference in the frequency of APC gene alterations identified in FAP-associated FGPs that were negative, indefinite, or positive for foveolar dysplasia ($P = 0.697$, log likelihood ratio test).

radic FGPs, based both on the differing epidemiology and frequent occurrence of foveolar dysplasia in FAP-associated but not sporadic FGPs. This study reveals that FGPs in patients with FAP have a unique molecular pathogenesis that is distinct from sporadic FGPs. FAP-associated FGPs arise in association with somatic APC gene alterations, whereas APC alterations are only infrequently identified in sporadic FGPs. Our results are therefore in agreement with and expand on those of Toyooka et al,²⁹ who found somatic APC mutations in three of 11 FAP-associated FGPs. The majority of the somatic APC mutations that we identified on sequencing (insertion A frameshift mutation in codons 1554 to 1556) correspond to a recently described hot spot for gastroduodenal polyps, found in two of 11 FAP-associated FGPs and nine of 29 gastric adenomas by Toyooka et al.²⁹

Our results contrast with earlier publications which have regarded both FAP-associated and sporadic FGPs as hyperplastic or hamartomatous lesions with identical morphology. Some investigators have reported no differences between the histological features or mucin histochemistry of FAP-associated and sporadic FGPs, suggesting instead that in both settings FGPs arise from the progressive formation and dilatation of secondary glandular buds, causing glandular dilatation.^{17,18} Declich et

al³⁴ have suggested that FGPs are hyperproliferative polyps based on higher proliferating cell nuclear antigen labeling index in FGPs than in normal fundic mucosa. These observations have led to the opinion by some investigators that dysplastic changes in the foveolar epithelium overlying FAP-associated FGPs are the result simply of superimposed gastric adenomas, which may develop at an increased frequency in association with FGPs because of increased proliferation and increased number of epithelial cells exposed to carcinogenic stimuli.²⁰ Several aspects of the findings presented here suggest that FGPs in patients with FAP are, in fact, neoplasms. First, the molecular pathogenesis of FAP-associated FGPs, attributable to second-hit APC gene alterations, is distinct from that of sporadic FGPs. Second, the same somatic APC gene alterations are consistently found in both the dilated fundic glands comprising the FGP and the overlying foveolar epithelium. Finally, there is no difference in the rate of somatic APC gene alterations detected in dysplastic, indefinite, and nondysplastic FAP-associated FGPs. These findings indicate that somatic APC alterations are intrinsic to the formation of FAP-associated FGPs and are not restricted to superimposed dysplastic, or adenomatous, foveolar epithelium.

The frequent presence of somatic APC gene alterations indicates that FGPs arising in the setting of FAP are neoplastic lesions. FGPs in FAP patients therefore show a similar molecular pathogenesis to that of adenomatous polyps of the colon, duodenum, and stomach, which have been well demonstrated to arise from second-hit APC gene alterations superimposed on the germline APC mutation.^{27,28} Our detection rates of 51% and 50% for somatic APC alterations in FAP-associated FGPs and gastric body adenomas, respectively, are likely an underestimation of the true frequency of second-hit APC events, because we sequenced only the mutation cluster region for gastroduodenal polyps in this study.²⁹ Although it was not possible in the majority of our cases to prove that the detected somatic APC gene alterations affected the wild-type rather than inherited mutant alleles, in one case (patient 11) we were able to detect the germline 5-bp deletion spanning codons 1544 to 1546 by sequencing of control mucosa. In this case, three FGPs that demonstrated allelic loss at 5q also showed a relative decrease in the intensity of the wild-type allele on sequencing gels, confirming allelic losses on the wild-type

Figure 4. Mutation of the *K-ras* gene in a single FGP with low-grade dysplasia but not in the corresponding normal mucosa from the same patient (patient 6). The **arrow** indicates an activating GGT→GTT mutation in codon 12.

APC allele. Interestingly, our data indicate that when multiple gastric polyps from the same patient are analyzed, only one pathway for somatic APC gene inactivation, either mutation or allelic loss, is identified. Recently, Lamlum et al³⁵ have reported that the site of the germline APC mutation strongly influences the nature of the second-hit APC alteration, with some FAP patients showing predominantly allelic loss in their colorectal adenomas and others showing primarily truncating mutations. Confirmation of a similar relationship in the stomach, however, requires analysis of a larger number of gastric polyps.

The findings in this study raise an interesting question about the role of the APC gene in gastric tumorigenesis. FAP-associated FGPs are the first polyps in the gastrointestinal tract shown to contain two APC hits without demonstrating an adenomatous morphology. It is not clear why, in certain instances, a second hit on the APC gene induces the formation of FGPs rather than adenomas. This phenomenon cannot be explained simply by asserting that all FGPs in FAP patients are secondary to the presence of foveolar dysplasia (morphologically equivalent to microadenomas in the colon), because only ~25% of FAP-associated FGPs show foveolar dysplasia.²¹ In fact, the results of this study indicate that somatic APC events bear little relationship to the presence or absence of foveolar dysplasia, because we detected no difference in the rate of somatic APC alterations in FAP-associated FGPs with and without foveolar dysplasia. This suggests that additional genetic alterations may account for the presence of foveolar dysplasia and contribute to neoplastic progression in a subset of FGPs. In this regard activating *K-ras* gene mutations do not seem to play a major role, as we were able to demonstrate a *K-ras* gene mutation in only one FAP-associated FGP with low-grade foveolar dysplasia. Additional genetic events underlying dysplasia remain to be elucidated.

The role of FGPs in gastric tumorigenesis in patients with FAP remains unclear. In Japanese and Korean populations, FAP has been associated clearly with an increased risk of gastric adenocarcinoma.^{2,36,37} In Western patients with FAP, this risk seems to be slightly (approximately twofold) increased, but not statistically significantly different from that of the general population in the study reported by Offerhaus et al.³⁸ Neoplastic progression of FGPs in Western patients with FAP has been demonstrated, including reports of a large fundic gland polyp with high-grade dysplasia and *K-ras* gene mutation, and occasional infiltrating adenocarcinomas arising in association with fundic gland polyposis.^{23–26} Despite the lack of more exact estimates of the risk of tumor progression in patients with FAP and fundic gland polyposis, molecular evidence indicates that FAP-associated FGPs are neoplastic polyps. Similar to the presence of other neoplastic polyps of the upper gastrointestinal tract in patients with FAP, the presence of fundic gland polyposis may warrant close endoscopic surveillance.

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