Sporadic Fundic Gland Polyposis: A Clinical, Histological, and Molecular Analysis

Michael Torbenson, M.D., Jae-Hyuk Lee, MD., Ph.D., Marcia Cruz-Correa, M.D., William Ravich, M.D., Khosrow Rastgar, M.D., Susan C. Abraham, M.D., Tsung-Teh Wu, M.D., Ph.D.

Department of Pathology (MT, SCA), and Department of Medicine, Division of Gastroenterology (MC-C, WR), The Johns Hopkins Hospital, Baltimore, Maryland; Department of Pathology, University of Texas M.D. Anderson Cancer Center (J-HL, T-TW), Houston, Texas; and Department of Pathology, Atlantic City Medical Center (KR), Atlantic City, New Jersey

Sporadic fundic gland polyposis (SFGP) is defined as multiple fundic gland polyps in patients without familial adenomatous polyposis syndrome (FAP). Although little is known about the genetic changes in SFGP, mutations in the Wnt signaling pathway have been recently linked to fundic gland polyps in other settings: sporadic polyps are linked to activating β-catenin mutations, whereas FAP-associated fundic gland polyps are caused by second somatic hits in the adenomatous polyposis coli gene. The relationship between SFGP, single sporadic fundic gland polyps, and FAP-associated polyps remains unclear, and SFGP remain poorly characterized at the clinical, histological, and molecular levels. A retrospective study was undertaken of eight patients with SFGP who had ≥10 polyps with at least five endoscopic biopsy specimens available for study. One additional patient with attenuated FAP who underwent partial gastrectomy was included as a control. The medical records and biopsy specimens were reviewed. Mutations of the β-catenin gene were evaluated in each fundic gland as well as in control nonpolypoid tissue by direct sequencing of a mutational hot spot in exon 3 of the β-catenin gene, which encodes the GSK-3β phosphorylation sites, and a *Hin*fI endonuclease digestion assay. The four men and four women in the study were an average of 57 years of age at biopsy. All patients were on acid-suppression therapy, 5/8 with proton-pump inhibitors (PPI) and 3/8 with Zantac. Sixty-two polyps were studied, and all were <10 mm, with most between 2 and 7 mm. The polyps were histologically identical to single sporadic fundic gland polyps. No dysplasia was seen. Forty-seven of 62 polyps (76%) had detectable β-catenin mutations. Mutations were found in all eight of the patients. All were point mutations in codons 32, 33, 34, and 37 and are either phosphorylation sites or immediately adjacent to phosphorylation sites, findings identical to that seen in single sporadic fundic gland polyps. Each polyp had a single mutation, and each patient had more than one unique mutation (median = 4), indicating a multifocal origin for the polyps. No mutations were found in nonpolypoid control tissue and in polyps from the attenuated FAP patient. The patients with SFGP in this series were all between 40 and 70 years of age and had histories of acid-suppressive therapy. The fundic gland polyps were histologically and genetically identical to single sporadic fundic gland polyps and demonstrated frequent somatic activating mutations in exon 3 of the β-catenin gene.

KEY WORDS: β-catenin gene, Mutation, Polyp, Sporadic fundic gland polyposis.

Mod Pathol 2002;15(7):718–723

Fundic gland polyps are common benign polyps of the gastric body and fundus that are typically small (most are <1 cm) and are composed of dilated glands lined by normal cell types of the oxyntic mucosa, with a mixture of parietal cells, chief cells, and mucus neck cells. Fundic gland polyps can be sporadic or associated with the familial adenomatous polyposis syndrome (FAP), which results from inherited germline mutations in the adenomatous polyposis coli (APC) gene coupled with second, somatic mutations, leading to inactivation of both copies of the APC tumor suppressor gene (1, 2). Although both groups of polyps are histologically similar, recent studies have shown that sporadic (3) and FAP-associated (2) polyps result from separate and distinct disruptions in the Wnt signaling pathway, with sporadic polyps showing activating

VOL. 15, NO. 7, P. 718, 2002 Printed in the U.S.A.
Date of acceptance: April 3, 2002.
Address reprint requests to: Tsung-Teh Wu, M.D., Ph.D., Department of Pathology, Box 85, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030; e-mail: twu@mdanderson.org; fax: 713-792-4049.

DOI: 10.1097/01.MP.0000018976.15044.9B

β-catenin mutations and FAP-associated polyps demonstrating second, somatic mutations of the APC gene. No other mutations have been described in fundic gland polyps, and their karyotypes are normal (4).

The Wnt signaling pathway is involved in a number of diverse physiological conditions, ranging from body axis formation (5) to liver regeneration (6). β-catenin plays a central role in the Wnt signaling pathway. Normally, β-catenin cytoplasmic levels are kept low via a degradation pathway (7). However, when the Wnt signaling pathway is activated, β-catenin is no longer degraded and accumulates in the cytoplasm, with eventual translocation to the nucleus, where it activates a number of downstream target genes including TCF/LEF (7), C-MYC (7), cyclin D1 (8), and gastrin (9). Mutations in the APC, AXIN-1, and β-catenin genes all lead to abnormal accumulation of β-catenin and excessive signaling from this pathway (10).

Many fundic gland polyps are sporadic and single, but cases with multiple fundic gland polyps have been reported as *fundic gland polyposis in patients without FAP* or in similar terms (11–14). In this study, the shorter term *sporadic fundic gland polyposis* (SFGP) was used. β-catenin gene mutations have been demonstrated in a few cases of multiple fundic gland polyps in patients without the FAP syndrome (3). However, a detailed molecular analysis has not been performed, and there are limited histological, clinical, and molecular data available on SFGP. Thus, we undertook a review of the clinical and histological features of eight cases of SFGP and sequenced exon 3 of the β-catenin gene, a mutational hot spot strongly associated with single fundic gland polyps (3). There is no formal definition of SFGP available in the literature; thus, we choose patients who had ≥10 polyps with ≥5 available for analysis. This selection criterion was based on a review of the (scant) literature that reported the distribution of polyps per case in the setting of patients on proton pump inhibitors (PPI), which suggested a possible bimodal distribution (15), with the number of 10 polyps as a potentially useful discriminator between those with and without SFGP. This potential bimodal distribution is less apparent in studies of patients that were conducted before the widespread use of PPI (11, 12, 16, 17).

MATERIALS AND METHODS

Case Selection

For the time period of January 1, 1990 to January 1, 2001, a retrospective search of the surgical pathology files of The Johns Hopkins Hospital revealed eight patients who had ≥10 separate fundic gland polyps with slides and blocks available for study on ≥five polyps. One of these patients (No. 2) had a few polyps that were included in a previous report (3) but separate polyps were used in this study. All SFGP tissue was from endoscopic biopsy specimens. As a control, a single patient with an attenuated form of FAP was also included. This 11-year-old girl had a clinical diagnosis of FAP but had no detectable APC gene mutations, and polyps were limited to the stomach. She underwent a partial gastrectomy for high-grade dysplasia in fundic gland polyps.

The medical records were reviewed for each patient. Each case had routine hematoxylin–eosin, periodic acid–Schiff/AB, and Diff-Quik stains available for review from formalin-fixed, paraffin-embedded biopsy specimens. Additional 5-μm sections were obtained for microdissection, which was performed under 40× magnification with a 271/2-gauge needle. From 5 to 10 polyps were microdissected (depending on availability) for each patient, for a total of 62 polyps. In each case, additional, nonpolypoid control tissue was also microdissected as follows: duodenum (n = 1), antrum (n = 3), nonpolyp body (n = 4), cardia (n = 1), or esophagus (n = 1). Ten polyps from the patient with attenuated FAP were also microdissected.

Mutational Analysis

Genomic DNA was extracted as previously described (18). Oligonucleotide primers were selected to amplify exon 3 of β-catenin, which encompasses the region for GSK-3β phosphorylation. PCR was performed in 35-μL volumes using a PCR master mix (Boehringer Mannheim, Mannheim, Germany) with 1 uM of both 5' (5'-ATGGAACCAGACAGAGGGGC-3') and 3' (5'-GCTACTTGTTCTTGAGTGAAG-3') oligonucleotides for 40 cycles. The following conditions were used: 94° C for 1 minute, 58° C for 1 minute, and 72° C for 1minute. PCR products were then purified using shrimp alkaline phosphatase and exonuclease I (Amersham, Buckinghamshire, United Kingdom) and directly sequenced using internal primers with the SequiTherm Excel II DNA Sequencing Kit (Epicentre, Madison, WI), for both the sense (5'-AAAGCGGCTGTTAGTCACTGG-3') and antisense directions (5'-CCTGTTCCCACTCATACAGG-3').

All cases were also analyzed with a *Hin*fI restriction endonuclease digestion assay (Life Technologies, Inc. Rockville, MD). With our primer set, PCR from a wild-type allele yields a 200-bp amplicon, and digestion with *Hin*fI leads to 7-bp, 55-bp, and 138-bp fragments. Mutations in codons 32 and 33 ablate one of the restriction sites, and mutations in the second position of codon 34 ablate the other site, yielding different fragment lengths than wild-type: 62/138- and 55/145-bp fragments, respectively (3).

RESULTS

Clinical

The four men and four women in this study had a mean age of 57 ± 12 years at the time of biopsy, with range of 41–70 years. All of the patients had histories of acid-suppressive therapy, including three patients with a history of Zantac use and five with histories of PPI use. The length of PPI therapy was available in two cases: 1 and 7 years. Serum gastrin levels were not available in any of the cases.

Endoscopic Features

The numbers of polyps observed in the body and fundic mucosa was recorded in many of the cases with descriptive terms such as "multiple" or "numerous." However, in two cases, the numbers of polyps were recorded as 24 and as between 20–40 (Table 1). A retrospective review of the endoscopic images showed that all cases had ≥10 polyps (Fig. 1). The gross sizes were recorded in five cases and ranged between 1 and 10 mm, with most under 7 mm. The polyps were variously described as nonbleeding, smooth, erythematous; or pale, sessile, or occasionally pedunculated (Table 1).

Histological Features

All of the polyps were typical fundic gland polyps, with dilated fundic glands lined by normal cell types of the oxyntic mucosa: parietal cells, chief cells, and mucus neck cells (Fig. 2). The cystically dilated glands were seen both superficially and deep within the mucosa. The lamina propria was generally scant with mixed inflammatory cells, occasional wisps of smooth muscle, and mild edema in a few cases. The histological appearances of these polyps were identical to that of the single fundic gland polyps reported earlier (3). No foveolar dysplasia was seen. The nonpolypoid oxyntic mu-

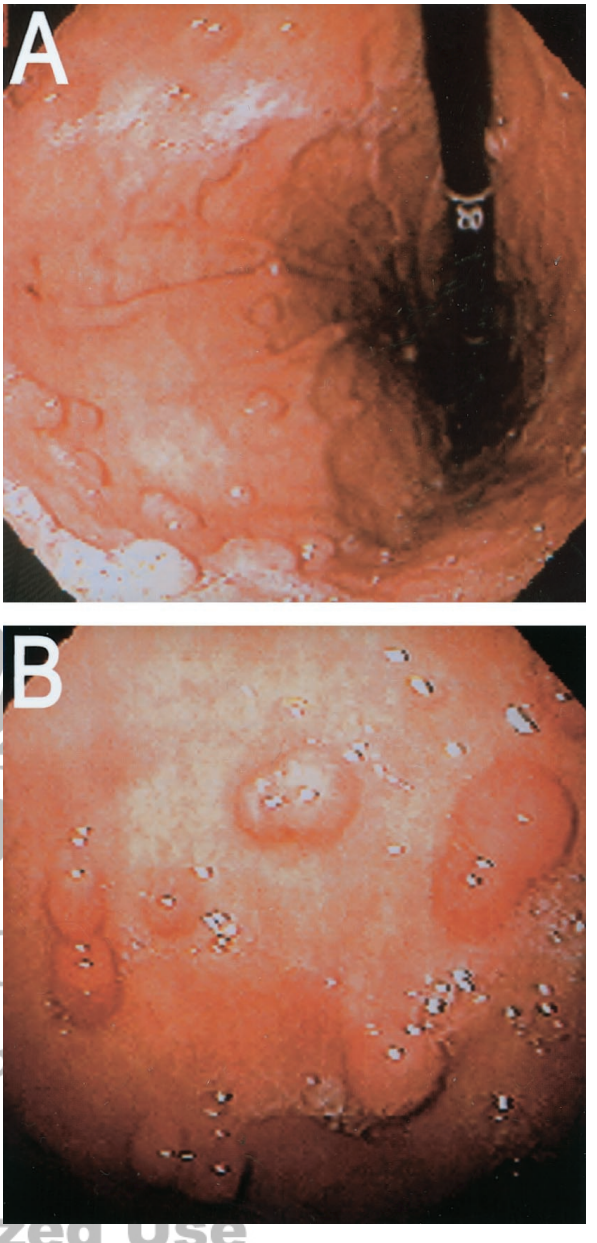

FIGURE 1. A, typical endoscopic findings in a patient with fundic gland polyposis. Multiple small polyps are seen. **B,** a higher magnification highlights the surface appearance of fundic gland polyps. The polyps are flat, small, and have smooth surfaces.

TABLE 1. Demographics, Number of Polyps Studied, and History of Proton Pump Inhibitor (PPI) therapy

Patient No.	Gender, Age (y)	Fundic Gland Polyps Studied (*N*)	PPI Therapy	Endoscopic Findings (*N*, Size, Description)
1	M, 66	10	Yes	24, 5–10 mm, erythematous, peduculated
2[a]	M, 67	7	Yes	15, 2–5 mm (two polyps at 1 cm), nonbleeding, erythematous, sessile
3[a]	F, 36	6	Yes	10, 3–6 mm (one at 1 cm), erythematous, sessile
4[a]	M, 41	7	Yes	20, 2–5 mm, smooth, sessile, and pedunculated
5	F, 70	10	No, but Zantac therapy	20–40, 5–7 mm, slightly hyperemic, smooth, sessile
6[a]	F, 63	6	No, but Zantac therapy	20, 1–6 mm, hyperemic, smooth, sessile, and semipedunculated
7[a]	M, 56	10	Yes	15, 3–5 mm, pale, smooth, sessile
8[a]	F, 61	10	No, but Zantac therapy	15, 1–10 mm, hyperemic, smooth, sessile

[a] In these cases, the number of polyps was not reported at the original endoscopy. We reviewed the endoscopic images in each case to ensure that all patients had ≥10 polyps. Because the available images did not routinely show the entire body or cardia, our retrospective counts of the number of polyps were for the available images only and were designed only to document the presence of ≥10 polyps, and these cases likely had many more than our count.

M, male; F, female; NA, not available.

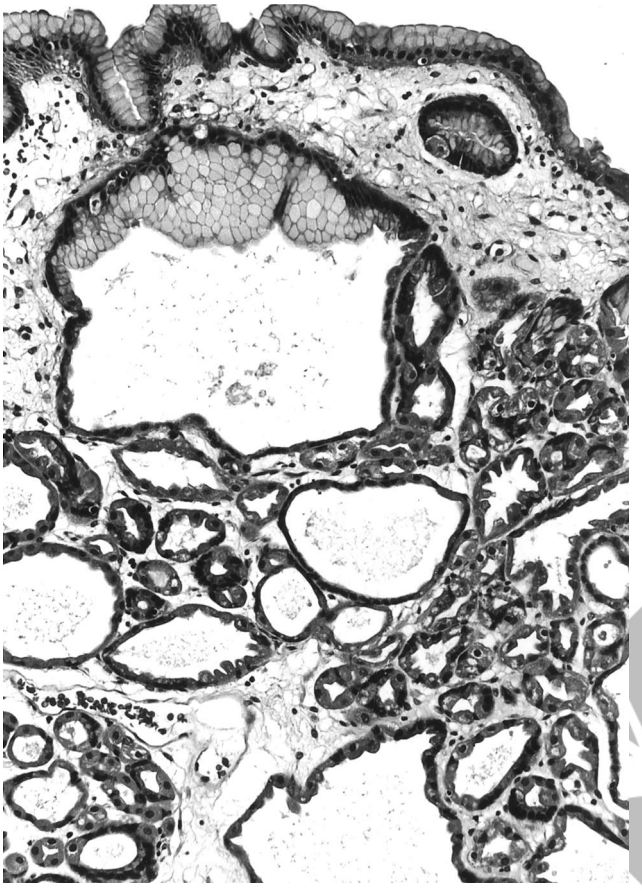

FIGURE 2. A representative fundic gland polyp showing cystically dilated glands lined by an admixture of parietal, chief, and mucus neck cells.

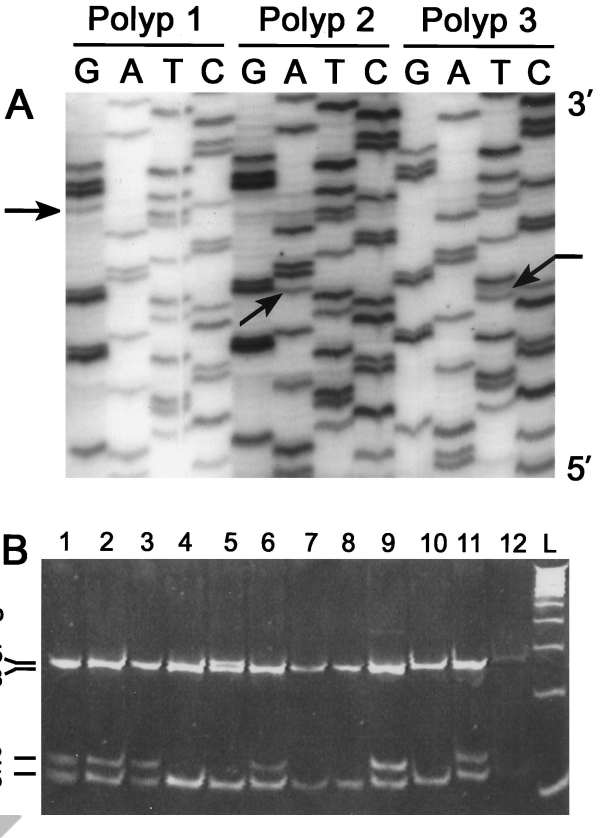

FIGURE 3. A, representative β-catenin gene mutations in SFGP from Case 8. DNA-sequencing autoradiograph of exon 3 of the β-catenin gene shows a TCT→TGT mutation in codon 37 (**arrow**) of Polyp 1, a GGA→AGA in codon 34 of Polyp 2 (**diagonal arrow**), and a TCT→TTT mutation in codon 33 of Polyp 3 (**bent arrow**). **B,** the *Hin*fI restriction endonuclease digestion assay shows changes in the normal lengths of digestion products from wild-type DNA (**lanes 4, 7, 8, 10, 12**) resulting from mutations in codons 32 and 33 (**lanes 1, 2, 3, 6, 9, 11**) and 34 (**lane 5**). With wild-type DNA, digestion leads to 7-bp (too small to be seen on gel), 55-bp, and 138-bp DNA fragments. In contrast, mutations in codons 32 and 33 yield an additional 62-bp band because of ablation of the first *Hin*fI site, and mutations in the second position of codon 34 lead to an additional 145-bp band because of ablation of the second *Hin*fI digestion site. A 50-bp molecular weight ladder is in **lane L**.

cosa showed parietal cell protrusions of the type seen in PPI therapy in five cases, in all of which PPI therapy was given. The antrum was biopsied in five of the cases and showed chemical gastritis (three cases) and inactive chronic gastritis (two cases). Diff-Quik stains for *H. pylori* were negative in all cases. No intestinal metaplasia was seen in the antrum or body from any of the biopsy specimens.

Mutational Analysis

In every patient, β-catenin mutations were detected in the polyps, but not the normal control mucosa. Overall, activating β-catenin gene mutations were detected in 47/62 polyps (76%; Fig. 3). In five of these polyps, the mutations were not observed on direct sequencing and were only detected with the *Hin*fI digestion assay. In the 42 cases with mutations identified by direct sequencing, the point mutations were clustered in codons 32, 33, 34, and 37 and all mutations led to changes in the amino acid sequence (Table 2). No clearly dominant mutation was seen. In each polyp, only one mutation was detected, but in each patient, multiple separate mutations were seen (range, two to six unique mutations; median, four). A previous study from this laboratory (3) described activating β-catenin mutations in 26 cases of single sporadic fundic gland polyps. Using the codon distribution from that study to define the expected distribution of mutated codons (codon 32: 12%, codon 33: 38%, codon 34: 23%, codon 37: 27%), the distribution of codon mutations in patients with SFGP was not significantly different from expected (χ^2, $P = 0.54$).

In contrast to the above findings, the patient with attenuated FAP had no detectable β-catenin mutations in the 10 polyps studied. The polyps showed extensive low-grade dysplasia and focal high-grade dysplasia but were otherwise histologically indistinguishable from single and SFGP polyps.

DISCUSSION

SFGP is characterized by numerous fundic gland polyps and was defined for this study as cases with

TABLE 2. Point mutations detected in Exon 3 of B-catenin

Codon	Mutation	No.	Change in Amino Acid
			Asp to
32, GAC	TAC	5	Tyr
	GGC	3	Gly
	CAC	1	His
	GTC	1	Val
		Total = 10	
			Ser to
33, TCT	TGT	6	Cys
	TTT	5	Phe
	CCT	3	Pro
	TAT	1	Tyr
		Total = 15	
			Gly to
34, GGA	AGA	3	Arg
	GTA	2	Val
	CGA	1	Arg
		Total = 6	
			Ser to
37, TCT	TTT	6	Phe
	TGT	4	Cys
	CCT	1	Pro
		Total = 11	

An additional five polyps had mutations detected by digestion only: codons 32/33 (four polyps), codon 34 (one polyp).

≥10 polyps. It is not clear whether SFGP forms a distinct entity from patients with a single or few polyps or whether there is a continuum between these two groups. Although data are limited, there is some evidence for a bimodal distribution of fundic gland polyps, with cases tending to show either a few polyps (<10) or numerous polyps (≥10; usually ≥20; 15). This study also was not designed to address that question directly, and additional studies will be required to clarify that point.

In this study, all patients with SFGP were between 40 and 70 years of age, and there was no clear gender association. Most studies have also shown a similar age range (11, 12, 16, 17). Although many studies have reported a female predominance (11, 12, 14, 16, 17, 19), other studies have not (15).

All of the patients in this study were on acid-suppressive therapy, typically PPI. A possible casual link between PPI and fundic gland polyps was first reported in 1992 (20) and has also been noted in a number of subsequent studies (15, 21, 22). One study (15) reported a remarkable case in which polyps appeared after introduction of PPI therapy, disappeared after withdrawal of PPI, and reappeared after the reintroduction of PPI therapy. Whatever the precise relationship between fundic gland polyps and PPI, the reports to date clearly indicate that most patients on PPI therapy do not develop fundic gland polyps and those that do have essentially no risk for malignancy. Although low-grade dysplasia has been reported in a small percentage of sporadic fundic gland polyps, there has been no report of progression to high-grade dysplasia and no report of carcinomas. No dysplasia was seen in the cases of SFGP in this study. This stands in marked contrast to fundic gland polyps in the setting of FAP, where dysplasia and adenocarcinoma have been noted in a significant percentage of polyps (23).

Seventy-six percent of the polyps in this study had activating β-catenin gene mutations. This frequency is less than the 91% frequency previously reported for single fundic gland polyps from this laboratory (3) but likely represents the use of a number of smaller-sized polyps in the current study. In the previous study, polyps were selected for ease of microdissection and generally used moderately sized polyps, though all were <1 cm. In this study, smaller polyps were often microdissected, and in these cases, the ratio of mutant DNA to wild-type DNA from blood vessels, inflammatory cells, and stromal cells may be lower than in the larger polyps and fall below the level of detection in some cases. An alternative explanation would be that the smallest polyps lack β-catenin mutations, but we detected mutations in some of the smaller polyps, making this possibility less likely.

All of the mutations were point mutation located in codons 32, 33, 34, or 37, which are either phosphorylation sites of the β-catenin protein (codons 33 and 37) or immediately adjacent to phosphorylation sites (codons 32 and 34). All of the mutations led to changes in the amino acid sequence, and that would likely interfere with normal phosphorylation and degradation of the β-catenin gene product. The distribution of point mutations in this study population was not significantly different from the distribution of point mutation in patients with single polyps. The presence of a single β-catenin mutation in each polyp and the finding of multiple unique β-catenin mutations in each person argues strongly against a single progenitor cell leading to multiple polyps and suggests a multifocal field effect with mutations in a number of separate progenitor cells. The lack of mutations in the nonpolypoid tissues confirms the somatic nature of the mutations in SFGP. In the one patient we studied who had a clinical diagnosis of attenuated FAP and numerous fundic gland polyps with dysplasia, no β-catenin mutations were detected. Thus, the presence of β-catenin mutations may serve as a useful marker for polyps with no malignant potential in cases in which FAP is clinically suspected but an APC mutation cannot be documented.

Despite the suspected link between PPI and some cases of fundic gland polyps, there is little information available on possible mechanisms. One possibility is that PPI may cause β-catenin mutations. However, in one of the cases, we used oxyntic mucosa with parietal cell protrusions (typically seen in PPI treatment) as control tissue, and no mutations were detected, suggesting that this early histologi-

cal change of PPI therapy is not associated with detectable β-catenin mutations. A second possibility is that PPIs secondarily lead to fundic gland polyps. In the Zollinger-Ellison syndrome, fundic gland polyps are strongly associated with elevated serum gastrin levels (24), and gastrin is recognized as a growth factor for the oxyntic mucosa (25). PPIs are also known to cause modest elevations in serum gastrin levels, but in several studies (22, 26), SFGP has not been associated with elevated serum gastrin levels. Interestingly, gastrin is also a known downstream target of the Wnt signaling pathway (9), raising the possibility of local, autocrine stimulation.

In conclusion, SFGP is typically seen in middle-aged adults of both genders with histories of PPI therapy. Most polyps were <1 cm and showed the typical histology of single fundic gland polyps. No dysplasia was detected in any of the cases. Activating β-catenin mutations were present in the majority of polyps, with each polyp showing a unique mutation and each person having multiple separate polyps or mutations. Finally, detection of β-catenin mutations may be helpful in excluding FAP in those rare cases of patients who have a clinical diagnosis of attenuated FAP but without detected mutation in the APC gene.

REFERENCES

1. Toyooka M, Konishi M, Kikuchi-Yanoshita R, Iwama T, Miyaki M. Somatic mutations of the adenomatous polyposis coli gene in gastroduodenal tumors from patients with familial adenomatous polyposis. Cancer Res 1995;55:3165–70.
2. Abraham SC, Nobukawa B, Giardiello FM, Hamilton SR, Wu TT. Fundic gland polyps in familial adenomatous polyposis: neoplasms with frequent somatic adenomatous polyposis coli gene alterations. Am J Pathol 2000;157:747–54.
3. Abraham SC, Nobukawa B, Giardiello FM, Hamilton SR, Wu TT. Sporadic fundic gland polyps: common gastric polyps arising through activating mutations in the beta-catenin gene. Am J Pathol 2001;158:1005–10.
4. Declich P, Isimbaidi G, Sironi M, Galli C, Ferrara A, Caruso S, *et al.* Sporadic fundic gland polyps: an immunohistochemical study of their antigenic profile. Pathol Res Pract 1996; 192:808–15.
5. Cadigan KM, Nusse R. Wnt signaling: a common theme in animal development. Genes Dev 1997;11:3286–305.
6. Monga SP, Pediaditakis P, Mule K, Stolz DB, Michalopoulos GK. Changes in WNT/beta-catenin pathway during regulated growth in rat liver regeneration. Hepatology 2001;33: 1098–109.
7. Akiyama T. Wnt/beta-catenin signaling. Cytokine Growth Factor Rev 2000;11:273–82.
8. Tetsu O, McCormick F. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. Nature 1999;398:422–6.
9. Koh TJ, Bulitta CJ, Fleming JV, Dockray GJ, Varro A, Wang TC. Gastrin is a target of the beta-catenin/TCF-4 growth-signaling pathway in a model of intestinal polyposis. J Clin Invest 2000;106:533–9.
10. Fearnhead NS, Britton MP, Bodmer WF. The ABC of APC. Hum Mol Genet 2001;10:721–33.
11. Iida M, Yao T, Watanabe H, Itoh H, Iwashita A. Fundic gland polyposis in patients without familial adenomatosis coli: its incidence and clinical features. Gastroenterology 1984;86: 1437–42.
12. Hizawa K, Iida M, Matsumoto T, Aoyagi K, Yao T, Fujishima M. Natural history of fundic gland polyposis without familial adenomatosis coli: follow-up observations in 31 patients. Radiology 1993;189:429–32.
13. Tsuchikame N, Ishimaru Y, Ohshima S, Takahashi M. Three familial cases of fundic gland polyposis without polyposis coli. Virchows Arch A Pathol Anat Histopathol 1993;422:337–40.
14. Venkataseshan VS, Woo TH, Thung SN, Wien FE. Gastric fundic gland polyposis without familial adenomatosis of colon: a report of 3 cases. Mt Sinai J Med 1987;54:525–8.
15. Choudhry U, Boyce HW, Coppola D. Proton pump inhibitor-associated gastric polyps: a retrospective analysis of their frequency, and endoscopic, histologic, and ultrastructural characteristics. Am J Clin Pathol 1998;110:615–21.
16. Sato T, Sakai Y, Ishiguro S, Fujita M, Kuriyama K, Narumi Y. Gastric hamartomatous polyp without polyposis coli: radiologic diagnosis. Gastrointest Radiol 1988;13:19–23.
17. Kinoshita Y, Tojo M, Yano T, Kitajima N, Itoh T, Nishiyama K, *et al.* Incidence of fundic gland polyps in patients without familial adenomatous polyposis. Gastrointest Endosc 1993; 39:161–3.
18. Moskaluk CA, Kern SE. Microdissection and polymerase chain reaction amplification of genomic DNA from histological tissue sections. Am J Pathol 1997;150:1547–52.
19. Iida M, Yao T, Watanabe H, Imamura K, Fuyuno S, Omae T. Spontaneous disappearance of fundic gland polyposis: report of three cases. Gastroenterology 1980;79:725–8.
20. Graham JR. Gastric polyposis: onset during long-term therapy with omeprazole. Med J Aust 1992;157:287–8.
21. Graham JR. Omeprazole and gastric polyposis in humans. Gastroenterology 1993;104:1584.
22. el-Zimaity HM, Jackson FW, Graham DY. Fundic gland polyps developing during omeprazole therapy. Am J Gastroenterol 1997;92:1858–60.
23. Wu TT, Kornacki S, Rashid A, Yardley JH, Hamilton SR. Dysplasia and dysregulation of proliferation in foveolar and surface epithelia of fundic gland polyps from patients with familial adenomatous polyposis. Am J Surg Pathol 1998;22: 293–8.
24. Declich P, Ambrosiani L, Grassini R, Tavani E, Bellone S, Bortoli A, *et al.* Fundic gland polyps: a still elusive entity on the eve of the year 2000. Pol J Pathol 2000;51:3–8.
25. Koh TJ, Chen D. Gastrin as a growth factor in the gastrointestinal tract. Regul Pept 2000;93:37–44.
26. Tsuchigame T, Saito R, Ogata Y, Ueno S, Arakawa A, Matsukawa T, *et al.* Clinical evaluation of gastric fundic gland polyps without familial polyposis coli. Abdom Imaging 1995; 20:101–5.