CASE REPORT

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A Novel Germline Mutation in Exon 15 of the *APC* Gene in Attenuated Familial Adenomatous Polyposis: A Report of Two Cases

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Attenuated familial adenomatous polyposis (AFAP) is a variant of familial adenomatous polyposis with fewer than one hundred colorectal polyps and a later age of onset of the cancer. Here, we report two cases of AFAP within family members. Each patient demonstrated the same novel germ line mutation in exon 15 of the adenomatous polyposis coli (*APC*) gene and was successfully managed with sulindac after refusal to perform colectomy: a 23-year-old man with incidentally diagnosed gastric adenoma and fundic gland polyps underwent colonoscopy, and fewer than 100 colorectal polyps were found; a 48-year-old woman who happened to be the mother of the 23-year-old man also showed fewer than 100 colorectal polyps on colonoscopy. Genetic analysis revealed a novel frameshift mutation in exon 15 of the *APC* gene. The deletion of adenine-guanine with the insertion of thymine in c.3833-3834 resulted in the formation of stop codon 1,287 in both patients. The patients were treated with sulindac due to their refusal to undergo colectomy. The annual follow-up upper endoscopy and colonoscopy in the following 2 years revealed significant regression of the colorectal polyps in both patients. **(Gut Liver 2013;7:120-125)**

Key Words: Attenuated familial adenomatous polyposis; Mutation; *APC*; Exon 15

INTRODUCTION

Attenuated familial adenomatous polyposis (AFAP) is a milder variant of familial adenomatous polyposis (FAP), which manifests with fewer than hundred colorectal polyps, later age of onset of polyps and cancer, and a predilection toward involvement of the proximal colon in clusters.[1-5]

Much of mutations in AFAP have already been reported.[4-9] Infrequently few mutations are still being discovered around the world. Herein, we report two cases of same novel germline mutation in the adenomatous polyposis coli (*APC*) gene of AFAP patients within family members who were treated with sulindac after they refuse to perform colectomy.

CASE REPORTS

1. Case 1

A 23-year-old man with no previous medical history and incidentally discovered multiple gastric polyps was referred to Gangnam Severance Hospital. The patient had gastric tubular adenoma with dysplasia in the antrum of the stomach. Endoscopic submucosal dissection (ESD) was performed for the gastric adenoma in the antrum, and multiple biopsies were done for the variable sized polyps in the upper body and fundus (Fig. 1A and B). Final pathologic report showed tubular adenoma with low grade dysplasia for the antral lesion (Fig. 1C). Polyps in the upper body and fundus were confirmed as fundic gland polyps. Suspected of having polyposis, the patient underwent colonoscopy which showed fewer than 100 colorectal polyps of 3 to 5 mm size from hepatic flexure to the rectum. The colorectal polyps confirmed as tubular adenoma with low grade dysplasia on pathologic report (Fig. 1D-F). Colonic polyps close or equal to 5 mm in size were endoscopically removed using polypectomy snare. Genetic analysis using polymerase chain reaction (PCR) denaturing high performance liquid chromatography and direct sequencing revealed a novel frameshift mutation in the exon 15 of the *APC* gene. Deletion of adenine-guanine (AG) and insertion of thymine (T) in codon 3833-3834 resulted in the formation of stop codon 1287 (c.3833-3834delAGinsT) (Table 1, Fig. 2).

2. Case 2

The patient's 48-year-old mother also performed upper endoscopy and colonoscopy. Upper endoscopy showed multiple

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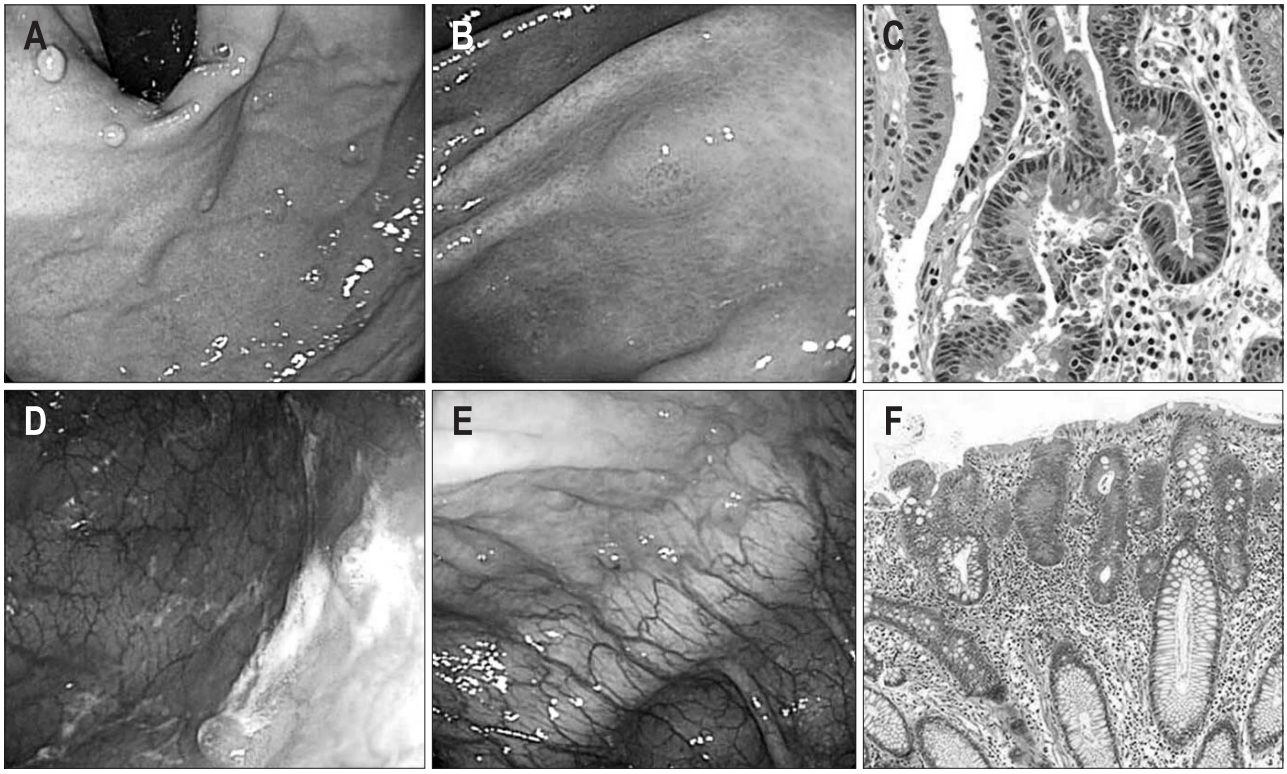

Fig. 1. Upper endoscopy and colonoscopy images of the son. (A) Multiple fundic gland polyps on the upper endoscopy. (B) Gastric adenoma in the antrum, which was resected with endoscopic submucosal dissection. (C) Tubular adenoma with low-grade dysplasia in the resected gastric adenoma specimen (H&E stain, ×400). (D, E) Multiple colonic polyps less than 100 in number on colonoscopy. (F) Tubular adenoma with low-grade dysplasia in polypectomized colonic polyps (H&E stain, ×200).

Table 1. Frameshift Mutation of c.3833-3834 in Exon 15 with the Deletion of Adenine-Guanine and the Insertion of Thymine in the Son

Gene	Exon	Nucleotide change	Amino acid change	Zygosity	Mutation type
APC	4 (int 3)	c.423-16insT		Hetero	P
	15	c.3833-3834delAGinsT	Ser1275fs	Hetero	FS
	15	c.4479G>A	Thr1493Thr	Homo	P

P, polymorphism; FS, frameshift mutation.

gastric polyps in the fundus and upper body. Pathologic examination confirmed them as fundic gland polyps (Fig. 3A and B). Multiple colonic polyps of 2 to 5 mm size were detected from ascending to sigmoid colon on colonoscopy (Fig. 3C and D). Colonic polyps close or equal to 5 mm in size were polypectomized and confirmed as tubular adenoma with low grade dysplasia. The patient's sibling died of lymphoma but there was no history of colorectal cancer in the first degree relatives. Genetic analysis also revealed same novel frameshift mutation in the exon 15 of the *APC* gene with deletion of AG and insertion of T in codon 3833-3834 resulting in the formation of stop codon in 1287 (c.3833-3834delAGinsT) which was identical to the son in the mother (Table 2, Fig. 4). Evaluation with abdomen computerized tomography revealed no demonstrable malignancy in both patients. Both patients were treated with sulindac 200 mg daily, as chemoprophylaxis after they refused to undergo colectomy.

Annual follow-up upper endoscopy for surveillance showed no evidence of recurrence at the site of previous ESD for 2 consecutive years. Colorectal polyps were much regressed in the first year and maintained that way in the second year on follow-up colonoscopy in both patients. Most of the polyps in the ascending, transverse, and descending colon were regressed, and only a few diminutive, sessile polyps were remaining in the rectum after sulindac treatment (Fig. 3E and F).

DISCUSSION

Germline mutation in the *APC* gene located on chromosome 5q21 or in some cases, biallelic mutation in the MutY homologue (*MYH*) gene are responsible for classic FAP.[3] Like classic *FAP*, *APC* mutations in AFAP are likely to be frameshift or single base pair changes that result in premature stop codons and

thus truncated protein.[5] Mutations at the 5' end of *APC* have been reported as both the first and most frequently encountered mutations related to AFAP.[4] Mutations at the 3' end, exon 9, or intron 9 of *APC* have also been reported to be the cause of AFAP.[6-8] Infrequently, mutations of *MYH* gene located in chromosome 1p32-34 is associated with development of AFAP with variable phenotypic expressions.[9,10]

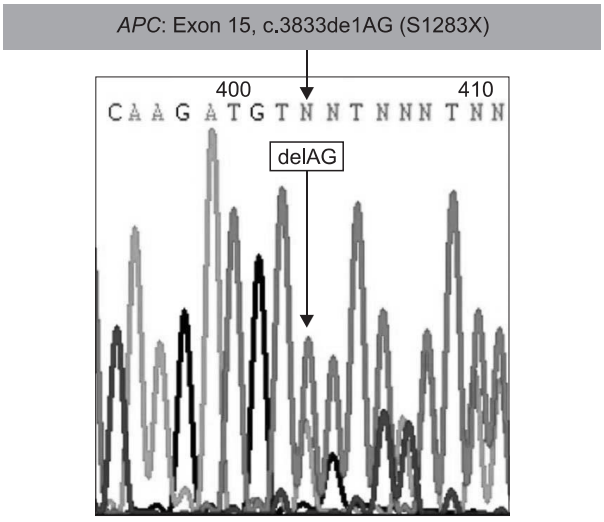

Fig. 2. Frameshift mutation in exon 15 of the adenomatous polyposis coli (*APC*) gene with the deletion of codon 3833-3844 (c.3833-3834delAGinsT), as detected by polymerase chain reaction and direct sequencing, in the son.

The classic FAP is characterized by early onset of numerous colonic adenomas, with inevitable progression to colorectal cancer.[3] Other manifestations include gastroduodenal polyps, desmoids tumors, and extraintestinal features such as congenital hypertrophy of the retinal pigment epithelium, osteoma, and other malignancies. Absolute life time risk of extracolonic cancer range from 0.6% in gastric to 15% in desmoids tumors.[3,11,12] Strict endoscopic surveillance is recommended for FAP patients and those who are at risk family members and the optimal treatment remains to be prophylactic colectomy.[3,13]

On the other hand, AFAP is much subtle in presentation with less than hundred colorectal polyps, delayed onset of colorectal cancer and death compared with FAP. Due to its right side preference and tendency for rectal sparing, colonoscopy is preferred to sigmoidoscopy for surveillance.[3-5] Even though there are some expectations that the prognosis of AFAP is better than FAP, the risk of missing early colorectal cancer during surveillance and limited knowledge of the risk and prognosis in AFAP still favors prophylactic colectomy with ileorectal anastomosis as standard option.[14,15] Surveillance for AFAP is different from that of FAP. Since there has been no case reported of colorectal cancer in AFAP under age of 20 years, full colonoscopy is recommended starting from age 18 to 20 years in contrast to 10 to 12 years in FAP with an interval of 2 years.[16]

There are reports of higher cumulative probability of cancer-

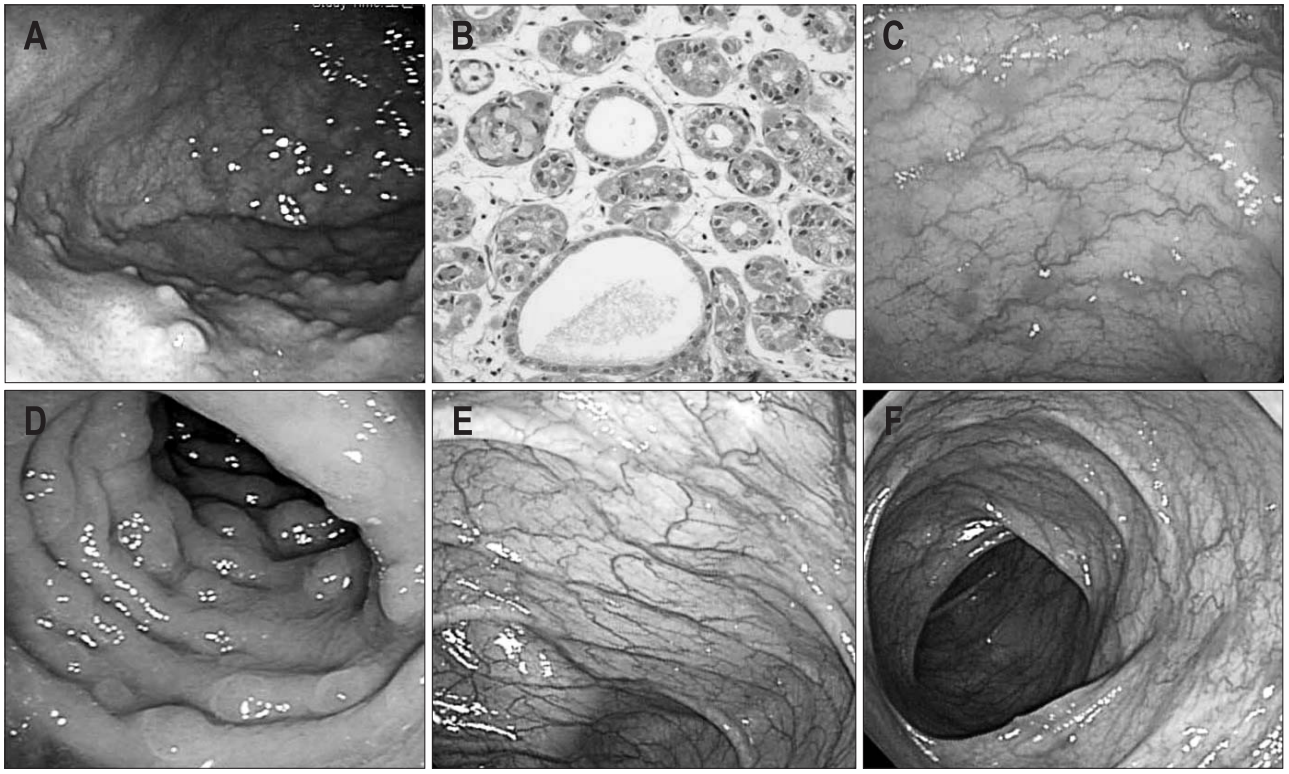

Fig. 3. Upper endoscopy and colonoscopy images of the mother. (A) Multiple fundic gland polyps in the fundus and upper body of the stomach. (B) Slightly dilated oxyntic glands of the fundic gland polyps taken from the gastric fundus (H&E stain, ×200). (C, D) Multiple colonic polyps ranging up to 2 to 5 mm in size on colonoscopy. (E, F) Nearly diminished colonic polyps 1 year after treatment with sulindac.

Table 2. Frameshift Mutation of c.3833-3834 in Exon 15 with the Deletion of Adenine-Guanine and the Insertion of Thymine in the Mother

Gene	Exon	Nucleotide change	Amino acid change	Zygosity	Mutation type
APC	4 (int 3)	c.423-16insT		Hetero	P
	15	c.2124G>A	Lys708Lys	Hetero	P
	15	c.3833-3834delAGinsT	Ser1275fs	Hetero	FS
	15	c.4479G>A	Thr1493Thr	Homo	P

P, polymorphism; FS, frameshift mutation.

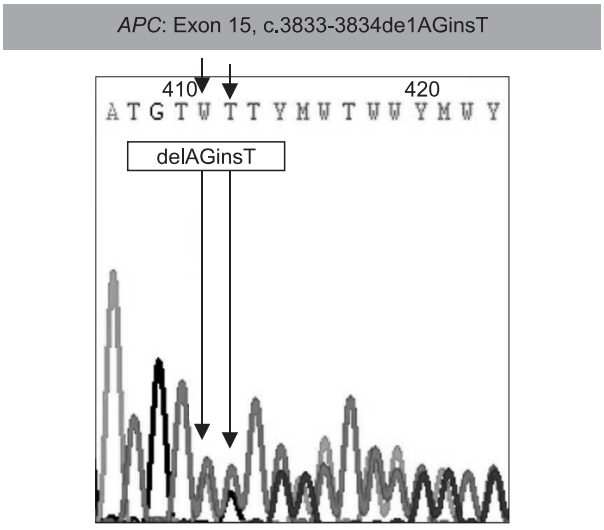

Fig. 4. Frameshift mutation in exon 15 of the adenomatous polyposis coli (*APC*) gene with the deletion of codon 3833-3844 (c.3833-3834delAGinsT), as detected by polymerase chain reaction and direct sequencing, in the mother.

free survival in AFAP compared to classic FAP even though its intra-familial heterogeneity and phenotypic expression.[17] Mounting evidence supports that endoscopic management with polypectomy might be sufficient enough to manage AFAP.[4] Recently, certain nonsteroidal antiinflammatory drugs are used to prevent polyp progression in patient with AFAP.[18] A Japanese study done with sulindac reduced colorectal adenomas of protruding type in uncolectomized FAP, and its effect is unrelated to the locus of *APC* mutations.[19] Other more recent report showed regression of polyps in long term treatment with cyclooxygenase-2 inhibitor in a patient with AFAP and previous colonic carcinoma.[20] Our cases also demonstrated statisfying results with sulindac showing regression of small colonic polyps in both patients, although more time and evidence is required to be certain.

Infrequently, some cases of AFAP with newly discovered mutation manifest far greater malignant potentials in gastrointestinal tract.[21] Reports of gastric cancer in fundic gland polyps without metaplasia or atrophy in AFAP suggest that other carcinogenesis pathway might play a role.[22] In other respect, lack of polyps or cancerous lesions in interpositioned large intestine for esophageal atresia during infancy suggests that various environmental differences also play important role in developing the expression of AFAP phenotype.[23] Phenotypic expression of benign course even in identical germline mutations in siblings warrants us to further study and puts absolute necessity for prophylactic colectomy in all AFAP patients in debate.[9,24] Ideal prophylactic colectomy age for AFAP is controversial and still under debate compared with 20 to 25 in FAP, and ileorectal anastomosis would be sufficient for AFAP in contrast to ileal pouch-anal anastomosis in FAP for surgery because of low risk of cancer formation in the remaining rectum.[25]

In regards to diagnosing AFAP or FAP, there are issues with detection of mutations. Nielsen *et al*.[26] reported that 19 out of 296 polyposis patients (6%) who had been previously tested negative for *APC* or *MUTYH* mutations by protein truncation test and sequence analysis, turned out to carry germline mutations when tested with multiplex ligation-dependent probe amplification. Routine mutation detection techniques such as DNA sequencing, protein truncation test, denaturing gradient gel electrophoresis, and single strand conformational analysis can only identify mutations in 70% of classical FAP and 10% of AFAP.[27] Use of real-time PCR allowed detection of *APC* germline mutation not apparent by conventional methods.[27] It should be noted that conventional mutation detection techniques can be misleading, especially in AFAP and further genetic testing using real-time PCR is necessary in case of no apparent mutation with polyposis patients.

Gastric and duodenal adenomas are most frequently seen extracolonic manifestations in AFAP as well as in FAP.[4] Rates of duodenal adenomas in FAP range from as high as 100% in the Japanese reports to 33% in Western reports.[28] Similar to the duodenum, stomach is also a major site of morbidity and potential mortality in FAP.[29] For unknown reasons, gastric cancer in FAP is increased in the some Asians (4.2% in Korea and 2.1% in Japan).[28,29] And the site of gastric cancers occurring in AFAP and FAP patients were mostly from fundic gland polyps.[29,30] Gastric cancer of adenomatous origin occurring sites other than fundus, especially in the antrum were rare.[29] Despite routine endoscopic surveillance, gastric cancers tend to develop in fundic gland polyps in AFAP and FAP patients, and the malignant risk increased as the polyps got bigger.[29] Some physicians argue that more aggressive approach, including complete excision of large fundic gland polyps and prophylactic gastrectomy for patients

with high grade dysplasia or large fundic gland polyps (>7 mm), but further study is obviously needed to confirm these assertions.[20]

In conclusion, we report a novel germline mutation in codon 3833-3834 at exon 15 of the *APC* gene of AFAP which were detected in both mother and son. High risk polyps were treated with endoscopic polypectomies in the colon in both patients, and remaining small polyps were managed with the treatment of sulindac. Consequently, it would be reasonable to have them under strict surveillance and chemoprophylaxis to control further growth of polyps, and hopefully regress them. Considering between son's young age versus the possibility of benign phenotypic expression in some AFAP mutations, early prophylactic colectomy is still a standard treatment option, as well as in the case of the mother, but sulindac has shown satisfactory results as an alternative treatment after they refused to go colectomy. Further investigations for the optimal treatment of AFAP according to genotypic and phenotypic difference are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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