

CLINICAL REPORT

Genetic alteration of colorectal adenoma-carcinoma sequence among gastric adenocarcinoma and dysplastic lesions in a patient with attenuated familial adenomatous polyposis

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Abstract

Background: Familial adenomatous polyposis (FAP) is characterized by colorectal polyposis and adenocarcinoma that is frequently accompanied by extracolonic neoplasm. The risk of gastric carcinoma is increasing in Western FAP patients as well as Asian patients.

Methods: We report the case of an FAP patient with fundic gland polyposis who developed gastric adenocarcinoma and metachronous pyloric gland adenomas. These tumors were endoscopically resected, and immunohistochemistry with gastric mucin (i.e., MUC6, MUC5AC) showed that the tumors belonged to the gastric subtype. Somatic mutation profiles were determined by target amplicon sequencing using a next-generation sequencer.

Results: Germline *APC* variant c.5782delC was found by direct sequencing and somatic *KRAS* mutations in these tumors were identified by next-generation sequencing. Different *KRAS* mutation alleles (*KRAS* p.Gly12Ala, p.Gly12Arg, and p.Gly12Asp) indicated these dysplastic lesions developed from a distinct origin in fundic gland polyposis. Sequential mutations of the *APC* and *KRAS* were judged—based on a database search—to be characteristic of the adenoma-carcinoma sequence in colorectal carcinogenesis.

Conclusion: The colonic adenoma-carcinoma sequence among gastric adenocarcinoma and dysplastic lesions was indicated in FAP-associated gastric carcinogenesis.

KEYWORDS

endoscopic submucosal dissection, fundic gland polyp, gastric cancer, next-generation sequencing, somatic mutation

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1 | INTRODUCTION

Familial adenomatous polyposis (FAP) is a rare autosomal dominant inherited condition characterized by colorectal polyposis and adenocarcinomas that are caused by germline variants in the adenomatous polyposis coli (*APC* OMIM *611731) gene. Variants at the terminal 5' and 3' ends of the *APC* are associated with an attenuated form of FAP (AFAP), which is associated with a significant risk of developing colorectal adenocarcinoma (Aghabozorgi et al., 2019; Spirio et al., 1993). It is worth mentioning that genotype–phenotype correlations for upper gastrointestinal FAP need to be investigated, because duodenal and gastric cancers remain life-threatening even after the risk of colorectal neoplasms is eradicated. Fundic gland polyposis in the body and fundus of the stomach is frequently observed by upper endoscopy in these patients, while gastric adenomatous lesions are less common (Burt, 2003; Kawase et al., 2009). Fundic gland polyps have a lower malignant potential, and a few case reports have mentioned that gastric adenocarcinoma is associated with fundic gland polyposis in patients with FAP (Hofgärtner et al., 1999; Zwick et al., 1997).

Gastric polyps generally arise from the foveolar or glandular compartments. Fundic gland polyps are usually sporadic, whereas fundic gland polyposis can develop in FAP patients. These polyps sometimes show dysplastic changes, characterized by nuclear enlargement, crowding, stratification, and hyperchromasia in the foveolar epithelium overlying the fundic gland polyps (Shibata et al., 2013). On the other hand, pyloric gland adenoma is a rare neoplastic proliferation of pyloric glands and is observed in 6% of FAP patients (Wood, Salaria, Cruise, Giardiello, & Montgomery, 2014). These dysplastic lesions reportedly have genetic *KRAS* (OMIM *190070) alterations; however, although there have been several studies on molecular alterations of gastric dysplastic lesion, there have been no reports on the molecular alterations of gastric carcinoma in patients with FAP (Hackeng et al., 2017). We herein report a case of gastric adenocarcinoma and pyloric gland adenoma arising in fundic gland polyposis in an FAP patient. These tumors were endoscopically resected and thoroughly investigated by immunohistochemical and genetic analyses.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by Asahikawa Medical University Ethics Committee (No 18169). A written informed consent was obtained from the patient.

2.2 | Clinical report

A Japanese woman was diagnosed with FAP and underwent a total colectomy at 36 years of age. The pathological examination revealed multiple colorectal adenomas with several early cancers presenting AFAP. A desmoid tumor was found 2 years later and was treated with chemotherapy (vinblastine and methotrexate).

During follow-up, upper gastrointestinal endoscopy demonstrated gastric fundic gland polyposis, which had been examined annually since then. A reddish large polyp and a few whitish flat polyps were observed in her stomach at 48 years of age. Magnifying endoscopy showed that the microsurface pattern of these areas was slightly irregular and that the microvascular pattern was irregular. Biopsy of the large polyp showed a tubular adenoma with focal high-grade dysplasia, and thus this lesion was subsequently resected by endoscopic submucosal dissection (tumor 1, Figure 1a,b). Histologically, the completely resected tumor contained multiple microscopic foci of intramucosal tubular adenocarcinoma within tubular adenoma (Figure 1c,d, Figure S1). Later, the white flat polyps were treated with endoscopic mucosal resections at 12 and 18 month after the first treatment, respectively (tumors 2 and 3, Figure 1e,f). These tumors were histologically pyloric gland adenomas with low- to high-grade dysplasia (Figure 1g,h, Figure S2). Multiple pink-colored polyps were also found and were histologically diagnosed as fundic gland polyps with foveolar hyperplasia (Figure S3). Stool antigen and blood antibody test for *Helicobacter pylori* were both negative.

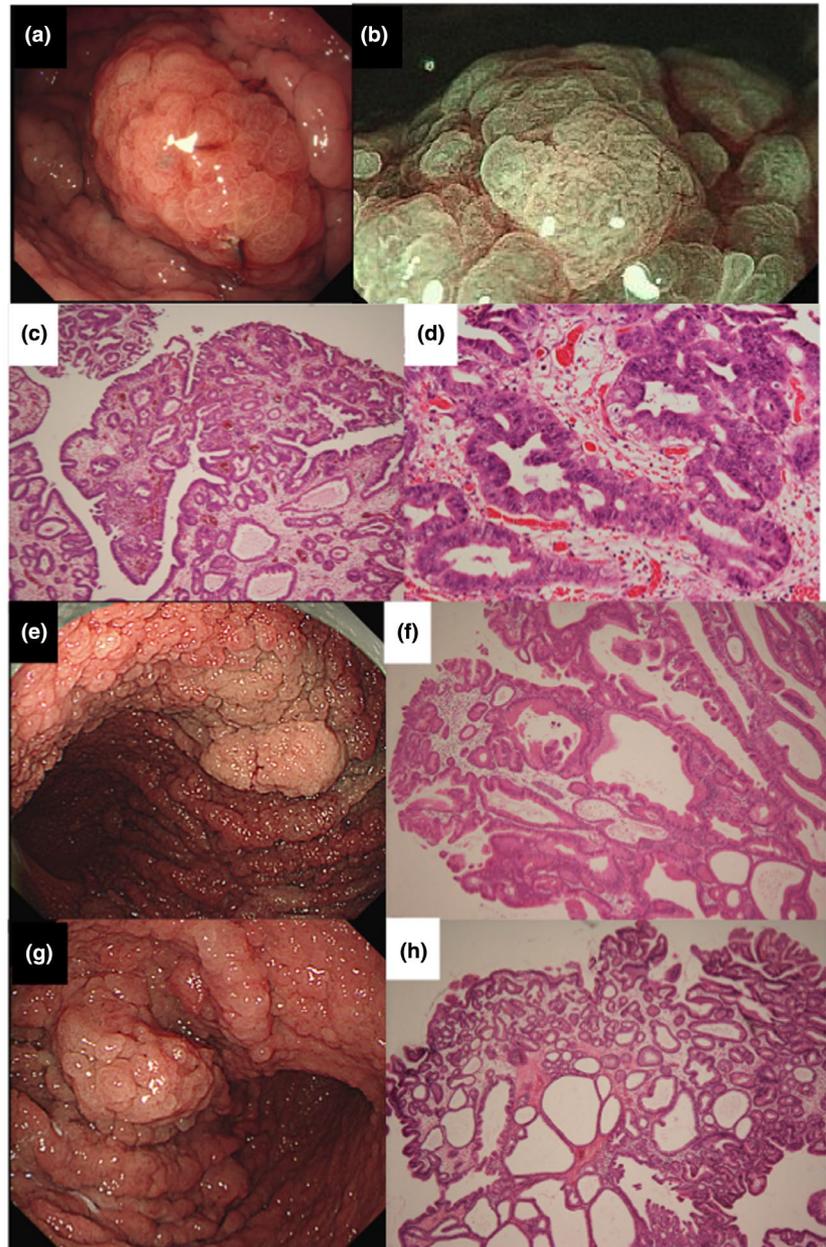
The patient's family history was significant, as her mother had died of colorectal carcinoma. Her son and daughter underwent colonoscopy and both were found to have a small number of adenomatous polyps (Figure 2a). Gastroduodenoscopy examinations also showed multiple fundic gland polyps in the fundus and body of the stomach of her son and daughter.

Based on the family history of the patient, which was strongly indicative of an autosomal dominant pattern of inheritance of colorectal neoplasms, and after genetic counseling, a genetic analysis of the *APC* was performed using peripheral blood specimens of the family members (Figure 2b).

2.3 | Sanger sequencing

Blood DNA was isolated using DNeasy blood and tissue kit (Qiagen) and DNA samples were amplified with KOD FX Neo polymerase (TOYOBO) using the polymerase chain reactions (2 min at 94°C; 10 s at 98°C, 30 s at 58°C, and 30 s at 68°C, 35 cycles; 2 min at 68°C). PCR amplification products were purified with a BigDye XTerminator Purification Kit (Thermo Fisher Scientific), and cycle sequenced using ABI PRISM Big Dye Terminator v3.1 cycle sequencing kits

FIGURE 1 Endoscopic and pathological examinations of the gastric polyps in the familial adenomatous polyposis patients. (a) Reddish polyps (tumor 1) were found in multiple fundic gland polyposis. (b) A magnified endoscopic view with narrow-band imaging showed an irregular vessel pattern, which represented adenocarcinoma. (c) Pathologically well-differentiated adenocarcinoma was observed in the superficial portion of the fundic gland polyps. (d) A high magnification view showed irregularly branching glands and micropapillae composed of atypical stratified nuclei. (e) A white flat polyp (tumor 2) was treated with endoscopic mucosal resection 12 months after the treatment of tumor 1. (f) The pathological diagnosis was pyloric gland adenoma with predominantly low-grade dysplasia. (g) A white flat polyp (tumor 3) was treated with endoscopic mucosal resection 18 months after the treatment of tumor 1. (f) Pathologically pyloric gland adenoma with dysplasia and cystically dilated fundic glands were observed. (H&E, original magnification (c, f and h) $\times 40$, (d) $\times 200$)



(Thermo Fisher Scientific) according to the manufacturer's protocols. The designed primers are shown in Table S1. Sequencing was performed by capillary electrophoresis on an ABI3700 sequencer (Thermo Fisher Scientific). Sequence data were aligned with NM_000038.5 (APC) and examined using the SnapGene software program (version 5.0.7; GSL Biotech).

2.4 | Next-generation sequencing

Formalin-fixed paraffin embedded (FFPE) specimens of gastric tissue from the endoscopic resection were prepared as 10- μm thin slides. Genomic DNA was then isolated using a GeneRead DNA FFPE kit (Qiagen) according to the manufacturer's instructions and finally eluted with 30 μl of elution

buffer. The sample was quantified using a Qubit dsDNA HS Assay Kit using a Qubit2.0 fluorometer (ThermoFisher Scientific).

Mutation profiles were determined by target amplicon sequencing using a next-generation sequencer. A colorectal cancer associated gene panel (Ion AmpliSeq™ Custom DNA Panel) was designed using the AmpliSeq Designer website (<https://www.ampliseq.com>); this panel consisted of 10 genes and 325 amplicons (Table S2). Genomic DNA (20–60 ng) was amplified using this gene panel and a sequencing library was prepared. Sequencing and data analyses were performed using a GeneStudio S5 system (Thermo Fisher Scientific). The sequence reads were demultiplexed, quality-filtered, and aligned to the human reference genome (hg19/GRCh37) using the Torrent Suite software program (version 5.0.4; Thermo Fisher Scientific). Variants were identified using

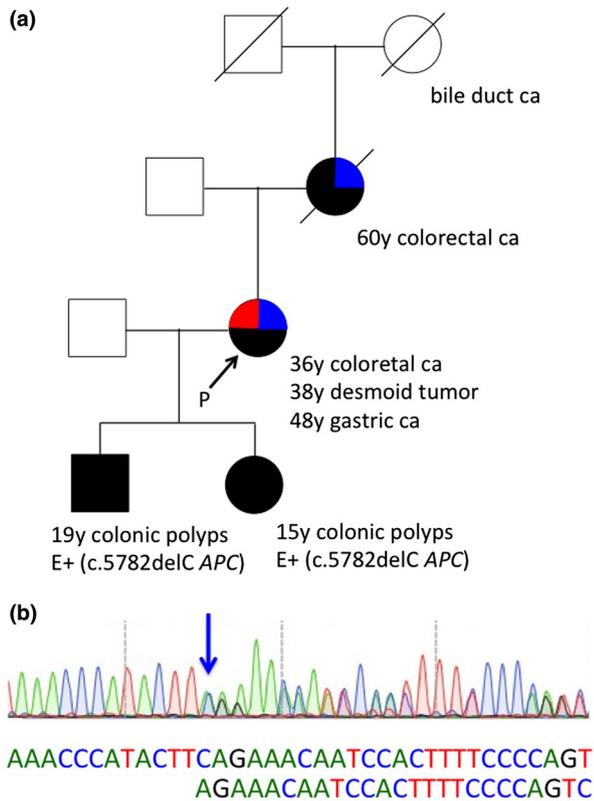


FIGURE 2 Genetic and molecular findings of familial adenomatous polyposis. (a) The partial four-generation pedigree of this patient (proband; indicated by 'P'). Closed symbols indicate that an individual is affected with familial adenomatous polyposis. Symbol key: Red quadrant indicates gastric carcinoma; blue quadrant indicates colorectal carcinoma. (b) Direct sequencing indicates heterozygous deletion of C (indicated by the arrow), resulting in a frameshift mutation

the Variant Caller plugin version 5.0.4.0 (Thermo Fisher Scientific). To identify somatic mutations, independent genotyping of each lesion and of a normal epithelial sample were subtracted; variants found in the normal sample were excluded from molecular profiling. The variant-calling analysis was performed using the somatic variant-calling mode optimized to detect low-frequency variants set to a minimum allele frequency of 0.02 and minimum coverage of 100. We also excluded putative false-negative variants by evaluating the phred-scaled variation call quality calculated by this plugin, and by manually confirming the alignment using the IGV software program (version 2.3.59; Broad Institute and Regents of the University of California).

3 | RESULTS

Polymerase chain reaction and direct sequencing were conducted and a frame shift variant, NM_000038.5(*APC*): c.5782delC (p.Gln1928fs*42), was found in exon 15 of the *APC* in tested family members. This is quite a rare variant

(Lagarde et al., 2020), given the fact that only one case with this variant has been deposited in the International Society for Gastrointestinal Hereditary Tumor (InSight) variant database (<https://www.insight-group.org/variants/databases/>) and that no cases have been reported in the ClinVar database.

A histopathological examination showed that both adenocarcinoma and pyloric gland adenoma were of the gastric type, based on their histology and immunohistochemical profile (i.e., positive immunoreactivity for MUC5AC and MUC6, but negative immunoreactivity for MUC2 and CDX2) (Figure 1, File S1, Figure S1). This profile further indicated that these tumors were of mixed pyloric and foveolar type. To investigate whether these tumors were derived from the similar genetic pathway, a genetic analysis using next-generation sequencing (NGS) was performed. The detailed results are shown in the Table S3. *KRAS* mutations were found in the neoplastic tumors (i.e., both adenocarcinoma and pyloric gland adenomas), but not in the fundic gland polyps (Table 1). The mutation alleles were different among the tumors (i.e., *KRAS* p.Gly12Ala, p.Gly12Arg, and p.Gly12Asp) indicating that the tumorigenesis may have been different. Adenocarcinoma was focally stained with p53 immunohistochemistry (File S1, Figure S1). NGS also confirmed the identical germline variant of the *APC* in all samples examined.

4 | DISCUSSION

We reported a case of adenocarcinoma arising in fundic gland polyposis in an FAP patient. Pyloric gland adenomas with low- and high-grade dysplasia were also shown to develop in fundic gland polyps. The differences in these polyps were distinctly discerned based on their endoscopic appearances and histopathological features, and a genetic analysis was conducted to explore their mutational profiles.

Gastric adenocarcinoma is a recently reported cancer risk in Western patients with FAP (Mankaney et al., 2017). A white mucosal patch was reported to be a worrisome endoscopic feature in the stomach of FAP patients (Leone et al., 2019; Walton, Frayling, Clark, & Latchford, 2017). Our patient showed whitish flat mucosal areas in the fundus and body of the stomach. Moreover, the reddish elevated tumor observed in the body of the stomach was primarily treated with endoscopic submucosal dissection and was diagnosed as adenocarcinoma in a background of fundic gland polyps. Magnifying endoscopy showed irregularity in the microvascular pattern. The endoscopic features of these neoplastic lesions had diagnostic value in the determination of adequate treatment.

A pathological examination with immunohistochemistry could reveal that mucin specific antibodies indicated differentiation of neoplasia. MUC6 and MUC5AC positivity indicated gastric-type tumors and the predominance of MUC6

TABLE 1 Genetic analysis of the gastric tumors

Tumor	Areas	Pathological diagnosis	KRAS (%)	APC (%)	PIK3CA (%)	BRAF (%)	Mean Depth	Uniformity	Target base coverage at 100x (%)	Target base coverage at 500x (%)
Tumor 1	1a	Well differentiated adenocarcinoma	G12A (41.1)				4,699	0.964	99.24%	97.34%
	1b	Well differentiated adenocarcinoma	G12A (23.3)		Q546P (7.1)		3,867	0.966	99.02%	97.65%
	1c	Pyloric gland adenoma with high-grade dysplasia	G12A (41.4)				3,648	0.965	99.02%	96.98%
Normal	1d	Normal epithelia					4,686	0.969	99.14%	97.75%
Tumor 2	2a	Pyloric gland adenoma with high-grade dysplasia	G12R (45.0)				3,911	0.964	98.99%	96.84%
	2b	Pyloric gland adenoma with low-grade dysplasia	G12R (45.0)		Q546R (9.7)		3,735	0.965	99.34%	96.69%
Polyp	2c	Mixed fundic gland polyp and foveolar hyperplasia		R845fs (6.9), R1450Ter (6.3)		D594G (6.2)	3,675	0.965	99.02%	96.98%
Tumor 3	3a	Pyloric gland adenoma with low-grade dysplasia	G12D (43.5)				3,940	0.967	99.14%	97.51%
	3b	Mixed fundic gland polyp and foveolar hyperplasia					4,266	0.964	99.34%	97.18%

confirmed that the tumor was enriched with glandular cells. Gastric adenocarcinoma is found in the foveolar epithelia covering the fundic gland. Immunohistochemistry is useful for investigating the characteristics of neoplasms (Choi et al., 2018; Mitsui et al., 2019). Pyloric gland adenomas are divided into three types based on the immunohistochemical patterns of MUC6 and MUC5AC positivity; pure pyloric type, predominant foveolar type, and mixed pyloric and foveolar type (Choi et al., 2018). A multicenter study of gastric pyloric adenomas revealed that high-grade transformation, intramucosal adenocarcinoma, and invasive adenocarcinoma were observed within 25.4%, 7.5%, and 9.0% of tumors, respectively. High-grade fundic gland adenoma was frequently found in mixed pyloric and foveolar type. MUC2, CDX2, and CD10 are also useful immunohistochemical markers that can be used to subclassify gastric cancers into the gastric, intestinal, and mixed gastrointestinal types (Mitsui et al., 2019). A case report on gastric cancers in a Japanese FAP patient showed that the tumors were of the gastrointestinal type (Yaguchi et al., 2017). Another case report showed that an FAP patient had a gastric-type adenocarcinoma whereas his pedigree had an intestinal-type adenocarcinoma (Mitsui et al., 2019). The latter carcinoma was observed in an *H. pylori*-positive patient with atrophic gastritis, representing a possible phenocopy of FAP-associated gastric cancer. The *H. pylori* status may be associated with the gastric carcinogenesis. Further immunohistochemical analyses may reveal the differentiation phenotype of gastric cancer from FAP patients.

In our study, a genetic analysis revealed a novel finding that gastric carcinoma from fundic gland polyposis in the FAP patient represented the *APC*-related adenoma-carcinoma sequence. Reported genetic mutations in gastric and colorectal cancers were identified from the COSMIC database (<https://cancer.sanger.ac.uk/cosmic/>). *KRAS* and *APC* mutations were found in 4% and 5% of gastric adenocarcinomas, respectively. These mutations were more frequently observed in colorectal cancer (34% and 48%, respectively) than in the stomach. One of the FAP-derived gastric carcinogenesis is the adenoma-carcinoma sequence, which is commonly seen in colorectal carcinogenesis. The germline *APC* variant in our patient could cause fundic gland polyposis and acquired *KRAS* mutation alleles generate gastric neoplasia. The different *KRAS* mutation alleles indicated that these gastric neoplastic lesions developed from distinct origins. This was followed by acquisition of genetic mutations, such as *PIC3CA*, which drove gastric carcinogenesis.

The *APC* germline variant found in our patient and her pedigrees was the frame shift variant (p.Gln1928fs*42), which corresponded to the result that AFAP with gastric cancer possesses the variant at the 3' distal end of the *APC*

(de Oliveira et al., 2019; Groves et al., 2002). These variants were different from those of gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) (Li et al., 2016). This is a rare variant of familial polyposis and is an autosomal-dominant cancer-predisposition syndrome with massive fundic gland polyposis, which is associated with a significantly high risk of developing gastric adenocarcinoma. Variants in promoter 1B of *APC* are associated with GAPPS syndrome. Prophylactic gastrectomy is recommended for the patients with this syndrome. However, there are only a few reports about the clinical course of FAP patients after the treatment of gastric lesions (Nakamura et al., 2017). There are no clear clinical recommendations for gastric neoplasms in FAP patients (Campos, Martinez, Sulbaran, Bustamante-Lopez, & Safatle-Ribeiro, 2019). Our patient refused gastrectomy and requested endoscopic resection of the gastric tumors based on the general indications for mucosal gastric cancer. We recommend biannual endoscopic surveillance and endoscopic resection is indicated if a neoplastic polyp is suspected.

We herein reported a case of adenocarcinoma arising in fundic gland polyposis in a patient with FAP, which was successfully treated with endoscopic resection. The endoscopic features were well correlated with the pathological features. Genetic examinations with NGS showed that multifocal gastric neoplasia occurred in the adenoma-carcinoma sequence.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in association with the present study.

AUTHOR'S CONTRIBUTION

HTan and KM: study design. HTan: analysis data and draft the manuscript. KT, YK, YM, TI, and TS: endoscopic procedures. YO and YM: genetic analysis (NGS). TK and KA: genetic analysis (Sanger sequence). NU and SK: immunohistochemical study. HTak: pathological analysis. MF and TO: study supervision and review the manuscript.

DATA AVAILABILITY STATEMENT

The variant data are publicly available in the International Society for Gastrointestinal Hereditary Tumor (InSight) variant database. (genomic variant number #0000628284).

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Density of colors indicates the rate of frequency. Different colors demonstrate difference in each signals.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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