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ORIGINAL ARTICLE

A novel insertion/deletion in *APC* promotor 1B is associated with both gastric and colon polyposis

Frankie Fann[1] · Marcy Richardson[1] · Douglas Riegert-Johnson[2] · Colin C. Young[1] · Brittany F. Sears[1,3]

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Abstract

Pathogenic variants in the *APC* gene are classically associated with autosomal dominant familial adenomatous polyposis (FAP), characterized by tens-to-thousands of colonic adenomatous polyps and a high-penetrance predisposition to colorectal cancer. More recently, specific PVs in the YY1 binding motif of *APC* promoter 1B have been associated with autosomal dominant gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), characterized by tens-to-thousands of fundic gland polyps and a predisposition to gastric cancer but which are only rarely associated with features consistent with FAP. Although management guidelines currently treat FAP and GAPPS as mutually exclusive conditions, the extent of phenotypic overlap is not well-characterized. Here, we present a multi-clinic and -laboratory collaboration reporting a previously undescribed *APC* promoter 1B insertion/deletion likely pathogenic variant in a family with mixed GAPPS and FAP phenotype. The family proband is a female of unspecified white ancestry. She was diagnosed with GAPPS at age 30 and, after developing gastric cancer at age 39, underwent curative gastrectomy. She is now 61 with a cumulative history of between 50 and 100 colon adenomas and recently completed subtotal colectomy. Her multi-gene panel testing in 2022 demonstrated a likely pathogenic insertion/deletion (indel) within the *APC* promoter 1B YY1 binding motif (*APC* c.-192_-191delATinsTAGCAAGGG). Review of a four-generation pedigree revealed the ages of gastric cancer presentation in the family ranged from 39–60's, with advanced gastric polyposis and prophylactic gastrectomy as early as ages 11 and 13 in the proband's daughter and nephew, respectively. Six of 10 (60%) family members known or presumed to carry the *APC* likely pathogenic variant underwent colectomy or hemicolectomy due to colon polyposis. The youngest known carrier in the family is a 12-year-old female, and the oldest living carrier is the proband's brother, age 66. A novel *APC* indel causes concomitant GAPPS and FAP presentations in this previously unreported large kindred. Mixed gastric and colon phenotypes have been rarely described in GAPPS families and the ages of presentation of gastric polyposis are strikingly young in the current family with prophylactic gastrectomies completed as early as age 11 and 13. These ages are significantly younger than the 15 years of age at which national guidelines currently recommend initiation of EGD for screening in GAPPS. Although the mechanism for this combined GAPPS-FAP phenotype is unclear, patients in this family and those with similar *APC* promoter 1B variants should be offered both gastric and colon cancer risk management.

Keywords APC promoter 1B · Hereditary polyposis · Cancer risk management · Surveillance guidelines

Introduction

Background

Pathogenic alterations in the coding region of the gene *APC* (OMIM 611731) classically cause familial adenomatous polyposis (FAP, OMIM 175100) a disease characterized by tens to thousands of colonic polyps, an 80–100% lifetime risk of colorectal cancer, and additional risks for extracolonic manifestations [1]. *APC* promoter mutations can also cause gastric adenocarcinoma and proximal polyposis

✉ Brittany F. Sears
bsears@ambrygen.com

[1] Ambry Genetics, 1 Enterprise, Aliso Viejo, CA 92656, USA

[2] Department of Clinical Genomics, Mayo Clinic Florida, 4500 San Pablo Rd S, Jacksonville, FL 32224, USA

[3] Tampa General Hospital, 1 Tampa General Circle, Tampa, FL 33603, USA

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of the stomach (GAPPS, OMIM 619182), which typically presents with hundreds to thousands of gastric fundic gland polyps and, in most reported cases, little-to-no colorectal or duodenal involvement. Although patients with FAP also have an increased risk of developing fundic gland and adenomatous polyps in the stomach, since the description of GAPPS in 2012 [4], the two conditions are considered distinct diagnoses [5–8] with independent management recommendations [9].

However, the research literature around *APC* indicates that the conditions are not entirely mutually exclusive. At least two kindreds are present in the literature with mixed gastric and colorectal phenotypes due to promoter 1B point mutations: (1) a study of FAP families in France from 2010 includes *APC* promoter 1B variants c. 192 A>T and c.-190G>A in families with mixed gastric and colorectal polyposis [10] and (2) an Australian family with *APC* c.-191T>C was affected by gastric polyposis, gastric cancer, and four reported cases of colon cancer [11]. In addition to these point mutations, a large, ~33 Kb deletion encompassing promoter 1B causing both colonic and gastric polyposis has been described from 19 individuals in a North American kindred [12]. However, older literature, especially that predating the description of GAPPS in 2012, has sometimes omitted description of a gastric phenotype in families with presentations also fitting FAP (e.g., [10]). The above examples illustrate that, to date, two pathogenic variant types have been described that cause GAPPS: point mutations in the YY1 binding site (c.-192–-189) within promoter 1B, and larger gross deletions affecting some or all of promoter 1B.

Here, we present a third mutation type affecting *APC* promoter 1B: a small insertion/deletion (indel), identified in a multi-generation kindred with a mixed GAPPS and FAP phenotype. Germline genetic testing identified *APC* c.-192_-191delATinsTAGCAAGGG which segregates in individuals affected by gastric polyposis severe enough to warrant prophylactic gastrectomy as young as age 13 and gastric cancer in the fourth decade of life. Unlike most of the previously reported GAPPS cases, however, this family history is also characterized by colon polyposis consistent with FAP, often warranting colectomies, and colon cancer in one individual heterozygous for this variant. To our knowledge, this family represents the first observation of an *APC* promoter 1B indel variant with mixed GAPPS and FAP phenotype.

Case presentation

A 61-year-old female was referred to the Mayo Clinic in Jacksonville, Florida for evaluation of a potential hereditary cancer syndrome given a personal and family history of significant colon and gastric polyposis and gastric cancer (Fig. 1). The proband had her first esophagogastroduodenoscopy (EGD) and colonoscopy at age 30. The colonoscopy was normal and EGD found three gastric adenomas, one of which was too large for endoscopic resection. Computed tomography (CT) of the abdomen with contrast evaluating this large mass showed a gastric polypoid mass, and she subsequently underwent subtotal gastrectomy. Following this procedure, she completed numerous upper endoscopies and dilation procedures over an eight-year period for esophageal stricture that were unremarkable for gastric polyposis. At age 39, a biopsy completed during EGD identified gastric adenocarcinoma and she completed total gastrectomy the same year.

She completed a sigmoidoscopy at age 31 and had annual colonoscopies between age 32 and 34, all of which were unremarkable. After undergoing the total gastrectomy at age 39, she followed up at several different institutions for screening colonoscopies that identified a cumulative 50–100 adenomatous polyps, with her polyp burden eventually requiring colonoscopy every 6 months. Due to this polyposis, she decided at age 63 to undergo subtotal colectomy (Fig. 2). She underwent comprehensive germline genetic testing in 2022 that identified a likely pathogenic variant in *APC*, c.-192_-191delATinsTAGCAAGGG.

Family history

The family history is significant for FAP and GAPPS, with multiple individuals in the kindred having a mixed GAPPS-FAP phenotype (Fig. 1; Table 1). No family members had reported use of proton pump inhibitors, which are known to be associated with the development of gastric fundic polyposis [15]. Information was gathered from the proband and a detailed family history document spanning the years 1963 to 2025. Of note, due to the historic nature of the available medical records, some diagnostic information is limited. Specifically, quotations are used here to describe language used by providers when no more precise language is available (e.g., “polyps” rather than “fundic polyps” vs. “adenomatous polyps”). For example, fundic gland polyposis was first described as a distinct pathology in 1977 [16], and pathology reports from prior to this date are therefore limited. Likewise, colonoscopy was not yet available for some individuals reported prior to the third generation in this family. To preserve anonymity, we do not report years of birth or death, but some relatives without apparent colon polyposis were deceased prior to introduction of general population colonoscopy surveillance or did not have access until late in life. We note this lack of access to procedures or information where possible.

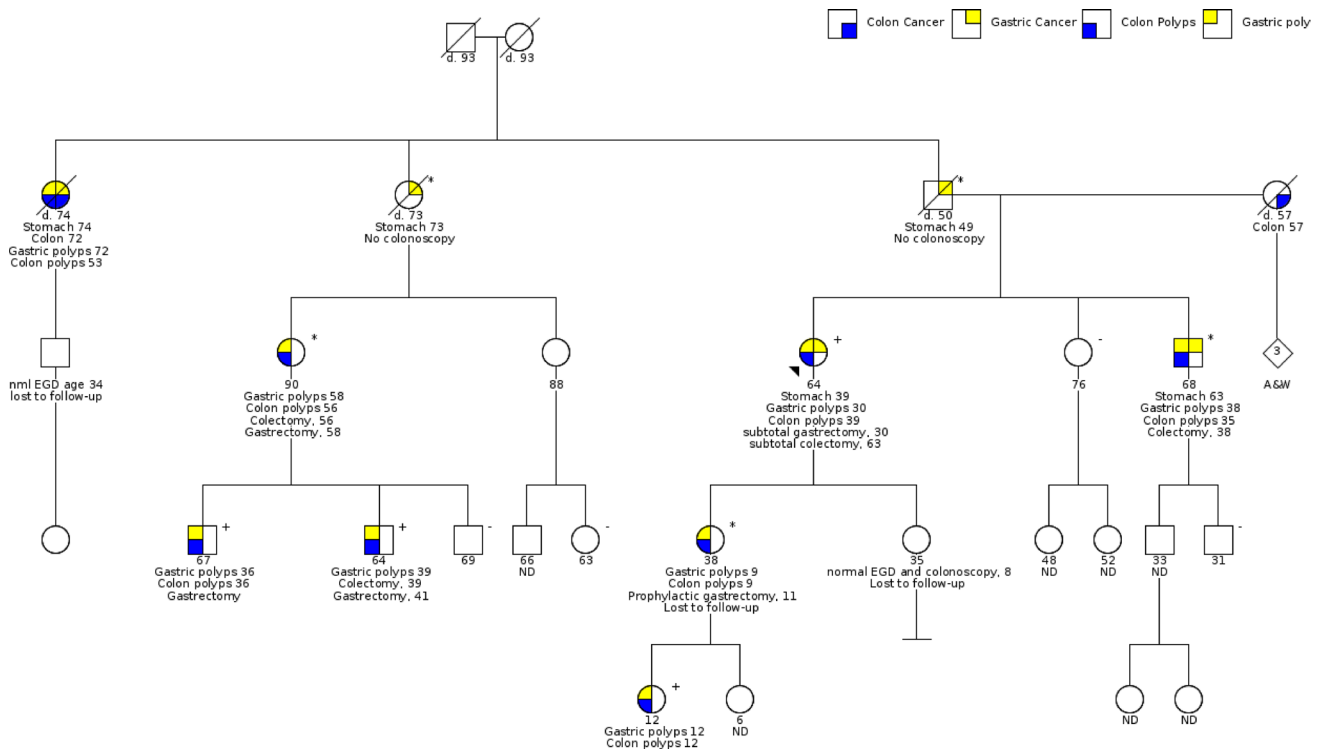

Fig. 1 Family history of kindred with private *APC*, c.-192_-191delATinsTAGCAAGGG promoter 1B likely pathogenic variant indicating age of phenotype presentation and preventative or curative surgeries. Where a specific age is not listed, age of diagnosis is unknown. Legend: + positive genetic testing, - negative genetic testing, * obligate carrier of familial variant

Children and grandchildren

One of the proband's daughters (IV-8) has a history of gastric polyposis first ascertained at age 9 (Fig. 3A–B), at least 3 sigmoid colon adenomas by age 11, and prophylactic gastrectomy at age 11. This patient is lost to follow-up, and no additional records are available after age 11. IV-8 was first seen at age 9 for upper endoscopy and colonoscopy due to the polyposis history in her mother. The fundus, cardia, and body of the upper stomach were found to have numerous small polyps, and a single "small" adenomatous polyp was found in the sigmoid colon. Although a pathologist initially described the gastric polyps as hyperplastic, the gastroenterologist notes on a later date that these polyps are more likely to be fundic gland polyps due to their absence from the antrum. EGD and colonoscopy at age 10 found additional multiple gastric polyps throughout the stomach. No colon polyps were found at that time. A colonoscopy and EGD at age 11 revealed one adenomatous polyp in the sigmoid colon and multiple fundic gland polyps in the cardia, fundus, greater curve, and lesser curve with high-grade dysplasia. Due to the gastric dysplasia and family history of gastric cancer, IV-8 underwent total gastrectomy at age 11 (Fig. 3C). Surgical pathology identified fundic gland polyposis with extensive multifocal, low-grade dysplasia and focal high-grade dysplasia, but no invasive carcinoma. While she has not had germline genetic testing herself, IV-8 is an obligate carrier because the family variant *APC* c.-192_-191delATinsTAGCAAGGG was also identified in one of her children.

IV-8 has two daughters, who are granddaughters to the proband. Her eldest daughter (V-4) underwent genetic testing at age 10 given the family history, which revealed she harbors the familial *APC* pathogenic variant. At age 12, V-4 completed EGD and colonoscopy. EGD identified one hundred to one thousand 20–30-mm raised fundic gland polyps covering the entire fundus and extending into the body of the stomach. Colonoscopy identified "multiple" 5–10-mm adenomatous polyps in the descending colon, in the transverse colon, in the ascending colon and in the cecum, and multiple 10–20-mm adenomatous polyps in the rectum and sigmoid colon; the total colon adenoma burden was estimated by the endoscopist to be 10–20 polyps (pers comm). V-5, the youngest daughter of IV-8, has not undergone evaluation given her young age.

Another daughter of the proband (IV-9) is apparently unaffected. She underwent an upper endoscopy and random gastric biopsies at age 8, which were unremarkable. She has been lost to follow-up but is not known to have undergone germline genetic testing.

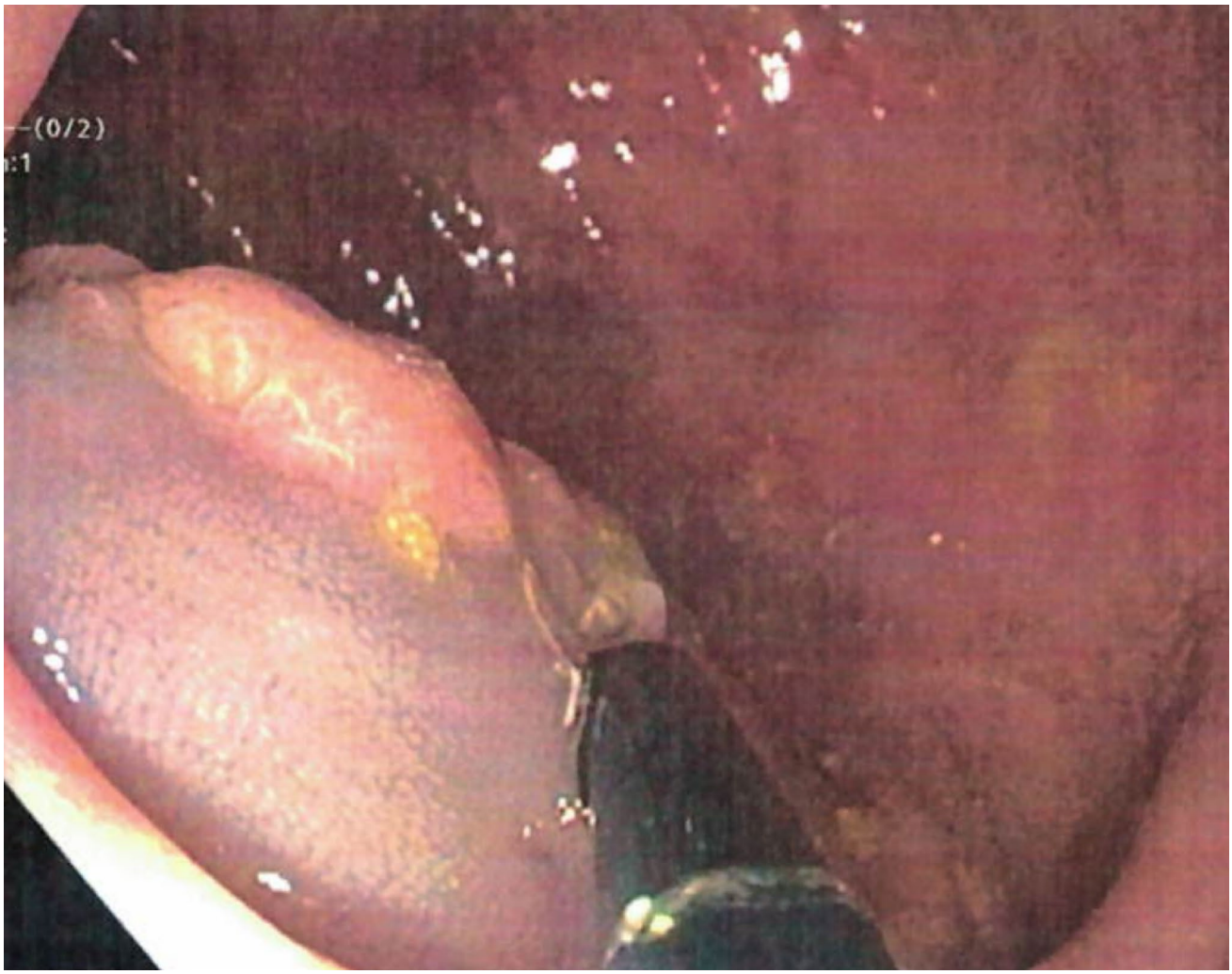

Fig. 2 A photograph taken during a colonoscopy for the proband (individual III-4) when she was 63 years old. Pictured is a partial view of a 30 mm tubulovillous adenoma in the ascending colon. The polyp is being injected with a cushion of saline to ensure safe removal (black injection catheter lower right). After injection, the polyp was removed by cautery snare. Following this colonoscopy, the patient opted for a subtotal colectomy

Siblings

A brother to the proband (III-6) has a reported cumulative history of approximately 35 colon polyps and a history of stomach cancer and gastrectomy at age 63. The following procedure and pathology reports were available for review. At age 34, III-6 completed an EGD that was unremarkable and colonoscopy that revealed one 2-mm tubular adenoma with minimal dysplasia at the mid transverse colon. Three years later, he began experiencing abdominal pain, and a subsequent EGD at age 38 identified multiple nodules of the gastric body and fundus. Biopsies indicated the nodules were "not adenomatous" and showed no tumors or dysplasia. A follow-up EGD three months later revealed the gastric body and fundus to be carpeted with nodules identified on biopsy to be "possible fundic gland polyp." III-6 has not undergone germline genetic testing.

Paternal family

The proband's paternal grandparents (I-1) and (I-2) were reportedly unaffected by cancer, living to their 90's before dying of "old age."

The proband's father (II-3) had a history of gastric cancer at age 49 from which he quickly passed at age 50. An autopsy report available for review describes gastric adenocarcinoma with extensive metastases to the liver arising from a fungating mass along the greater curvature of the stomach; the large bowel was described as "distended" but did not note polyposis. II-3 never completed colonoscopy prior to his death. He did not complete germline genetic

Table 1 Phenotypes of affected individuals within kindred with private *APC*, c.-192_-191delATinsTAGCAAGGG promoter 1B likely pathogenic variant

Individual	Sex assigned at birth, age	Germ-line genetic testing	Colon phenotype	Colectomy	Colorectal polyposis	Colorec-tal cancer	Gastric phenotype	Gastric polyposis	Gastric cancer	Gastrec-tomy
II-1	Female, d. 74	Untested	Y, 53	8-inch resection age 53	33 adenomas	Yes	Y, 72	Y, 72	74	74
II-2	Female, d. 73	Obligate carrier	ND	No	ND	No	Y, 73	ND	73	N
II-3	Male, d. 50	Obligate carrier	ND	ND	ND	ND	Y, 49	ND	49	N
III-2	Female, 90	Obligate carrier	Y, 58	Y, 58	"mul-tiple and extensive" adenomas	No	Y, 58	Y, 58	N	58
III-4*	Female, 63	Family variant	Y, >39	Y, 63	50–100	No	Y, 30	Y, 30	39	39
III-6	Male, 75	Untested	Y, <38	Y, 38	~35	No	Y, 38	Y, 38	63	63
IV-2	Male, 66	Family variant	Y, 36	Recommended	>20 at age 36	ND	Y, 36	Y, 36	N	Y (age unknown)
IV-3	Male, 57	Family variant	Y, "childhood"	Y, 39	"100 polyps in childhood"	No	Y, 39	Y, 39	N	41
IV-8	Female, 37	Obligate carrier	ND	ND	3 adenomas between age 9–11. Now lost to follow-up	ND	Y, 9	Y, 9	N	11
V-4	Female, 12	Family variant	ND	No	"multiple" adenomas in rectum and colon	ND	Y, 12	Y, 12	N	N

Colon and gastric phenotype: age at first features or age at assessment. *Family proband

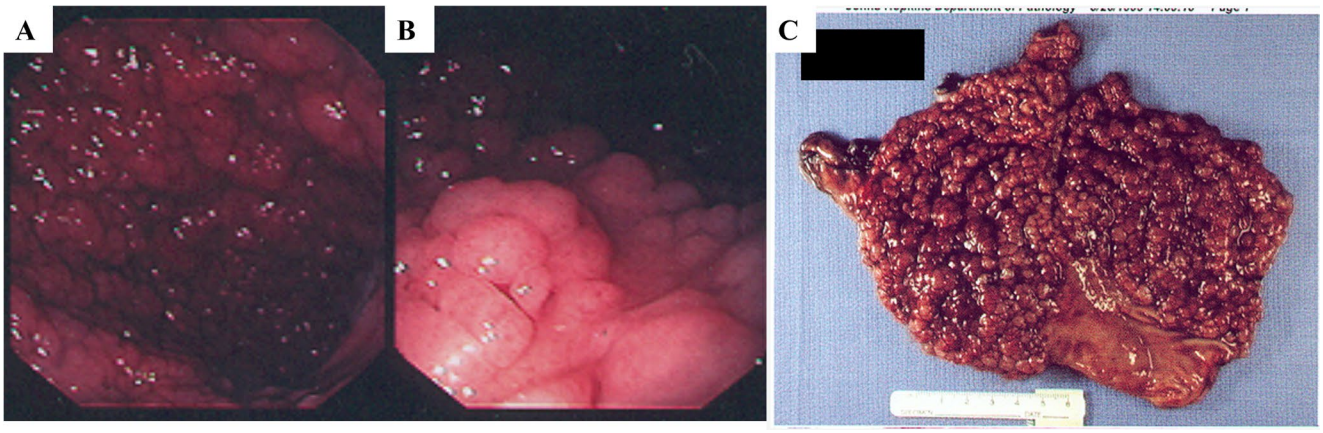

Fig. 3 Pediatric gastric polyposis in an affected family member (IV-8). (**A**–**B**) Photographs taken during an upper endoscopy for individual IV-8 (proband's daughter) showing carpeting of large stomach polyps at age 9. The patient underwent preventative gastrectomy (**C**) at the age of 11

testing but is an obligate carrier, as the mutation identified in the proband was also identified in two grandnephews (IV-2 and IV-3).

One of the proband's paternal aunts (II-1) has a reported history of at least 33 adenomatous colon polyps, two intramucosal colon adenocarcinomas, and metastatic gastric adenocarcinoma. At age 53, she underwent an 8-inch colon resection due to colon polyposis (polyp quantity and pathology not available). She underwent colonoscopy at age 63, which identified four to five sessile polyps less than 0.4 cm in the left and sigmoid colon. Per the procedure report, these polyps were not large enough for biopsy or removal.

A subsequent colonoscopy at age 65 identified one polyp in the rectum; biopsy showed no evidence of dysplasia or hyperplasia. A colonoscopy at age 68 found three tubulovillous adenomas in the ascending colon. A colonoscopy at age 69 identified six tubular adenomas. Another colonoscopy at age 71 found six sessile tubulovillous adenomas: two in the proximal transverse colon, two in the sigmoid colon, one in the rectum, and one in the descending colon. Two of these adenomas contained intramucosal adenocarcinoma. A colonoscopy at age 73 showed two 3-4-mm polyps in the cecum, three to four 3–4-mm polyps near the hepatic flexure, two polyps in the transverse colon, and one polyp in the upper rectum. These polyps were reported as tubular adenomas. A colonoscopy two years later at age 74 showed three 5-mm sessile polyps in the cecum, ascending colon, and transverse colon. A consult note reports hyperplastic gastric polyps identified on EGD at age 71, but no pathology report is available to distinguish these from fundic gland polyps (as noted by physician of IV-8). II-1 completed a "negative" EGD at age 73 per consult notes but was unfortunately diagnosed with metastatic gastric adenocarcinoma the following year at age 74. She did not complete germline genetic testing. Her son (III-1) reportedly had a normal EGD at age 34, but no additional information is available for him or for his daughter (IV-1).

Another paternal aunt (II-2) was diagnosed with metastatic adenocarcinoma of the stomach by gastroscopy with gastric biopsy at age 74. She passed away from gastric cancer shortly after diagnosis. No records of EGD or colonoscopy prior to this diagnosis are available. She did, however, complete barium enema radiograph at the time of her gastric cancer diagnosis, which did not identify obstructions or diverticula. II-2 did not complete germline genetic testing but is an obligate carrier, as the mutation identified in the proband was also identified in two of her grandsons (IV-2 and IV-3).

III-2, first cousin to the proband and daughter of II-2, had a history of "multiple" adenomatous colon polyps and underwent subtotal colectomy with ileorectal anastomosis at age 56. III-2 was found to have numerous adenomatous and fundal inclusion gastric polyps in the fundus and upper body of the stomach underwent total gastrectomy at age 58. It is unknown whether III-2 has undergone germline genetic testing, but she is an obligate carrier, as the mutation identified in the proband was also identified in two of her sons (IV-2 and IV-3).

III-2 has three sons, two of which have reported histories of adenomatous gastric polyps and gastrectomies (IV-2 and IV-3). IV-2 has a history of colon polyposis of "at least 20 polyps" by age 36, for which colectomy was recommended, but available records are unclear if or when this was completed. He underwent an upper endoscopy at age 36 showing "numerous small polyps diffusely in upper proximal body to cardia," for which he was reported by the proband to have completed prophylactic gastrectomy. IV-3 is reported by the proband to have had over 100 colon polyps in childhood, though there are no pediatric records available for review. At age 37, he underwent colonoscopy that identified approximately 20 sessile colon polyps; at that time, he self-reported a prior history of 1–2 adenomatous gastric polyps and approximately 4 colon polyps. He is reported to have underdone colectomy at age 39 and prophylactic gastrectomy at age 41, though no records are available for these surgeries.

Another first cousin to the proband (III-3) is reported to be unaffected after colonoscopy and two EGDs at ages 58 and 62. Random biopsies of the antrum and gastric body were unremarkable. A colonoscopy at age 62 revealed one distal sigmoid polyp, which pathology revealed to be a tubular adenoma. She has two reportedly unaffected children (IV-5 and IV-6).

Discussion

Here, we describe four generations of a large family carrying a private, likely pathogenic indel variant affecting the YY1 binding motif in *APC* promoter 1B. Although point mutations in this same binding motif have previously been associated with GAPPS phenotypes sparing the colon, in this family, of the eight individuals who have completed both upper endoscopy and colonoscopy, all have concomitant gastric and colon phenotypes ranging from polyposis to adenocarcinoma. However, an important limitation of this kindred is the historical nature of access to diagnostic procedures such as colonoscopy, which were not available to some affected members, or pathology classifications of gastric adenoma versus fundic gland polyps. We propose that the novelty of this mixed phenotype is due to two factors: (1) relatively greater disruption of the promoter due to this family's indel as compared to the better-described point missense mutations, and (2) potential ascertainment bias due to failure to investigate or report gastric polyposis in families meeting clinical FAP, especially prior to the description of GAPPS.

An element of this family's unique *APC* variant is its insertion/deletion combination. *APC* promoter 1B has four highly conserved transcription factor binding sites (positions −192 A, -191T, -190G, and −189G) [11]. This family's variant, *APC* c.-192_-191delATinsTAGCAAGGG, changes three of these and we therefore expect it to be more disruptive than a single missense change. Single nucleotide changes at c.-192 A and c.-191T have

been identified as pathogenic alterations associated with GAPPS but without reported colon polyposis [11, 17, 18], and, in vitro, c.-195 A>C, c.-192 A>G, and c.-191T>C have significantly less expression but do retain some residual activity [11]. It is therefore possible that the differential phenotype observed in our family versus other GAPPS families is due to a dosage effect, with c.-192_-191delATinsTAGCAAGGG resulting in a complete loss of 1B promoter activity. This dose-effect hypothesis of missense versus more disruptive variants may also help explain the observation that full deletions of the 1B promoter that leave the 1 A promoter intact have been observed in individuals with both colon and gastric polyps [12]. Complete loss, such as that we propose for this family's c.-192_-191delATinsTAGCAAGGG, or a full promoter deletion, may reduce APC protein activity below the threshold necessary to prevent the development of colon polyps.

Although this hypothesis is under development, it raises important issues with current management guidelines that suggest a GAPPS phenotype is exclusive of colorectal concerns [1, 9]. Even among classic GAPPS families with single nucleotide variants, the rate of sub-FAP colon polyposis (i.e., <20 lifetime adenomas) approached 17% in a recent meta-analysis [19]. Not only does the current family's case study illustrate the potential for mixed GAPPS/FAP presentation, we have highlighted prior research, perhaps overlooked, documenting that other families with a mixed presentation have also been previously described [10, 11]. We therefore suggest that individuals recently diagnosed with APC promoter 1B mutations initiate baseline colonoscopy at an age consistent with guidelines for FAP, with interval management tailored based on personal and family history.

For timing of first colonoscopy, we recommend all individuals with GAPPS should have their first colonoscopy by age 15. If an individual with GAPPS has an upper endoscopy performed younger than 15, a colonoscopy should be considered at the time of that upper endoscopy. If an individual with GAPPS has a colonoscopy and no adenomas are found, we recommend the interval to the next colonoscopy be 3 years. The 3-year recommendation places individuals with GAPPS without adenomas in the same time frame as members of the general population with a high-risk adenoma (e.g. high-grade dysplasia), but a longer time frame than individuals with FAP. If adenomas are found, an interval shorter than 3 years could be recommended based on the number, size and histology of the adenomas. Finally, where EGD is recommended at early ages, such as in this family, it is essential that individuals are seen in high-volume medical centers familiar with the management of fundic polyposis, as discussion of prophylactic gastrectomy is not typically warranted until high-grade dysplasia is present [9].

Conclusion

There are currently no professional recommendations for the timing of first colonoscopy and the interval between colonoscopies for individuals with GAPPS. We offer our recommendations for colonoscopy based on this family's history, reports of other families with GAPPS, and current society recommendations for the general population and for more common hereditary polyposis disorders, such as FAP. These recommendations are also informed by our experience with individuals with GAPPS and other hereditary polyposis disorders, who usually opt for close screening with the goal of preventing colon cancers. Additionally, GAPPS families without concerning colorectal histories should be carefully advised of screening, at a minimum, based on general population guidelines, as they still possess sporadic risks. Additional case, population, and mechanistic studies are warranted to continue to investigate the relationship between GAPPS and FAP.

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Author contributions All authors contributed to writing the main text and reviewing the manuscript. D.R.G. obtained endoscopy images and provided additional clinical details of the proband. B.S. prepared all figures.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest FF, MR, CY, and BS are full-time, salaried employees of Ambry Genetics.

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