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β-Catenin activation in fundic gland polyps, gastric cancer and colonic polyps in families afflicted by 'gastric adenocarcinoma and proximal polyposis of the stomach' (GAPPS)

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Abstract

Aim—To evaluate possible colon involvement in the 'gastric adenocarcinoma and proximal polyposis of the stomach' (GAPPS) gastrointestinal polyposis syndrome.

Methods—Prospective clinicopathological evaluation of two GAPPS families and expression of nuclear β-catenin, p53 and Ki67 measured by immunohistochemistry on endoscopic and surgical specimens from patients with GAPPS.

Results—Patients with the GAPPS phenotype were more frequently affected by colonic polyps than patients at risk within the same families ($p<0.01$). Colonic polyps shared immunohistochemical features of fundic gland polyps and gastric cancers including increased expression of nuclear β-catenin, Ki67 and p53. Both gastric and colonic lesions harboured activating somatic variants of β-catenin signalling.

Conclusions—Similarities in expression markers in fundic gland and colonic polyps, together with an enrichment of colonic adenomas in family members affected by GAPPS phenotype compared with family members at risk, support mild colonic involvement of this rare cancer syndrome. Colonoscopic screening might be warranted.

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INTRODUCTION

The clinical features of the recently described ‘gastric adenocarcinoma and proximal polyposis of the stomach’ (GAPPS) syndrome are an autosomal dominant inheritance with incomplete penetrance, dysplastic and adenomatous fundic gland polyposis of the stomach with sparing of the antrum and gastric adenocarcinoma.[12] To date, the following diagnostic criteria have been proposed for GAPPS: (1) >100 polyps in the index patient and >30 polyps in a first-degree relative, (2) histopathologically predominant fundic gland polyps (FGP), (3) polyps restricted to the body and fundus with no colorectal or duodenal polyposis, (4) autosomal dominant pattern of inheritance and (5) exclusion of other heritable gastric polyposis and gastric cancer syndromes.[1] Detection of gastric polyposis has occurred in family members as young as 10 years of age, with the earliest associated gastric cancer reported at 33 years of age.

To date, non-gastric manifestations in GAPPS are poorly defined. Worthley *et al* note a ‘mild colonic phenotype’ in a large family who underwent colonoscopic screening. While no patients were reported to harbour colon cancer, 9 out of 36 family members with a complete or a partial GAPPS phenotype were found to have adenomatous lesions involving either the left or right side of the colon. In contrast, colonoscopic screening in a family of Asian descent with GAPPS identified no colonic lesions.[2]

Here, we report on the results of colonoscopic screening of two families affected by GAPPS. Affected family members by GAPPS more frequently harboured colonic polyps including colonic adenomas. WNT signalling activation measured by nuclear β-catenin translocation was seen in both the disease-defining gastric lesions and colonic polyps.

METHODS

Written informed consent for genetic testing and analysis of pathology samples was obtained following enrolment of patients into institutional review board approved protocols (CCR NCI-09–0079). Family history and pedigrees were obtained by a genetic counsellor and outside medical records were reviewed for patients not treated at our institution. Genetic testing in family 1 included the multiplexed targeted deep sequencing (OncoVar) assay targeted exons of 197 commonly mutated cancer genes.[34]

Immunohistochemical stains for β-catenin (clone 17C2, Leica Biosystems Newcastle, Newcastle Upon Tyne, UK, #B-CAT-L-U, 1:100), E-cadherin (clone 36B5, Leica Biosystems Newcastle, #E-CAD-L-CE, 1:100), Ki-67 (clone KI-67, #M7240, 1:300) and p53 (clone Do-7, #M7001, 1:1000) were carried out after antigen retrieval. The primary antibody was incubated for 30 min. BondMax (#DS9800) was used with diaminobenzidine as chromogen. Histopathology and immunohistochemistry was reviewed by the two study pathologists (MQ and MM).

Targeted next-generation sequencing was performed on 10–20 ng of genomic DNA extracted from formalin-fixed, paraffin-embedded (FFPE) macrodissected tissue sections

using the Ion AmpliSeq Cancer Hotspot, Panel V2 and Ion AmpliSeq Library Kit 2.0 according to the manufacturer's instructions (Thermo Fisher, Ion Torrent). The amplicon panel includes 207 primer sets covering approximately 2800 COSMIC hotspot mutations in 50 genes. The targeted genes are provided in the accompanying online supplementary appendix 1. Sequencing was performed using an Ion Torrent Personal Genome Machine, and analysed with Torrent Suite Software (Life Technologies). The average read depth is over 1000×. Annotation and interpretation of all variants were performed using the Ion Reporter cloud-based software that links to multiple databases, such as RefSeq, OMIM, Oncomine, COSMIC and dbSNP. Reported mutations were confirmed by inspection of alignments using the Integrative Genomics Viewer.

Family 1

The index patient of family 1 was diagnosed at 55 years of age (figure 1). Upper endoscopy for complaints of dyspepsia and epigastric discomfort showed polyposis carpeting the cardia, fundus and body of the stomach, with sparing of the antrum at the level of the incisura angularis (figure 2A). Colonoscopy showed a total of 16 colonic polyps distributed across all parts of the colon and rectum (table 1). There were four adenomas including one villous adenoma in the descending colon and one tubovillous adenoma in the right colon. The others were tubular adenomas. All of these polyps were removed endoscopically (table 1).

Figure 2B shows the opened intraoperative gastrectomy specimen, which demonstrates a sharp demarcation between the proximal region of the stomach, carpeted by diffuse polyposis, and the uninvolved antrum characteristic of GAPPS. Histopathology confirmed FGPs with low-grade and high-grade dysplasia (figure 2C). There was a T1 foveolar type adenocarcinoma embedded in the FGPs (figure 2D). Colonoscopy in the index patient's father identified four adenomatous lesions involving both the left and right side of the colon. Of note, the daughter (I-45) of the index patient's cousin underwent an esophagectomy at age 57 for adenocarcinoma of the cardia of the stomach, but did not have fundic gland polyposis or FGPs, and was diagnosed at age 26 with a stage III left-sided colon cancer. Germline testing on the index patient and her daughter did not identify any mutation of APC, CDH1, MUTYH, SMAD4, BMPR1A or other genes known to gastrointestinal cancer syndromes. Mismatch repair mutation testing was normal in patient I-50.

Family 2

This family had been described by Worthley *et al* with colonoscopic information only available for two family members. We performed colonoscopies on 13 patients. Gastrectomy was performed in patients II-11 and II-12 due to inability to appropriately sample fundic gland polyposis (>1000 polyps) on upper endoscopy (figure 2E–G). Histopathology confirmed FGPs (figure 2F) without invasive cancer. A total of eight members of this family had the GAPPS phenotype. Four were found to have gastric adenocarcinoma, and three family members died of metastatic gastric cancer. A total of 13 family members at risk for being a carrier underwent colonoscopic screening at our institution, identifying adenomatous lesions in two, both of whom had phenotypic GAPPS. Other notable colonoscopic abnormalities included the finding of a hyperplastic polyp in the rectum of family member

II-12 at 23 years of age and a benign caecal polyp at 20 years of age in patient II-14. Of all patients in this family who underwent colonoscopic screening, five out of seven patients with GAPPS had colonoscopic abnormalities. Of the patients who did not have GAPPS, zero of six patients had any colonic pathology on colonoscopic screening.

RESULTS SUMMARY

We examined if there was an enrichment of polyp incidences in patients with GAPPS phenotype versus family members at risk/non-obligate carriers to account for interfamilial risk variations. When data from both families are combined, a total of 12 patients with the classic GAPPS phenotype and six first-degree relatives of patients with GAPPS at risk for GAPPS were identified (table 1). Nine out of the 12 GAPPS patients and six family members at risk underwent colonoscopy: seven of nine GAPPS patients screened had colorectal pathology, whereas none of the at-risk patients had colorectal pathology (Fisher's exact test; p=0.007; figure 3). There was no difference in age distribution between the two groups (p=0.21). We next confirmed the hyperproliferative nature of both gastric and colonic lesions. Figure 4A, B shows overexpression of Ki67 in FGPs for patients I-1 and II-11. Figure 4C shows diffuse nuclear staining of p53 in FGPs of patient I-1. Ki67 and p53 expression in adenomatous colonic polyps of patient I-1 is shown in figure 4D, E. Consistent with the lack of CDH1 mutation, there was no loss of E-cadherin in fundic polyps of patient I-1 (figure 4F). Fundic gland lesions of gastric specimens in both families, including FGPs as well as the invasive cancer of patient I-1, showed increased nuclear β-catenin staining compared with uninvolved gastric mucosa (figure 5A, B). Colonic adenomatous polyps removed from patient I-1, although more focal, also showed similarly increased nuclear β-catenin staining (figure 5C). To show that neoplastic mechanisms involving β-catenin activation are different in GAPPS from sporadic FGPs, gastric or colon cancer, we genotyped specimens from patient I-1 and II-12. Table 2 shows alternative activating β-catenin signalling mutations in GNAS (known hotspot R201C (transcript NM_000516), FBXW7 (hotspot p.R465H) and KRAS.

DISCUSSION

GAPPS is a recently described upper gastrointestinal polyposis cancer syndrome with few families described to date. Definition of a possible colonic phenotype in GAPPS is particularly important considering some of the shared clinical similarities with previously described atypical presentations of familial adenomatous polyposis (FAP).[5,6] FGPs develop in FAP in up to 80%–93% of patients.[7,8] However, their malignant potential, despite a low-grade dysplasia rate of 44%–54%, has been estimated as very low with only a few cases of patients with classical FAP having developed adenocarcinoma of the stomach with only one reported description of gastric adenocarcinoma in a family member with atypical FAP.[9–13] The unique non-involvement of the antrum in patients with GAPPS, coupled with the absence of a colonic polyposis phenotype is an important clinical feature that distinguishes GAPPS and FAP. The diagnostic importance of this distinction is augmented when one considers that in nearly 20% of patients with clinical features of FAP, no APC mutation is detected and that APC-negative FAP families have been described to harbour a more variable clinical phenotype including upper gastrointestinal involvement.[14,15] Thus, our

finding of an increased incidence of colonic polyps sans colonic polyposis seems congruent with the unique phenotype of this novel cancer syndrome.

The natural history and clinical significance of colonic polyps in GAPPS remains largely unknown. In the series by Worthley *et al*, 16 of 32 family members that underwent colonoscopy had a pathological finding ranging from simple colonic hyperplastic polyps to multiple tubular adenomas. The largest number of adenomas found in one individual was 8. The youngest affected family member with colonic adenomas was 31 years of age. In contrast, no colonic abnormalities were detected in the study by Yanaru-Fujisawa *et al*.[2] There appears to exist a considerable degree of heterogeneity in the penetrance of possible colonic involvement.[1] While it is tempting to speculate that patient I-50, who was diagnosed at age 26 with stage III colon cancer, might represent a patient with a malignant colonic phenotype due to GAPPS, it is important to remember that, while at risk, her mother did not have GAPPS. Although the patient tested negative for hereditary non-polyposis colon cancer (HNPCC), the patient could harbour an early onset colon cancer with no connection to GAPPS.

Is it thus possible that the observed colonic involvement might simply reflect the baseline risk of developing sporadic colonic adenomas of these families? Cumulative incidence rates of colonic adenomas in Western countries in persons ≥50 years of age have been reported above 10%, and some close to 30%. Colonic adenomas, such as colorectal cancer, are known to have a familial inheritance pattern, although weak.[1617] The observed enrichment of colonic lesions in family members with the GAPPS phenotype compared with at-risk, non-GAPPS family members (7/9 vs 0/6; p=0.007) with no difference in median age and gender distribution between family members affected by GAPPS and family members at risk suggests a link to GAPPS. On the other hand, family members were not randomly chosen for colonoscopy. Genotyping of the gastric cancer and polyps of patient I-1 and II-12 suggests a mechanism of β-catenin activation unique to GAPPS. While none of the exon 3 β-catenin hotspots previously described in sporadic FGPs or gastric cancer were affected by somatic variants, the detected GNAS R201C variant has been shown to be associated with β-catenin signalling activation in the rare gastric adenocarcinoma of the fundic gland subtype.[18] Gastric adenocarcinoma of the fundic gland type is, however, not associated with gastric polyposis or any of the clinical features of GAPPS. Additionally, loss of the tumour suppressor FBXW7, due to inactivating mutations, like due to the identified known hotspot variant p.R465H in patient II-12 has been reported in 6%–9% of gastric and colon cancers and shown to activate β-catenin signalling.[19–21] Thus, we suggest that in the presence of an elevated cancer risk due to the cancer predisposition GAPPS; syndrome, ‘second-hit variants’ known to activate the WNT signalling network in gastric or other gastrointestinal cancers contribute to the observed β-catenin signalling activation and polyp and tumourigenesis in our patients with GAPPS; and that there is heterogeneity among these second events, as known for other cancer predisposition and polyposis syndromes including hereditary diffuse gastric cancer (HDGC) and FAP, across the different sites.[22–24] The increased rate of colonic polyps, however, in the families afflicted by GAPPS, the occurrence of adenomatous polyps in patients in their third and fourth decade of life, the lack of a male gender preference as observed in sporadic colon polyps, and involvement of the right and left colon in GAPPS families screened with colonoscopy seem to make it less

likely that colonic adenomas are unrelated to this syndrome, supporting a common pathogenesis in the context of this rare cancer predisposition syndrome.

In conclusion, we present two families with elevated incidence of colonic polyps in family members with the GAPPS phenotype. Increased nuclear β-catenin expression in both gastric cancer and adenomatous colonic polyps, which harbour variants in β-catenin signalling-related genes, may point to a common mechanism of neoplastic transformation at both organ sites. In the presence of an evolving phenotype of this novel cancer predisposition syndrome, we advocate inclusion of colonoscopic screening and surveillance into the routine work-up of patients with GAPPS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

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Take home messages

- GAPPS is an autosomal dominant hereditary gastric cancer syndrome with an as of yet undefined extragastric phenotype.
- Malignant transformation in GAPPS is not a product of typical genetic mutations seen in other hereditary cancer syndromes.
- Malignant transformation of gastric polyps in GAPPS occurs through the WNT signalling pathway.
- There appears to be an increased frequency of adenomatous polyps in the colon in patients with GAPPS.
- Routine colonoscopic screening in patients with GAPPS is advocated.

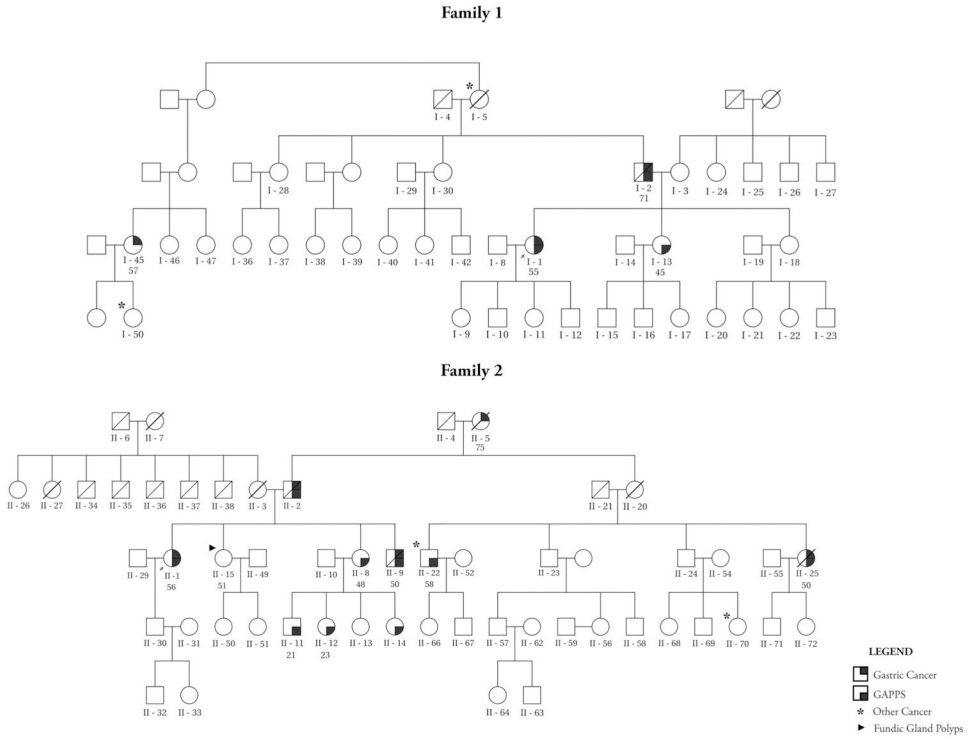

Figure 1.

Pedigrees of families with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). Squares indicate males; circles indicate females. Symbols with a shaded portion in the upper right quadrant identify individuals who have been diagnosed with gastric cancer. Symbols shaded in the right lower quadrant identify individuals who have been diagnosed with GAPPS. The age of diagnosis is indicated underneath the patient number. Symbols with slashes indicate deceased family members. Patients with other cancers are denoted with an asterisk. Patients with fundic gland polyps that do not meet the criteria for the GAPPS phenotype are denoted with an arrowhead. See table 1 for other malignancies.

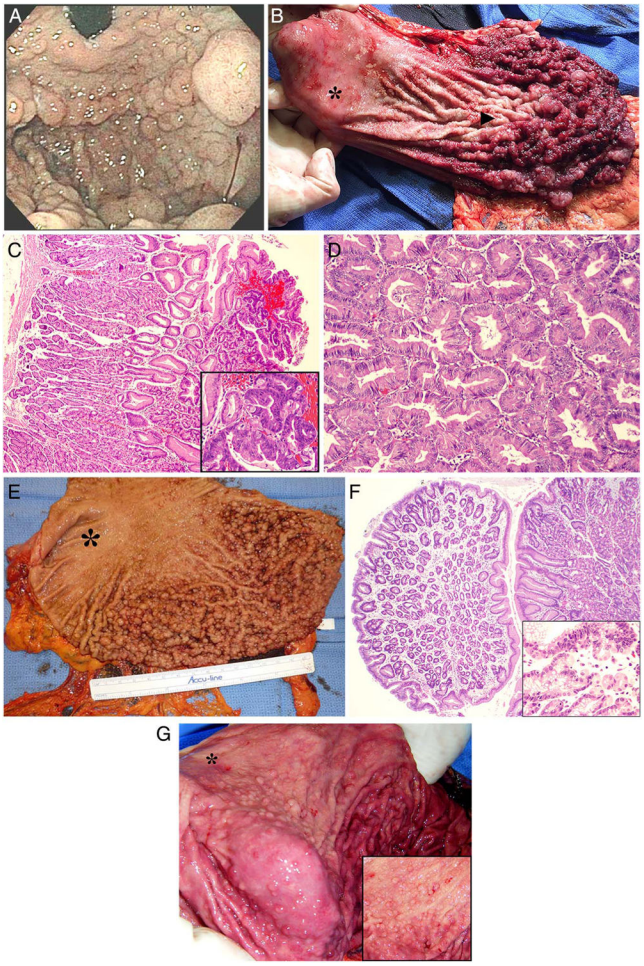

Figure 2.

Endoscopy, gastrectomy and histopathology of family members affected by gastric adenocarcinoma and proximal polyposis of the stomach. (A) Retroflexed gastric endoscopy in patient I-1 showing fundic polyposis. (B) Total gastrectomy specimen opened at lesser curvature shows polyposis in the fundus, cardia and body of the stomach (arrowhead) with typical non-involvement of the antrum (asterisk). (C) Fundic gland polyp with high-grade dysplasia (inset 20×) in gastrectomy specimen of patient I-1. (D) T1a well-differentiated intestinal-type gastric adenocarcinoma at lesser curvature in patient (I-1). (E) Gastric polyposis with antral sparing (asterisk) in patient II-11. (F) Fundic gland polyp with focal area of low-grade dysplasia in patient II-11. (G) Gastrectomy specimen from patient II-12 showing diffuse gastric polyposis with antral sparing (asterisk). Inset shows direct view of polyps in the fundus (zoomed in).

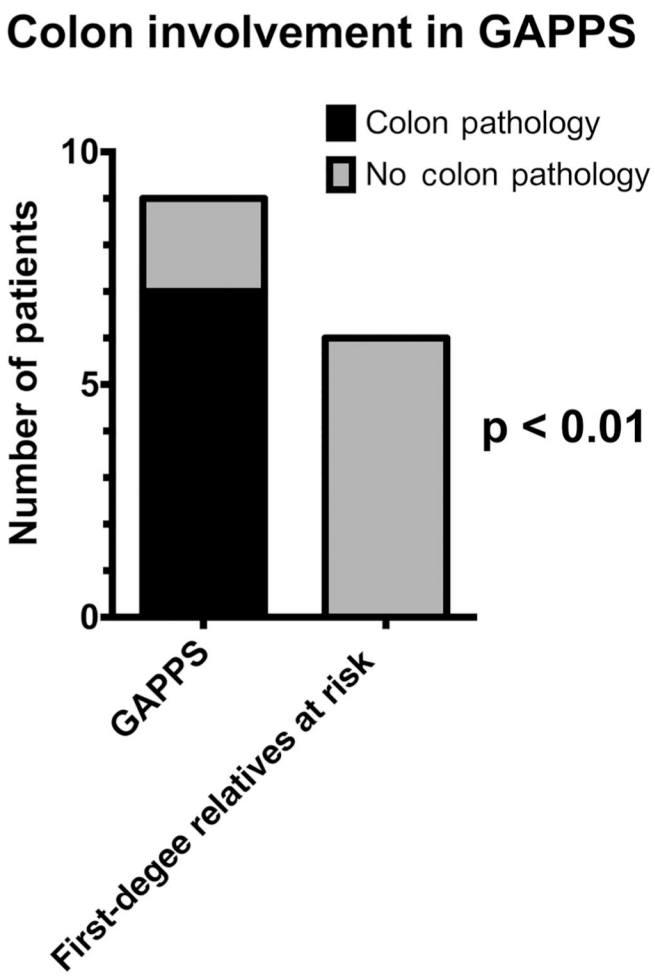

Figure 3.

Colonoscopic screening results. Patients with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) have a higher incidence of colon pathology than at-risk family members.

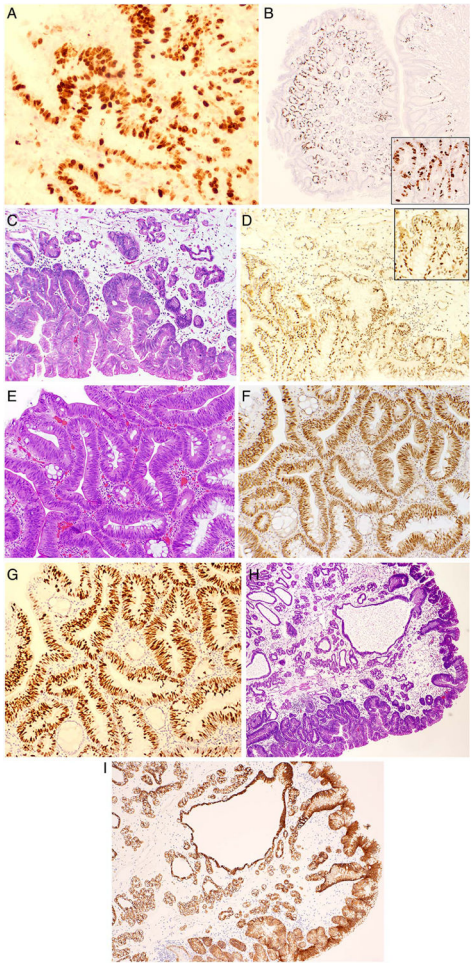

Figure 4.

Ki-67, p53 and E-cadherin expression in stomach and colon polyps of family members affected by gastric adenocarcinoma and proximal polyposis of the stomach. (A) Increased proliferation measured by Ki-67 expression in fundic gland polyps in gastrectomy specimen of I-1. (B) Increased proliferation highlighted by Ki-67 staining in fundic gland polyp in gastrectomy specimen of patient II-11 (see figure 2F for H&E). H&E staining (C) and increased nuclear p53 staining (D) in fundic gland polyp of patient I-1. H&E staining (E), increased proliferation measured by Ki-67 (F), and increased nuclear p53 staining (G) in colonic adenoma from patient I-1. H&E staining (H) and preserved E-cadherin expression (I) in fundic polyp of patient I-1.

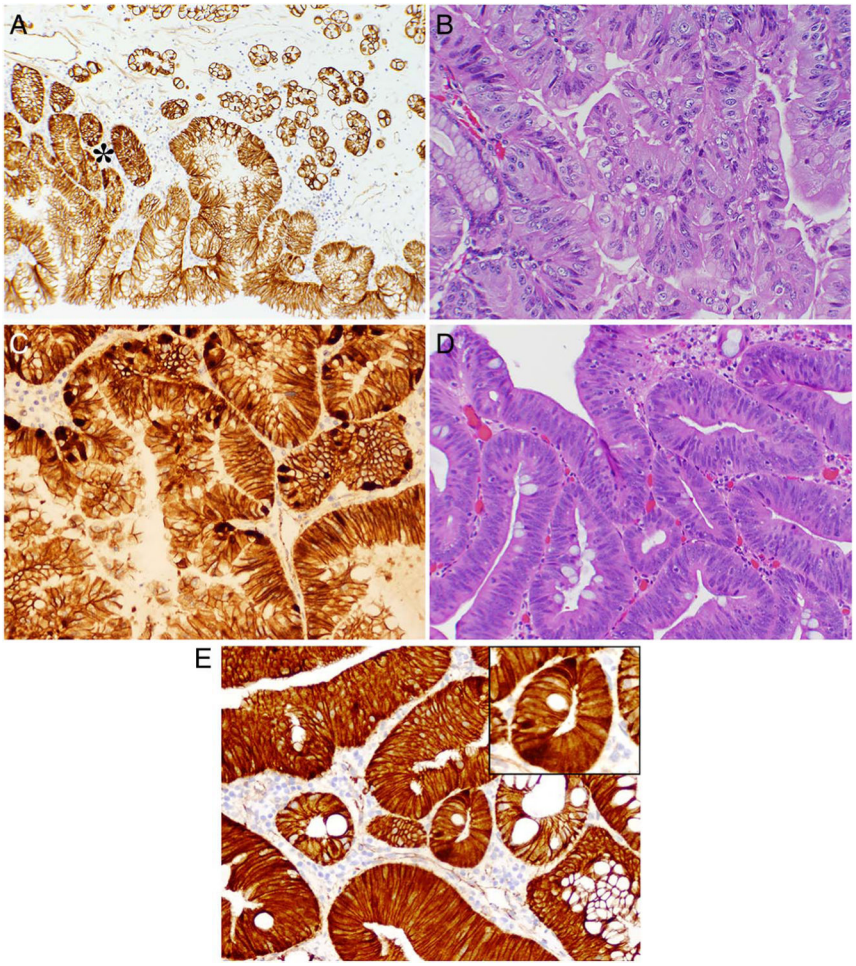

Figure 5.

Nuclear β-catenin expression in gastric and colonic polyps. (A) Fundic gland polyp with strong nuclear β-catenin expression (asterisk) in polyps from patient I-1 (see figure 4C for H&E). H&E staining (B) and high-intensity nuclear β-catenin staining (C) in gastric cancer of transverse colon adenoma from patient I-1. H&E staining (D) and high-intensity nuclear staining (E) in colonic polyp removed from patient I-1. GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach.

Table 1

Clinicopathological features of gastric and colonic pathology for families affected by gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)

			Stomach diagnosis		Colon diagnosis		
ID	**Age at diagnosis**	**Gender**	**EGD findings**	**Gastric cancer**	**Colon polyps**	**Pathology**	**Other cancers**
Family 1							
I-1	55	F	GAPPS	Adenocarcinoma	16 polyps distributed through colon	1 tubulovillous adenoma on right, 1 tubulovillous adenoma and 3 tubular adenomas on left, 12 hyperplastic polyps	None
I-2	71	M	GAPPS	Adenocarcinoma	6 polyps distributed through colon	4 tubular adenomas, 2 hyperplastic polyps	None
I-5	Unknown	M	Unknown	Unknown	Unknown	Unknown	Thought to have either gastric or kidney cancer
I-9	32	F	Normal	No	Normal	Normal	None
I-13	45	F	GAPPS	No	Unknown	Unknown	None
I-45	57	F	Gastro-oesophageal junction mass	Adenocarcinoma	Unknown	Unknown	None
I-50	25	F	Normal	No	Sigmoid mass	Stage III adenocarcinoma	None
Family 2							
II-1	56	F	GAPPS	Adenocarcinoma	Normal	Normal	None
II-2	Unknown	M	GAPPS	Adenocarcinoma	Multiple polyps	Unavailable—reported to be benign	None
II-5	75	M	Unknown	Adenocarcinoma	Unknown	Unknown	None
II-8	48	F	GAPPS	No	Rectal polyps	Tubular adenoma	None
II-9	50	M	GAPPS	Adenocarcinoma	Unknown	Unknown	None
II-11	21	M	GAPPS	No	Normal	Normal	None
II-12	23	F	GAPPS	No	Rectosigmoid polyp	Hyperplastic polyp	None
II-13	18	F	Normal	No	Normal	Normal	None
II-14	20	F	GAPPS	No	Caecal polyp	Inflammatory polyp	None
II-15	51	F	Multiple fundic polyps	No	Normal	Normal	None
II-22	57	M	GAPPS	No	Sigmoid polyp	Tubular adenoma	Thyroid
II-24	51	M	Normal	No	Normal	Normal	None
II-25	50	F	GAPPS	Adenocarcinoma	Unknown	Unknown	None
II-30	41	M	Normal	No	Normal	Normal	None
II-50	26	F	Normal	No	Normal	Normal	None

			Stomach diagnosis		Colon diagnosis		
ID	**Age at diagnosis**	**Gender**	**EGD findings**	**Gastric cancer**	**Colon polyps**	**Pathology**	**Other cancers**
II-51	27	F	1 fundic polyp, 4 antral polyps	No	Normal	Normal	None
II-70	Unknown	F	Unknown	Unknown	Unknown	Unknown	Leukaemia

EGD, esophagoduodenoscopy.

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Table 2

Targeted cancer gene mutational analysis from gastric adenocarcinoma and colon polyps of patients affected by gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)

Patient	Site/pathology	Gene	Genomic coordinate	Transcript and nucleotide	Amino acid	Cosmic ID
I-1	Gastric adenocarcinoma	GNAS	chr20:57484420	NM_000516; c.601C>T	p.R201C	COSM27887
		KRAS	chr12:25398284	NM_033360.3; c.35G>T	p.G12V	COSM520
		PIK3CA	chr3:178916945	NM_006218.2; c.332_334delAGA	p.K111del	COSM750
	Colonic villous adenoma	KRAS	chr12:25398285	NM_033360; c.34G>T	p.G12C	COSM516
		CDKN2	chr9:21971186	NM_000077.4; c.172C>T	p.R58del	COSM12473
II-8	Colonic tubular adenoma	FBXW7	chr4:153249384	NM_033632.3; c.1394G>A	p.R465H	COSM22965