Rare *APC* promoter 1B variants in gastric cancer kindreds unselected for fundic gland polyposis

Although multiple demographic, environmental and genetic factors contribute to gastric cancer (GC) risk, familial clustering occurs in around 10%–15% of cases.[1] A strong genetic predisposition underlies 1%–3%, with hereditary diffuse GC (HDGC) accounting for the majority of GC kindreds. Familial clustering of intestinal type GC is observed in gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) and familial intestinal GC (FIGC).[2] While the genes involved in FIGC have not been well defined, variants in the promoter 1B of *APC* have been identified in individuals with GAPPS and in rare families with familial adenomatous polyposis.[3] However, the prevalence of *APC* promoter variants in molecularly undiagnosed GC kindreds unselected for fundic gland polyposis is unknown.

To investigate the contribution of *APC* promoter variants to GC predisposition in families lacking causal germline variants *CDH1*, which account for 19%–40% of HDGC, we performed multigene sequencing in 259 individuals from 254 families ascertained on the basis of personal and/or family history of GC (table 1). This included 174 individuals meeting International Gastric Cancer Linkage Consortium criteria for HDGC and one meeting criteria for FIGC.[4] The majority (76.8%) of individuals had a personal history of GC, with 85.4% diffuse GC and median age of diagnosis of 42 years (range 9–87). Six additional individuals were potential obligate carriers for GC predisposition. The *APC* promoter 1B was analysed by next-generation sequencing (n=232) or Sanger sequencing (n=27) in all index cases.

We identified a pathogenic variant (*APC* c.-191T>C) in an obligate carrier meeting clinical criteria for HDGC (figure 1). The index case (III-8) was diagnosed with prostate cancer at the age of 73, following a diagnosis of GC in two children. IV-2 initially presented with lower abdominal pain, distension and ascites at 37 years of age. Upper GI endoscopy revealed a gastric mass and multiple 3 mm polypoid lesions throughout the stomach and fundus with sparing of the distal half of the gastric antrum. The patient subsequently succumbed to a stage IV diffuse GC within 3 weeks of the initial presentation. IV-4 presented with severe abdominal pain, anorexia and emesis at 39 years of age and had guaiac-positive stool on admission to hospital. Tumour metastases of unknown

Table 1 Personal and family GC history in index cases assessed for germline variants in the *APC* promoter 1B

		Family history of GC, no of index cases*			
Personal cancer history	**No of index cases**	**HDGC**	**FIGC**	**Any GC**	**None**
Personal history of GC†	199	149	1	16	33
Other cancer history‡					
Obligate carrier	2	2	0	0	0
Non-obligate carrier	38	12	0	26	0
Unaffected					
Obligate carrier	4	4	0	0	0
Non-obligate carrier	16	7	0	9	0
Total	259	174	1	51	33

*Family history of GC in first-degree and second-degree relatives.
†Index case GC subtypes: diffuse GC (n=170), intestinal GC (n=10), mixed (n=4), not otherwise specified (n=15).
‡Other cancer types: breast (n=31), colon (n=4), ovarian (n=1), prostate (n=2), skin (n=2), thymoma (n=1), uterine (n=1). Two index cases were affected by more than one cancer type.
DGC, diffuse gastric cancer; FIGC, familial intestinal gastric cancer; GC, gastric cancer; HDGC, hereditary diffuse gastric cancer; IGC, intestinal gastric cancer.

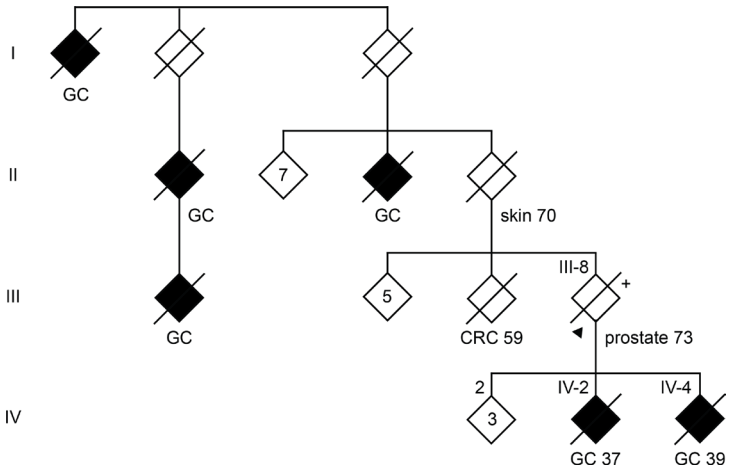

Figure 1 Pedigree of an unreported family meeting clinical criteria for hereditary diffuse gastric cancer (GC) and found to carry a pathogenic variant in the *APC* promoter 1B. CRC, colorectal cancer; GC, gastric cancer.

origin were identified in the liver, but the patient passed away prior to the diagnosis of a primary intestinal type GC identified on autopsy. Notably, despite diffuse tumour involvement in the gastric mucosa, coarsely granular to polypoid texture was observed and suggests the possibility of precancerous gastric polyposis. Unfortunately, we were unable to assess segregation of the *APC* c.-191T>C variant in this family, nor were we able to investigate florid gastric polyposis in the index case. However, fundic gland polyposis with antral sparing identified in one child and possible gastric polyposis in another was consistent with the characteristic GAPPS phenotype.

Although several families have been reported in the literature, clinical knowledge of GAPPS is limited.[5–9] Our findings suggest that GAPPS-associated variants are rare among individuals at risk for inherited predisposition to primarily diffuse GC, identified in one kindred with a history of gastric polyposis evaluated retrospectively. Based on current clinical criteria, this phenotype would have indicated genetic assessment for GAPPS. Thus, genetically undiagnosed GC families with a history of fundic gland polyposis should undergo testing of *APC*, including the promoter 1B, to exclude the possibility of GAPPS. Genetic assessment of families meeting multiple syndromic criteria can be achieved by multigene sequencing. Consequently, as inclusion of the *APC* promoter 1B becomes more widely adopted in clinical panels, genetic testing in individuals unknown to have a history of gastric polyposis may reveal previously unrecognised GAPPS families.

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