

A rare upstream regulatory region mutation in APC presenting as classical familial adenomatous polyposis: A case report and literature review

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Abstract. Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary syndrome primarily characterized by extensive colorectal adenomatous polyps and a substantially increased risk of colorectal cancer (CRC). FAP typically results from germline mutations within the coding regions of the adenomatous polyposis coli (*APC*) gene. However, mutations involving noncoding regulatory regions, particularly *APC* promoter 1B, have recently been identified. The present study reports a rare pathogenic variant (c.-30266G>A) located far upstream from the typical promoter 1B region in a 63-year-old patient presenting with classical features of FAP, including extensive colorectal polyposis and CRC. Notably, despite this variant's known association with gastric adenocarcinoma and proximal polyposis of the stomach, the patient exhibited no gastric involvement. Cascade genetic testing identified the same variant in the patient's daughter, who remains asymptomatic. Overall, this case highlights the phenotypic variability and diagnostic challenges associated with noncoding *APC* mutations and underscores the importance of including distal regulatory regions in genetic

testing panels for patients with FAP lacking coding-region mutations. Further research is required to elucidate the exact molecular mechanisms and broader clinical implications of these noncoding variants.

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited syndrome that predisposes individuals to colorectal cancer (CRC), primarily due to germline mutations in the adenomatous polyposis coli (*APC*) gene located on chromosome 5q21-22. Affected individuals typically develop numerous colorectal adenomatous polyps during adolescence or early adulthood, which inevitably progress to CRC if left untreated (1-3). *APC*-associated polyposis conditions include classic FAP, attenuated FAP, and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), all of which are linked to germline *APC* mutations but exhibit distinct clinical presentations (4).

In FAP, *APC* mutations are most commonly located within the gene's coding regions; mutations in the promoter region are relatively rare. Germline point mutations in the promoter 1B region of the *APC* gene have been identified as a major cause of GAPPS, which is an autosomal dominant syndrome. GAPPS is primarily characterized by extensive fundic gland polyposis and a markedly increased risk of gastric cancer; however, it does not involve colorectal polyposis, which is typically observed in FAP. The present study reported a rare case involving a pathogenic variant located in a noncoding upstream regulatory region of *APC*, beyond the typical promoter 1B region, in an individual who presented with clinical features characteristic of classical FAP (5).

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Case report

A 63-year-old man with no previous personal or family history of CRC presented to Kaohsiung Medical University Chung-Ho Memorial Hospital (Kaohsiung, Taiwan) in March 2023 with a 1-week history of abdominal pain and hematochezia. A colonoscopy revealed >100 polyps distributed from the upper rectum to the ascending colon (Fig. 1A), along with a suspicious lesion near the hepatic flexure of the ascending colon (Fig. 1B). A biopsy of the lesion confirmed adenocarcinoma. Contrast-enhanced abdominal computed tomography revealed a colonic malignancy at the hepatic flexure with pericolic infiltration, and the clinical stage was cT4bN1M0 (Fig. 2A).

Given the extensive colonic polyposis and confirmed malignancy at the hepatic flexure, the patient underwent a subtotal colectomy with end-to-end ileorectal anastomosis. Postoperative histopathological analysis confirmed a moderately differentiated adenocarcinoma of the hepatic flexure, which was staged as pT3N0M0 (Stage IIA), along with >100 tubulovillous adenomas observed throughout the resected colon (Fig. 2B). Paraffin-embedded tissue sections were stained with hematoxylin and eosin (H&E) according to a standard protocol. Briefly, tissue samples were fixed in 10% neutral buffered formalin at room temperature (~22°C) for 8 h before being embedded in paraffin. Sections 4- μ m thick were cut using a microtome. H&E staining was performed with hematoxylin at room temperature for 10 min followed by eosin for 2 min. Histopathological examination revealed irregular dysplastic glands infiltrating into the submucosa and muscularis propria, accompanied by a prominent desmoplastic stromal reaction (Fig. 3). At higher magnification, the tumor was found to have an atypical glandular structure with nuclear pleomorphism, hyperchromasia and loss of normal glandular polarity within a fibrotic stroma, consistent with moderately differentiated adenocarcinoma (Fig. 4).

Postoperatively, the patient received six cycles of adjuvant chemotherapy with the FOLFOX-6 regimen, which consisted of oxaliplatin (85 mg/m² on day 1), leucovorin (400 mg/m² on day 1) and 5-fluorouracil administered as an intravenous bolus (400 mg/m² on day 1) followed by continuous infusion (2,400 mg/m² over 46 h), repeated every 2 weeks. After completion of adjuvant chemotherapy, the patient was regularly followed up at the outpatient clinic. Postoperative surveillance was scheduled every 3 months, including physical examination and measurement of serum carcinoembryonic antigen levels. In addition, abdominal computed tomography and colonoscopic examinations were performed annually. The most recent follow-up visit was in July 2025.

Owing to the extensive number of adenomatous polyps, FAP was suspected, prompting genetic testing. Genomic DNA was extracted from peripheral blood and analyzed externally by Invitae Corporation, using the Invitae Multi-Cancer Panel according to the manufacturer's instructions. This panel includes sequencing and deletion/duplication analysis of 100 cancer-related genes, including *APC*, *CDHI* and *RECQL4*. Target regions were enriched using a hybridization-based capture protocol and sequenced on an Illumina next-generation sequencing platform (Illumina, Inc.). All coding exons, \pm 20 base pairs of flanking intronic regions, and selected clinically relevant noncoding regions, including the *APC* promoter

1B, were analyzed. Variants were identified by alignment to the GRCh37 reference genome, and results were interpreted using clinically validated transcripts. Copy number variants were assessed using a validated read-depth-based algorithm, and variant classification was conducted according to the American College of Medical Genetics and Genomics guidelines. Confirmatory testing, when required, was performed using orthogonal methods (6). Genetic testing revealed a heterozygous pathogenic variant in *APC* (c.-30266G>A), located in a noncoding upstream region beyond the typical promoter 1B (Fig. 5). This variant has been predominantly associated with GAPPS, rather than classical FAP (5). However, in the present case, the patient exhibited a clinical phenotype consistent with FAP, including extensive colorectal polyposis and progression to CRC.

Given the presumed germline origin of this pathogenic variant, cascade testing was recommended. Neither the patient nor the patient's family had a history of CRC or FAP-related conditions. After establishing the diagnosis, genetic testing was recommended for all three of the patient's children - two sons and one daughter. However, only the daughter underwent testing, for whom the results of the analysis revealed the same heterozygous pathogenic variant (c.-30266G>A) in the upstream regulatory region of *APC*, located beyond the classical promoter 1B region. At the time of drafting this manuscript, upper endoscopy and colonoscopy of the daughter showed no evidence of FAP or GAPPS, indicating the absence of phenotypic expression despite the daughter's confirmed genetic predisposition (data not shown). Despite being asymptomatic, regular surveillance was recommended. The daughter was advised to return to the Outpatient Clinic annually for clinical evaluation and endoscopic examination to allow early detection of any adenomatous changes.

Discussion

GAPPS is a rare autosomal dominant hereditary syndrome characterized by fundic gland polyposis and a markedly increased risk of gastric adenocarcinoma. Germline point mutations in the *APC* promoter 1B region, such as c.-191T>C and c.-195A>C, have been shown to disrupt transcription factor binding sites, resulting in reduced *APC* expression in gastric mucosa. Iwatsuki *et al* (7) demonstrated the diagnostic significance of these mutations, particularly in families without classic colorectal polyposis. Similarly, Dixon *et al* (8) reported a pathogenic *APC* promoter 1B variant in a family meeting the criteria for hereditary diffuse gastric cancer, with a retrospective analysis revealing clinicopathological features consistent with GAPPS. Overall, these findings support the inclusion of *APC* promoter 1B in multigene panels for individuals or families with an unexplained predisposition to gastric cancer, even in the absence of overt polyposis or colonic involvement.

In the present case, the detected mutation (c.-30266G>A) is located considerably farther upstream from the transcription start site when compared with the classical *APC* promoter 1B mutations, such as c.-191T>C and c.-195A>C. Specifically, c.-30266G>A is situated ~30,266 bases upstream of the translation initiation codon (ATG), whereas c.-191T>C and c.-195A>C are located only 191 and 195 bases upstream, respectively. Given this substantial distance, c.-30266G>A may lie outside

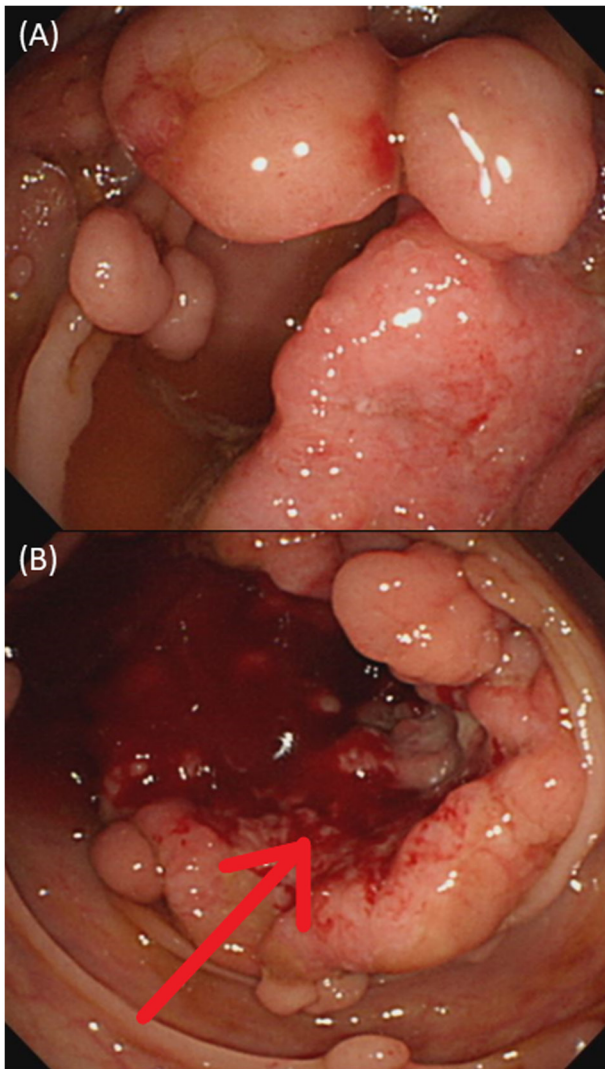


Figure 1. (A) Colonoscopy revealed hundreds of polyps distributed from the upper rectum to the ascending colon. (B) Colonoscopy demonstrated a malignant lesion at the hepatic flexure of the ascending colon (red arrow).

the currently defined *APC* promoter 1B region and may involve more distal regulatory elements that have yet to be completely characterized. Despite the lack of functional evidence, this variant may affect the expression of *APC* by altering its transcription factor binding or local chromatin structure. This positional difference suggests that although these variants all affect the noncoding regulatory regions of *APC*, they may modulate gene expression through different mechanisms or act on different tissue-specific transcriptional controls. Therefore, c.-30266G>A should be considered distinct from the classical promoter 1B mutations described in the literature. However, there is currently a lack of studies investigating the pathogenic mechanism of this specific variant, and further research is needed to elucidate its underlying biological significance.

Notably, although both the patient and the patient's daughter carried the germline c.-30266G>A mutation, neither has exhibited gastric fundic gland polyposis or gastric adenocarcinoma to date. Disruptions in the upstream regulatory elements of *APC* can reduce transcriptional activity and diminish *APC* protein levels. Such promoter-level defects alter the gene's dosage effect and may clinically present as classical

FAP rather than GAPPS, indicating the functional relevance of promoter integrity in modulating disease phenotype. Similarly, rare cases of early-onset CRC associated with *APC* germline mutations have been reported, including a case involving a 10-year-old patient who developed advanced CRC harboring both germline and somatic *APC* mutations (9). These findings underscore the phenotypic heterogeneity associated with *APC* alterations, extending beyond the classical FAP and GAPPS presentations. Accordingly, this case highlights the phenotypic variability associated with *APC* noncoding mutations and demonstrates the importance of considering a broader clinical spectrum—including both FAP and GAPPS presentations - when evaluating individuals carrying such variants. This discussion systematically compares the current c.-30266G>A variant with previously reported *APC* promoter 1B mutations and highlights potential molecular and regulatory mechanisms underlying the observed phenotypic differences.

Recent evidence reveals that deletions involving the *APC* promoter 1B region may be an underrecognized cause of classical FAP, particularly in patients who were initially negative for coding-region mutations. Kadiyska *et al* (10) identified a novel deletion involving the entire *APC* promoter 1B in a Bulgarian family with a classical FAP phenotype, despite negative results from standard sequencing and multiplex ligation-dependent probe amplification (MLPA) assays. Performing an updated MLPA assay with probes specific for promoter 1B, together with high-resolution array comparative genomic hybridization and long-range polymerase chain reaction, could enable accurate breakpoint characterization of this deletion. This combined approach demonstrates how complementary techniques can reliably detect and validate structural changes in the noncoding regulatory regions of *APC*. Functional assays confirmed the pathogenicity of this regulatory region alteration by demonstrating significantly reduced *APC* expression. Similarly, Azzopardi *et al* (11) identified *APC* promoter 1B deletions in multiple unrelated Italian families, indicating a founder effect; the affected individuals consistently presented with classical FAP features, including hundreds to thousands of colonic adenomas, but lacked gastric polyposis, suggesting a phenotype distinct from GAPPS. Overall, these findings demonstrate the clinical significance of promoter 1B deletions in the pathogenesis of FAP and underscore the importance of including this noncoding region in routine genetic testing for patients with an FAP phenotype who are negative for coding-region mutations in *APC*.

Yang *et al* (12) identified a rare point variant (c.-190G>A) in the *APC* promoter 1B region in a family exhibiting classical FAP features, despite negative results from conventional gene panels and MLPA analysis. By using whole-exome sequencing and functional dual-luciferase reporter assays, Yang *et al* (12) demonstrated that this noncoding variant significantly suppressed *APC* transcriptional activity, supporting its pathogenicity. These findings demonstrate the critical role of noncoding regulatory regions, such as promoter 1B, in the genetic evaluation of FAP, particularly in cases that test negative on standard diagnostic panels.

Although the present case also involves a noncoding regulatory variant upstream of *APC*, the c.-30266G>A mutation is located considerably beyond the classical promoter 1B region. Nevertheless, the patient's presentation with classical FAP supports the notion that mutations in *APC* regulatory elements,

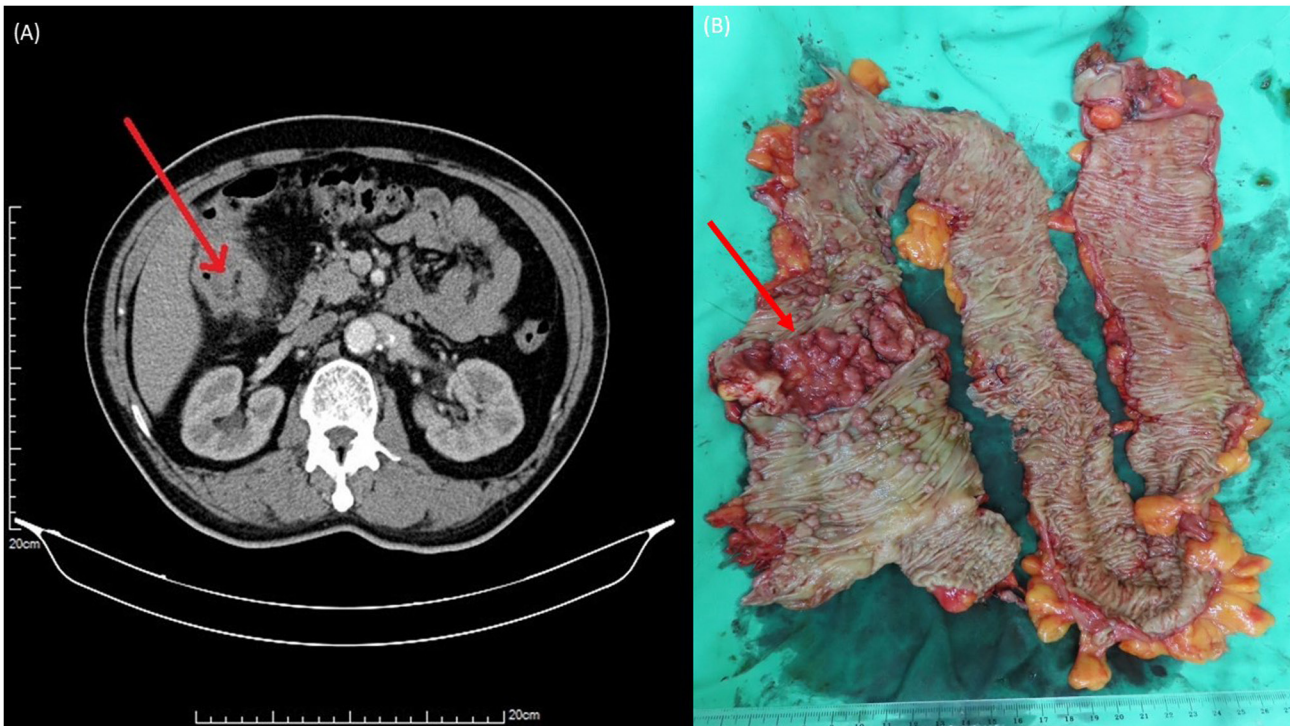


Figure 2. (A) Abdominal computed tomography revealed a colonic malignancy at the hepatic flexure with pericolic infiltration, and it was clinically staged as cT4bN1M0 (red arrow; scale bar, 20 cm). (B) The figure shows the gross appearance of the excised colon specimen, demonstrating a circumferential ulcerative lesion at the hepatic flexure (red arrow), consistent with adenocarcinoma. Multiple tubulovillous adenomas, numbering over 100, were observed throughout the resected colon.

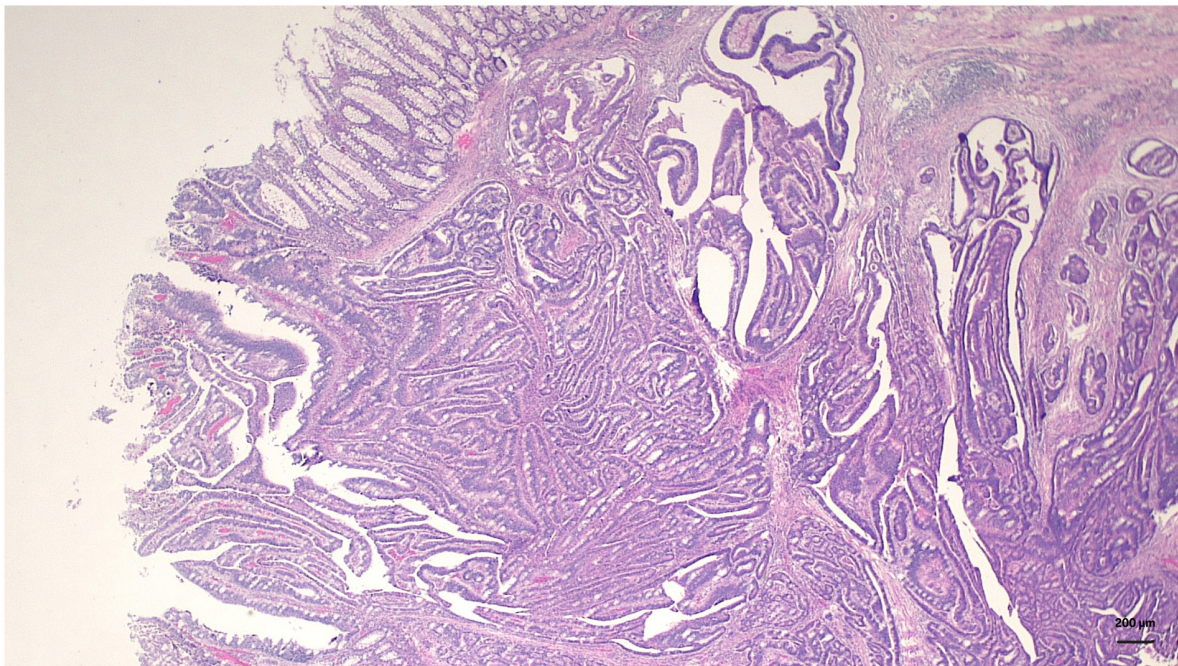


Figure 3. Histopathological examination at low magnification, revealing irregular dysplastic glands infiltrating into the submucosa and muscularis propria, accompanied by a prominent desmoplastic stromal reaction (hematoxylin and eosin; magnification, x100; scale bar, 200 μ m).

whether within or beyond promoter 1B, may contribute to FAP development. Despite these observations, the exact molecular mechanisms through which regulatory region mutations contribute to FAP pathogenesis remain elusive and warrant further investigation. As the present findings were derived

from a single patient, they should be interpreted with caution. Generally, the intrinsic limitation of case reports is the absence of statistical power and external validity. Therefore, the present findings should be regarded as preliminary and hypothesis-generating, pending confirmation in larger cohorts.

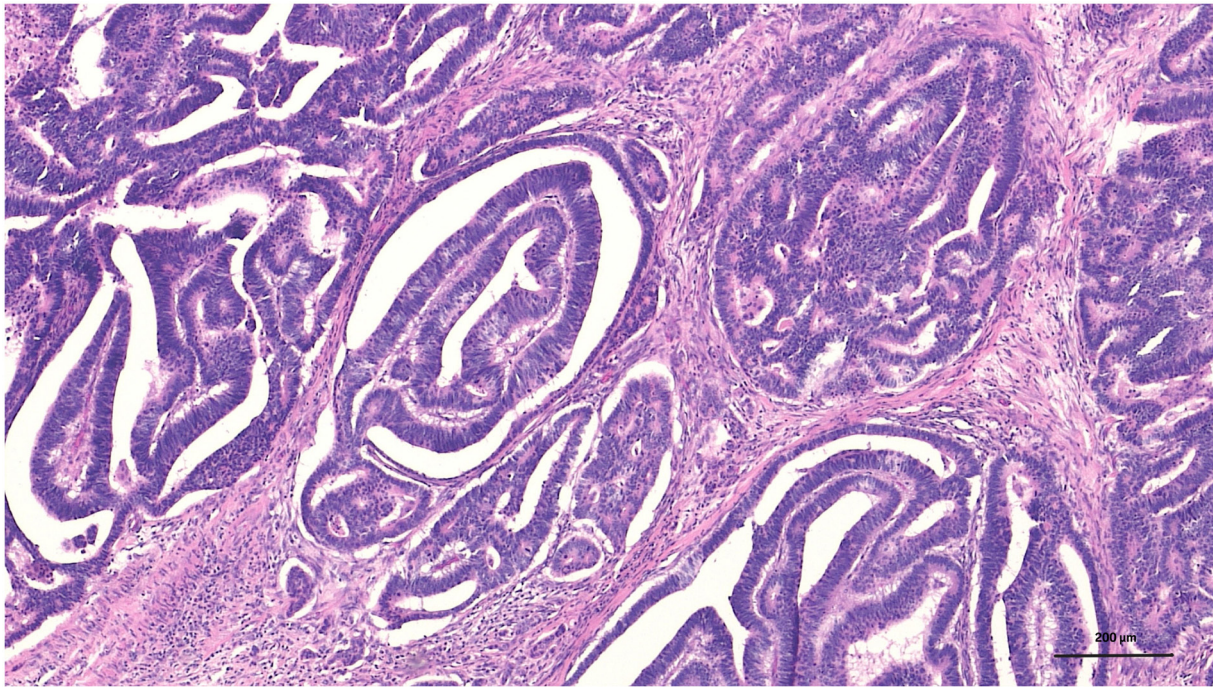


Figure 4. Histopathological examination at high-power view demonstrating atypical glandular structures with nuclear pleomorphism, hyperchromasia, and loss of glandular polarity within a fibrotic stroma, consistent with moderately differentiated adenocarcinoma (hematoxylin and eosin; magnification, x400; scale bar, 200 μm).

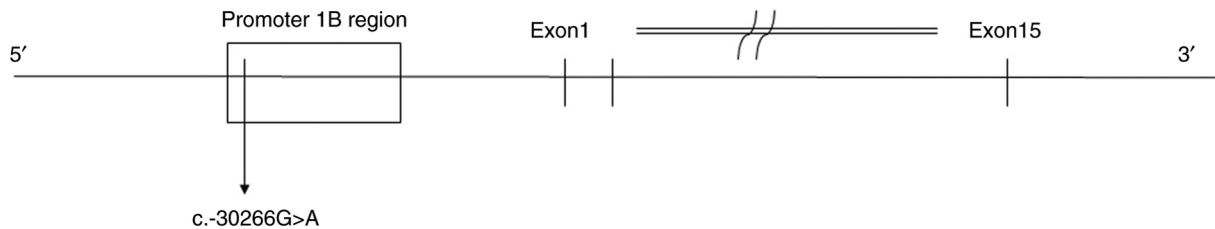


Figure 5. Schematic of the *APC* structure depicting the promoter 1B region and exons. The pathogenic germline variant identified in the patient, c.-30266G>A, is located in an upstream region of promoter 1B, farther from the commonly reported core hotspot variants (e.g., c.-191T>C and c.-195A>C). For simplicity, only exons 1 and 15 are depicted

In conclusion, this rare case of FAP associated with a point mutation in the noncoding upstream regulatory region of *APC*, located beyond the classical promoter 1B region, highlights the pathogenic role of distal regulatory elements. The findings underscore the importance of including both promoter 1B and adjacent upstream regions in extended genetic testing panels for patients with unexplained FAP phenotypes. However, due to the single-case nature of this report, the results should be interpreted with caution and validated through larger studies.

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Availability of data and materials

The data generated in the present study may be found in the Sequence Read Archive under accession number

RJNA1338078 or at the following URL: <https://www.ncbi.nlm.nih.gov/sra/PRJNA1338078>.

Authors' contributions

JYW and HLT were involved in the study conception and design. CWH, WCS, TKC performed data collection. YCC contributed by performing analysis and interpretation of results. CHY drafted the manuscript. All authors reviewed the results and approved the final version of the manuscript. JYW and YCC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB) [Kaohsiung, Taiwan; approval no. KMUHIRB-E(I)-20230267].

Patient consent for publication

The patient and the patient's daughter provided written informed consent for publication of this case report and any accompanying data and images.

Competing interests

The authors declare that they have no competing interests.

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