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A novel indel in APC Promotor 1B is associated with both stomach and colon polyposis

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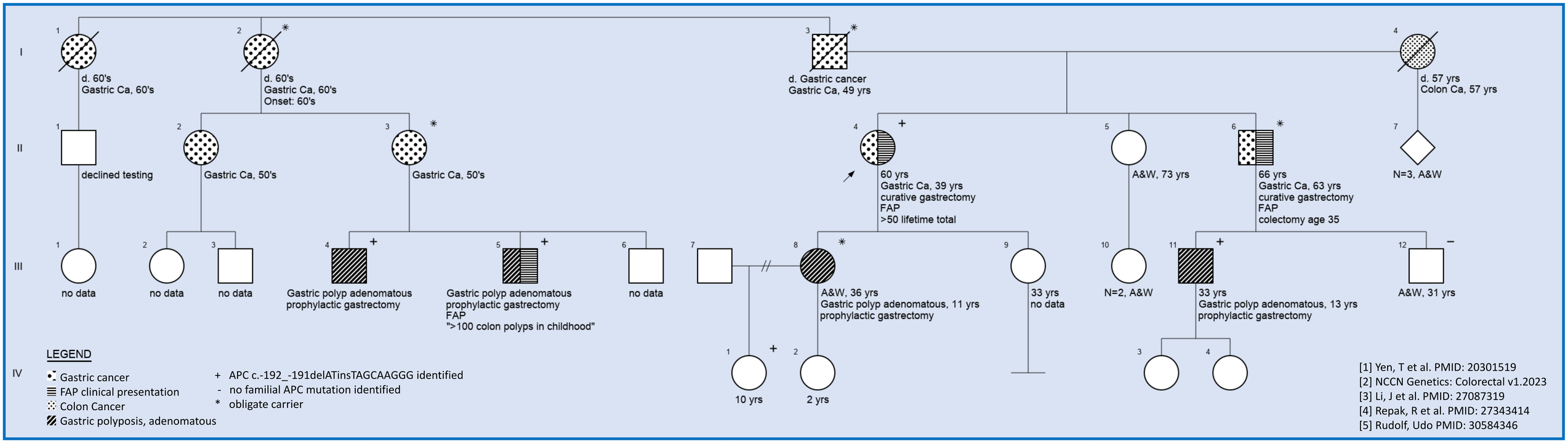

[1] Yen, T et al. PMID: 20301519
[2] NCCN Genetics: Colorectal v1.2023
[3] Li, J et al. PMID: 27087319
[4] Repak, R et al. PMID: 27343414
[5] Rudolf, Udo PMID: 30584346

Background

- Pathogenic alterations in *APC* cause the autosomal dominant conditions familial adenomatous polyposis (FAP) and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS).
- GAPPS and FAP are treated as distinct diagnoses with different NCCN screening guidelines [2].
- *APC* has two main transcripts which have different promoters, referred to as Promoter 1A (NM_000038) and promoter 1B (NM_001127511).
- Most pathogenic alterations identified in patients with FAP are associated with the promoter 1A **transcript**, whereas GAPPS has only been shown to be caused by pathogenic alterations in the 1B promoter region [1].

Case Description

- Genetic testing ordered for proband due to personal history of gastric cancer with curative gastrectomy at age 39 and colon polyposis.
- Family history reported to be significant for gastric cancer, numerous relatives with prophylactic gastrectomies due to gastric polyposis, colon polyposis, and colectomies (see pedigree).
- Genetic testing identified an *APC* 1B promoter variant: c.-192_-191delATinsTAGCAAGGG (NM_001127511)
- Cascade testing in this family identified additional affected carriers and obligate carriers of this alteration.
- Early onset gastric cancer, gastric polyposis, and adenomatous colonic polyposis co-occur with *APC* c.-192_-191delATinsTAGCAAGGG in this family.

1B Promoter

A T G G
-192 -191 -190 -189

- Promoter 1B positions -192A, -191T , -190G, and -189G are highly conserved transcription factor binding sites for promotor 1B [3].

T A G C
-192 -191 -190 -189

- *APC* c.-192_-191delATinsTAGCAAGGG changes three of these highly conserved nucleotides and is expected to disrupt transcription.
- Single nucleotide changes at c.-192A and c.-191T have been identified as pathogenic alterations associated with GAPPS but without reported colon polyposis [3-5].

Conclusions and Next Steps

1. Other complex *APC* promoter 1B pathogenic alterations have been reported in association with colonic polyposis in GAPPS patients.
2. Patients with GAPPS should have colonoscopy at diagnosis and at intervals after diagnosis.
3. Further research is needed to clarify the optimal colonoscopy interval as the genotype-phenotype relationship is better characterized.