Bridging the Gap in GAPPS: Clinical Testing, Characteristic Features, and Gastric Cancer Screening

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Background

- Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a newly-described syndrome characterized by diffuse fundic gland polyps (FGPs) and an increased risk of gastric cancer.[1-3]
- Point mutations in the YY1 binding motif of *APC* promoter 1B were recently found to cause GAPPS.
- We aimed to describe the results of clinical testing for GAPPS in individuals primarily suspicious for familial adenomatous polyposis (FAP) and/or attenuated FAP.

APC-only and *APC* plus MUTYH positive and VUS rates

	APC-only		*APC* plus *MUTYH*	
	N	%	N	%
Total tests	28	100%	58	100%
Total *APC* positive	9	32.1%	5	8.6%
YY1 positive	1	3.6%	0	0.0%
Total VUS	1	3.6%	2	3.5%
YY1 VUS	0	0.0%	0	0.0%

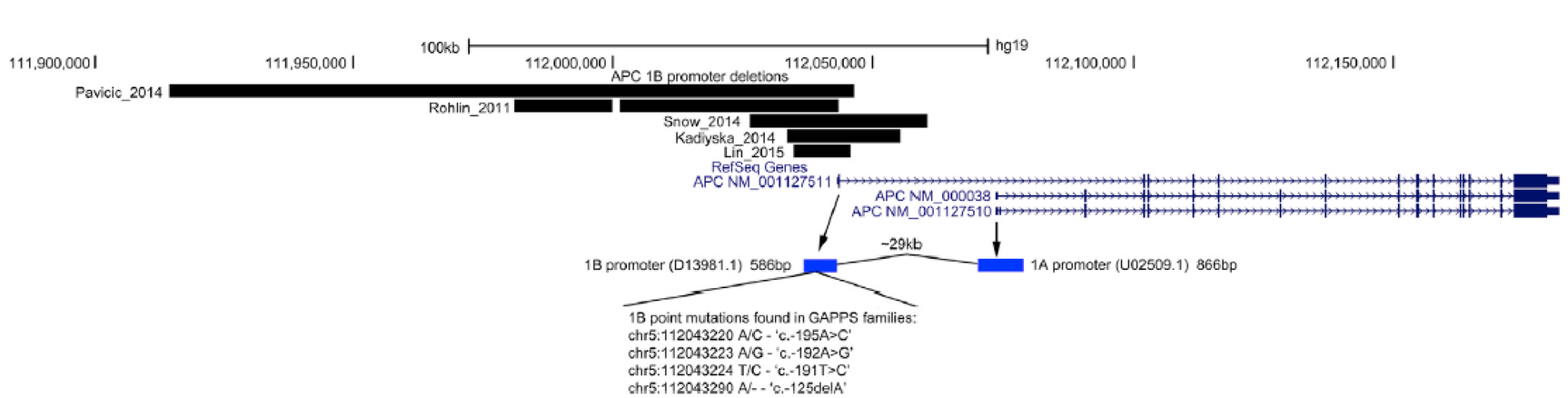
Methods

- Data from clinical testing of *APC*-only and *APC* plus MUTYH from 01/06/2017-03/31/2017 at Ambry Genetics were retrospectively reviewed.
- Comprehensive *APC* testing was performed, including sequencing of the YY1 binding motif.
- Multi-gene panel tests (MGPTs) were excluded.
- Both pathogenic and likely pathogenic alterations in *APC* were considered positive. Variants of uncertain significance (VUSs) were evaluated separately.

Results

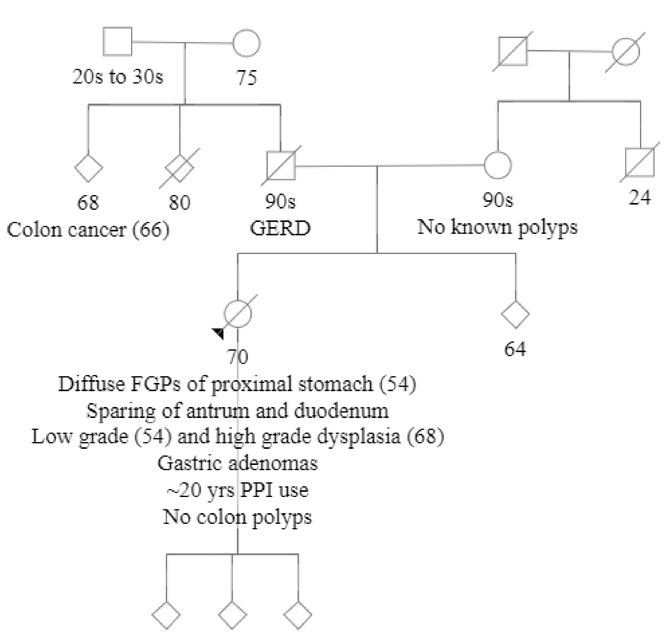
- There were 28 *APC*-only and 58 *APC* plus *MUTYH* tests, with nine and five *APC* mutations found, respectively.
- One YY1 point mutation (c.-191 T>C) was found in the *APC*-only cohort and accounted for 11.1% of all mutations detected in that group.
- No YY1 point mutations were found in the *APC* plus *MUTYH* cohort and no YY1 variants of unknown significance were found in either group.
- Cascade testing revealed two additional positive family members and both were subsequently found to have fundic gland polyposis and low grade dysplasia after undergoing screening endoscopies.

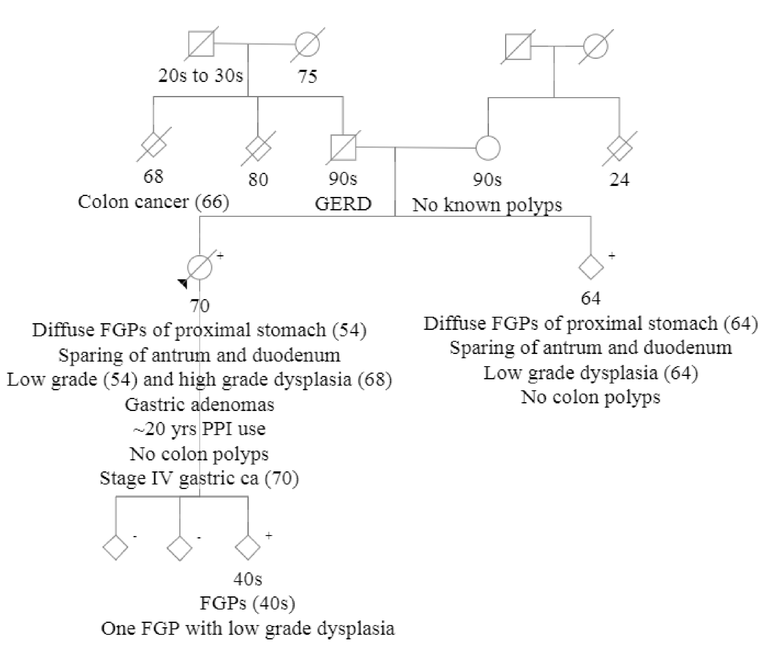
Schematic of promoters 1A and 1B in *APC*, including deletions reported in FAP and point mutations in GAPPS



Li J et al. Point Mutations in Exon 1B of APC Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant. Am J Hum Genet. 2016 May 5;98(5):830-842.

Personal and family history before and after genetic testing





Conclusions

- Promoter 1B YY1 sequencing is now clinically available and should be included in *APC* testing.
- Dysplasia in FGPs is common in GAPPS and rare in the general population
- Dysplasia in a FGP is a red flag for GAPPS and should be including in the genetic testing criteria for *APC*.
- A positive family history may not be conveyed in cases with GAPPS, as FGPs may be underreported in these families.
- Gastric cancer screening in the proband described here was unsuccessful, as over 20 gastroscopies revealed no cancer, even though a stage IV gastric cancer was present.

References

1. Li J et al. Point Mutations in Exon 1B of APC Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant. Am J Hum Genet. 2016 May 5;98(5):830-842.
2. Repak R et al. The first European family with gastric adenocarcinoma and proximal polyposis of the stomach: case report and review of the literature. Gastrointest Endosc. 2016 Oct;84(4):718-25.
3. Jasperson et al. APC-Associated Polyposis Conditions. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.