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N-terminal Truncating Variants in APC in Patients Without Overt Familial Adenomatous Polyposis

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BACKGROUND

Truncations: Pathogenicity and Exceptions

- Pathogenicity of nonsense and frameshift variants in loss-of-function (LOF) genes is due to premature protein truncation and/or nonsense-medicated decay (NMD)
- However, N-terminal truncations may not be subject to NMD[1,2]

Phenotype and *APC*

- Truncating variants in the *APC* gene are associated with a classic or attenuated form of familial adenomatous polyposis (FAP/AFAP)
- Review of phenotype in patients with *APC* truncating variants is relevant for confirming the molecular diagnosis
- Although there is variable age of onset and polyp burden[4], patients with truncating variants generally have at least one or more features associated with FAP/AFAP, which may not become apparent until an initial screening colonoscopy after age 45

Aims

- Here, we identify *APC* truncations in which the premature termination codon (PTC) is within the first several amino acids of coding exon 1 in patients without an overt FAP/AFAP phenotype.

METHODS

- Clinical curation for all internal patients with N-terminal truncations with PTC upstream of the first alternate start codon, p.M18, in *APC*. Review and comparison of this phenotypic data compared to typical FAP/AFAP presentation.

REFERENCES

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2. Lambertz S, Ballhausen WG. Identification of an alternative 5' untranslated region of the adenomatous polyposis coli gene. Hum Genet. 1993 Feb;90(6):650-2.
3. Stanich PP, Pearlman R, Hinton A, Gutierrez S, LaDuca H, Hampel H, Jasperson K. Prevalence of Germline Mutations in Polyposis and Colorectal Cancer-Associated Genes in Patients With Multiple Colorectal Polyps. Clin Gastroenterol Hepatol. 2019 Sep;17(10):2008-2015.

Figure 1: APC Coding Exon 1

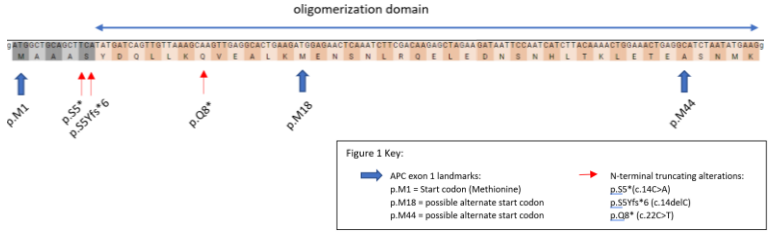

Figure 2: Pedigrees

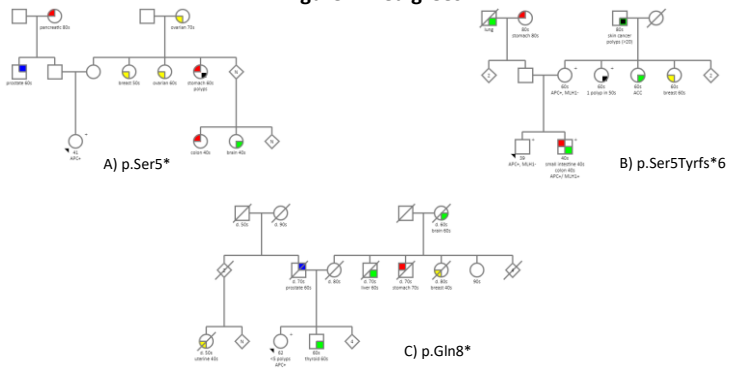

Table 1: Phenotypic data

APC alteration	Proband Phenotype	Family Phenotype
c.14C>A (p.Ser5*)	41-year-old apparently unaffected* female	SDRs • grandmother ovarian cancer 70s • aunt breast 50s • aunt ovarian 60s • aunt stomach 60s (unspecified **colon polyps**) • cousin **colon cancer** 40s • cousin brain 40s • grandmother pancreatic 80s • uncle prostate 60s
c.14delC (p.Ser5Tyrfs*6)	39-year-old apparently unaffected* male	FDRs • brother **small intestine cancer** and metachronous **colon cancer** in early 40s – *APC*+ and has a **pathogenic gross deletion in *MLH1*** • apparently unaffected* mother (60s) *APC*+, *MLH1*- SDRs • aunt *APC*+ (**one tubular adenoma** in 50s) • aunt adrenocortical carcinoma • grandfather (80s) with reported multiple skin cancers and >20 unspecified **polyps** • grandmother stomach 80s
c.22C>T (p.Gln8*)	62-year-old female with <5 unspecified **polyps** identified over 3-4 colonoscopies	FDRs • brother thyroid 60s • father prostate 60s SDRs • aunt breast 40s • uncle stomach 70s • grandmother brain 60s • cousin endometrial 40s • half-aunt breast in 40s and ovarian in 50s

* "Apparently unaffected" denotes individuals whose colonoscopy status is unknown

TAKE-HOME POINTS

- N-terminal truncations may not be associated with overt FAP/AFAP phenotype
- Pathogenicity for N-terminal truncating variants may be mitigated by other, yet unidentified, mechanisms.
- Utilization of phenotype for highly penetrant genes for variant classification and clinical management is valuable and relevant

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