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

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Background: Individuals with truncating alterations in the *APC* gene typically present with a classic or attenuated form of familial adenomatous polyposis (FAP/AFAP). The mechanism for pathogenicity of nonsense and frameshift alterations in loss-of-function genes is well established to be premature protein truncation and/or nonsense-medicated decay (NMD); however, N-terminal truncations may be an exception due to incorrect annotation or several rescue mechanisms including use of multiple translational start codons, translation re-initiation, use of unconventional (non-AUG) translational start sites, and/or escape of NMD. As such, review of genotype-phenotype correlations for N-terminal truncations in highly penetrant genes may reveal atypical clinical presentations. Here, we identify a group of *APC* truncations in which the premature termination codon is within the first several amino acids of coding exon 1 in patients without a polyposis phenotype.

Case Presentation: The clinical data for three patients, tested at a commercial diagnostic laboratory, with unique truncating alterations in *APC* and whose personal and/or family histories do not exhibit the classic or attenuated colon polyposis/ cancer diagnoses are presented (Table 1). Information was ascertained through the test requisition form. Limited family member testing is available for only one case.

Discussion: Although the identified alterations are located near or within a highly conserved amino-terminal oligomerization domain that has been established as a critical region for proper dimerization to occur (Figure 1), there is a lack of published data on truncating alterations impacting only the 5' region of this domain. Further, there is a lack of truncating alterations detected in patients with a FAP/AFAP phenotype in multiple databases (including HGMD, ClinVar, and LOVD) upstream of p.R24*, a well described pathogenic alteration. We postulate that one mechanism for this phenomenon may be related to the presence of an in-frame methionine at amino acid position 18, that may serve as an alternate translational start. The variants associated with the phenotypes described here fall short of the attenuated phenotype typically described in distal APC truncations. This case series highlights the importance of careful consideration for N-terminal truncating variants and the historic assumption that they unequivocally produce loss-of-function transcripts or polyposis phenotype.