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APC mosaicism, not always isolated: two first-degree relatives with apparently distinct APC mosaicism

APC mosaicism is briefly mentioned in the recently published BSG guidelines on hereditary colorectal cancer.¹ We wish to present a family that underlines its relevance.

A 26-year-old woman presented at the department of Clinical Genetics at Leiden University Medical Center with osteomas, lipomas, extra tooth and bowel problems. Using Sanger sequencing on leucocyte DNA, a pathogenic APC variant (NM_000038.6:c.4391_4394delAGAG) was detected with variant allele frequency of 20%–40%, indicating mosaicism. Subsequent colonoscopy and gastroduodenoscopy showed >200 colorectal adenomas in a patchy pattern and large variation in size and morphology, extended duodenal and gastric fundic gland polypoidosis. As summarised in table 1, targeted next-generation sequencing (NGS) on three adenomas and multiple normal tissues showed the same APC variant in all samples, suggesting an extensive mosaic pattern.

Seven years earlier, her father presented with >40 colorectal adenomas without germline pathogenic APC or MUTYH variants. However, NGS on colorectal adenomas showed another mosaic APC variant (NM_000038.6:c.3712_3713delAG) while in leucocyte and urine DNA this

Table 1 Overview of all tissues tested with NGS and variant allele frequencies of the detected mosaic variant

Tissue analysed with NGS	Mosaic APC variant	Cov	VAF (%)
Patient 1 (daughter)			
Adenoma 1	c.4391_4394delAGAG	1084	37
Adenoma 2	c.4391_4394delAGAG	1969	45
Adenoma 3	c.4391_4394delAGAG	1806	49
Normal mucosa	c.4391_4394delAGAG	1957	29
Lymph node	c.4391_4394delAGAG	1965	18
Leucocyte	c.4391_4394delAGAG	772	21
Urine	c.4391_4394delAGAG	1119	16
Buccal swab	c.4391_4394delAGAG	666	14
Patient 2 (father)			
Adenoma 1	c.3712_3713delAG	>2000	44
Adenoma 2	c.3712_3713delAG	>2000	24
Adenoma 3	c.3712_3713delAG	>2000	13
Adenoma 4	c.3712_3713delAG	>2000	33
Adenoma 5	c.3712_3713delAG	>2000	33
Adenoma 6	c.3712_3713delAG	94	16
Adenoma 7	X		
Adenoma 8	c.3712_3713delAG	1992	10
Adenoma 9	c.3712_3713delAG	1975	31
Adenoma 10	c.3712_3713delAG	1976	26
Leucocyte	X		
Urine	*		
Buccal swab	X		

In all tissues tested from the daughter (patient 1) the mosaic variant c.4391_4394delAGAG was detected with VAF ranging from 14% to 49%. The mosaic variant of the father (patient 2), c.3712_3713delAG, was solely detected in colonic tissue with a VAF ranging from 10% to 44%.

*Analysis not succeeded due to low amount of DNA in the sample

Cov, coverage, sequencing read count; NGS, next-generation sequencing; VAF, variant allele frequency; X, mosaic variant not found.

variant was absent, suggesting APC mosaicism limited to the colon. Figure 1 illustrates the family.

Previous studies on multiple *de novo* variants^{2,3} discuss two hypotheses: (1) an underlying heritable defect in a DNA

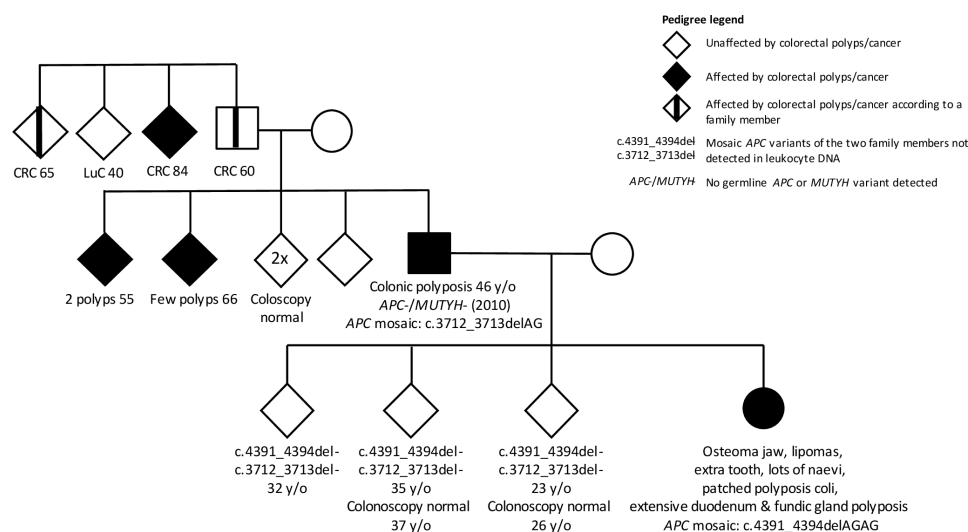


Figure 1 Pedigree of the paternal family of both mosaic patients. The other children of the father were all genetically tested for the two mosaic APC variants in the family (c.4391_4394delAGAG and c.3712_3713delAG) and tested negative. Two of the three children underwent a colonoscopy without detection of polyps. Two of the father's siblings were diagnosed with a few polyps above the age of 55. Three of the siblings of the father's father suffered from colorectal cancer above the age of 60.

repair gene or (2) an underestimated *de novo* variant rate.

(1) To elucidate possible underlying genetic explanation for two mosaic cases in this family, whole-exome sequencing (WES) and mutational signature analysis by using whole-genome sequencing (WGS) were performed on leucocyte DNA and colorectal adenoma DNA respectively. WES data revealed seven rare truncating variants shared by both family members, however, these do not offer a relevant explanation of multiple mosaics in this family. In addition, the patients shared >300 rare non-synonymous coding or splicing variants. The three variants in genes associated with DNA damage repair were unlikely pathogenic.

As both patients have a mosaic deletion of AG, the search for mutational signature analysis could hint towards a specific underlying gene defect. Using SigProfiler,⁴ mutational signatures were assigned on WGS data. All analysed adenomas with single base substitutions show SBS1 and SBS5, both associated with ageing and observed across many tissue types.⁵ No other signature was shared between the adenomas.

(2) Le Caignec *et al*³ determined the probability of finding three *de novo* variants in *TSC2* in one family using a mathematical formula based on the *de novo* variant rate of *TSC2*. The *de novo* variant rate of *APC* is estimated between 4×10^{-6} and 9×10^{-6} .⁶ When imported into the same formula, these rates result in a probability of two *de novo APC* variants between 1:6 250 000 000 and 1:1 230 000 000 families with five members; parents with three children in this particular case. Since we hypothesise that the prevalence of *APC* mosaics might be higher than germline *de novo* variants, we used our previously reported cohort^{7,8} to estimate an *APC* mosaicism rate. We found *APC* mosaicism in 7% of patients with >10 adenomas, which is 1.4x lower than biallelic *MUTYH* variants in this same cohort (10%). As biallelic *MUTYH* is known to have a population rate of 1:10 000, we roughly estimate the *APC* mosaic rate to be 1:14 000. Using this *APC* mosaicism

rate in the formula, the estimated probability of 2 *APC* mosaics in a family of 5 members is 1:20 400 000, which is still extremely low.

Our estimation, the discrepancy in pattern and phenotype and previous studies^{9,10} underline the need for *APC* mosaicism testing guidelines. Our finding furthermore emphasises caution of ruling out *APC* mosaicism in patients with a positive family history for adenomas. Finally, whenever *APC* mosaic patients have affected family members, *APC* mosaicism testing should be considered.

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