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

Terlouw, D.; Hes, F.J.; Suerink, M.; Boot, A.; Langers, A.M.J.; Tops, C.M.; ... ; Nielsen, M.

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

Table 1 Overview of all tissues tested with NGS and variant allel 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.

Previous studies on multiple *de novo* variants[2 3] discuss two hypotheses: (1) an underlying hereditable defect in a DNA

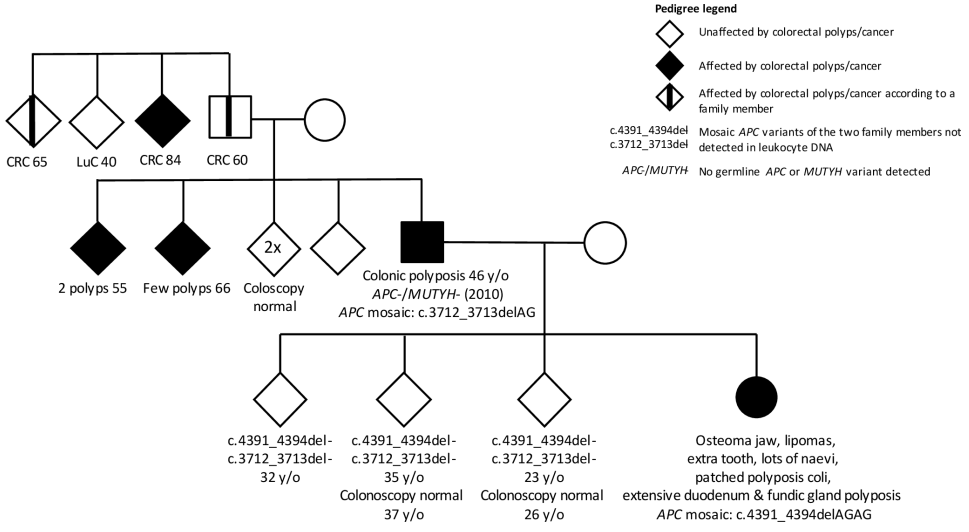

Figure 1 Pedigree of the paternal family of both mosaic patients. The other children of the father were all genetically tested for the two mosaic *APC* variants in the family (c.4391_4394delAGAG and c.3712_3713delAG) and tested negative. Two of the three children underwent a colonoscopy without detection 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.

Diantha Terlouw ,[1,2] **Frederik J Hes**,[3] **Manon Suerink** ,[1] **Arnoud Boot**,[4] **Alexandra M J Langers**,[5] **Carli M Tops**,[1] **Monique E van Leerdam**,[5] **Christi J van Asperen**,[1] **Steve G Rozen**,[4] **Emilia K Bijlsma**,[1] **Tom van Wezel**,[2] **Hans Morreau**,[2] **Maartje Nielsen**[1]

[1]Department of Clinical Genetics, Leids Universitair Medisch Centrum, Leiden, The Netherlands
[2]Department of Pathology, Leids Universitair Medisch Centrum, Leiden, The Netherlands
[3]Centre for Medical Genetics, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium
[4]Department of Cancer and Stem Cell Biology, Duke-NUS Medical School, Singapore
[5]Department of Gastroenterology and Hepatology, Leids Universitair Medisch Centrum, Leiden, The Netherlands

Correspondence to Dr Maartje Nielsen, Department of Clinical Genetics, Leiden University Medical Center, Leiden 2300 RC, The Netherlands; m.nielsen@lumc.nl

Contributors DT: acquisition of data, analysis and interpretation of data, drafting of the manuscript. FH, MS: acquisition of data, critical revision of the manuscript. AB, SR: providing mutational signature knowledge, critical revision of manuscript. AMJL: acquisition of clinical data, interpretation of data, critical revision of the manuscript. CT, MEvL: interpretation of data, critical revision of manuscript. CJvA: acquisition of clinical data, revision of manuscript. EKB: providing probability measurement knowledge, critical revision of manuscript. TvW, HM and MN: study concept and design, obtained funding, analysis and interpretation of data, critical revision of the manuscript.

Funding This study is supported by the Dutch Cancer Society, project number: 11292.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by B18.042. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Terlouw D, Hes FJ, Suerink M, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2022-328540

Received 23 August 2022
Accepted 16 October 2022

Gut 2022;**0**:1–2. doi:10.1136/gutjnl-2022-328540

ORCID iDs
Diantha Terlouw http://orcid.org/0000-0002-8090-8806
Manon Suerink http://orcid.org/0000-0001-7058-6973

REFERENCES

1 Monahan KJ, Bradshaw N, Dolwani S, *et al*. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut* 2020;69:411–44.
2 Garcia B, Catasus N, Ros A, *et al*. Neurofibromatosis type 1 families with first-degree relatives harbouring distinct *NF1* pathogenic variants. Genetic counselling and familial diagnosis: what should be offered? *J Med Genet* 2022;59:1017–23.
3 Le Caignec C, Kwiatkowski DJ, Küry S, *et al*. Three independent mutations in the TSC2 gene in a family with tuberous sclerosis. *Eur J Hum Genet* 2009;17:1165–70.
4 Boot A, Ng AWT, Chong FT, *et al*. Characterization of colibactin-associated mutational signature in an Asian oral squamous cell carcinoma and in other mucosal tumor types. *Genome Res* 2020;30:803–13.
5 Alexandrov LB, Jones PH, Wedge DC, *et al*. Clock-Like mutational processes in human somatic cells. *Nat Genet* 2015;47:1402–7.
6 Hes FJ, Nielsen M, Bik EC, *et al*. Somatic APC mosaicism: an underestimated cause of polyposis coli. *Gut* 2008;57:71–6.
7 Terlouw D, Suerink M, Singh SS, *et al*. Declining detection rates for APC and biallelic MUTYH variants in polyposis patients, implications for DNA testing policy. *Eur J Hum Genet* 2020;28:222–30.
8 Terlouw D, Suerink M, Boot A, *et al*. Recurrent APC Splice Variant c.835-8A>G in Patients With Unexplained Colorectal Polyposis Fulfilling the Colibactin Mutational Signature. *Gastroenterology* 2020;159:1612–4.
9 Aretz S, Stienen D, Friedrichs N, *et al*. Somatic APC mosaicism: a frequent cause of familial adenomatous polyposis (FAP). *Hum Mutat* 2007;28:985–92.
10 Jansen AML, Crobach S, Geurts-Giele WRR, *et al*. Distinct Patterns of Somatic Mosaicism in the APC Gene in Neoplasms From Patients With Unexplained Adenomatous Polyposis. *Gastroenterology* 2017;152:546–9.