Case Report

Rare germline chromosome 1 duplication identified in young male with colon cancer: a case report investigating causality

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Background: The occurrence of colorectal cancer (CRC) is increasing among young adults, but the etiology is still largely unknown. In addition to germline monogenetic variants also polygenic risk scores (PRS) have been proven to correctly estimate the risk of CRC.

Case Description: We present a 24-year-old male with disseminated colon cancer who carried a germline duplication on chromosome 1 spanning 200 kb and covering *CD101*, *TTF2*, *MIR942*, *TRIM45*, and parts of *PTGFRN* and *VTCN1*. The duplication was located in tandem. A similar duplication was previously reported in a family with CRC among two brothers aged 52 and 61 years old at diagnosis. Particularly, *MIR942* was an interesting finding as it is involved in the regulation of the Wnt signaling pathway. Disruption of the Wnt pathway is known to cause CRC. However, in our case the duplication did not segregate with disease in the family. Calculation of a PRS in our patient found an average PRS for CRC.

Conclusions: Our findings do not support that this duplication is a monogenetic cause of CRC, nor did a PRS point towards an increased risk in this 24-year-old male. Whether the duplication is a risk factor in combination with other genetic and non-genetic risk factors requires further studies.

Keywords: Chromosomal duplication; colorectal cancer (CRC); germline duplication; chromosome 1; case report

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Introduction

Colorectal cancer (CRC) is the third most common cancer in both males and females (1). The occurrence is highest in patients older than 50 years of age. While the occurrence and mortality have decreased for patients older than 50 years—largely due to screening programs which have proven to reduce mortality (2-4), the occurrence among young adults (particularly those <40 years at diagnosis) have increased (5). Twin studies have shown that the heritable component in CRC is estimated to be up to 35% (6). While polygenic risk scores (PRS) have proven to be useful in estimating individual risk among patients with no family history of CRC (7,8), their use in a clinical setting has not yet been implemented.

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In the following letter, we present a case of a 24-year-old man who developed colonic cancer and carries a rare duplication on chromosome 1 previously identified in a family also burdened by CRC and considered a likely cause of disease (9). We present this case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-148/rc).

Case presentation

A 24-year-old male was admitted to the hospital with one month's history of abdominal pain, bloating, nausea, vomiting, and obstipation. The patient's medical history was otherwise uneventful. Blood work came back with increased levels of hemoglobin, leucocytes, neutrophils and C-reactive protein (CRP). Upon admission the patient was suspected of having inflammatory bowel disease, coeliac disease, or an infection, however, all additional tests came back negative. Fecal culturing, however, revealed growth of clostridium difficile. A subsequent computed tomography (CT) scan revealed a pre-stenotic dilatation of the terminal ileum and unspecific hepatic changes, suggested by the radiologist to be cysts or hemangiomas. The patient underwent a diagnostic laparoscopy revealing a tumor located in the lateral cecal wall. In addition, the laparoscopy showed two peritoneal white elements highly suspect of being metastases. Histopathologic characterization of the tumor showed that the tumor was an adenocarcinoma with a pathogenic variant in *KRAS* [p.(Gly12Asp)]. Immunohistochemistry analysis (including expression of MMR proteins) and somatic genetic testing came back without other pathogenic findings. A magnetic resonance imaging (MRI) scan determined the hepatic changes were in fact metastases and peritoneal carcinosis. Subsequently, the patient was referred to oncological treatment. Even though the patient had disseminated disease the initial treatment had a curative aim with neoadjuvant chemotherapeutic treatment to allow for surgical removal. The patient was treated with fluorouracil, calcium folinate, and irinotecan, but after 8 weeks of treatment blood work revealed increased levels of carcinoembryonic antigen (CEA). A follow-up CT scan showed disease progression resulting in a change of treatment adding bevacizumab and oxaliplatin to the chemotherapeutic treatment. Follow-up scans showed regression of the metastases and the primary tumor, but the patient's treatment was complicated by numerous episodes of sub-ileus and ileus. A novel ileostomy was placed to alleviate the pain, however, during this procedure, carcinosis was observed in all four quadrants. After 6 months of treatment, no substantial regression was obtained, and the patient and his family were informed that further treatment would be palliative. Seven months after the initial diagnosis the patient died.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the index patient's family for the publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Highlight box

Key findings

- Our findings refute that a duplication covering *TTF2*, *MIR942*, and *TRIM45* on chromosome 1 is a monogenetic cause of colorectal cancer (CRC).

What is known and what is new?

- Monogenetic germline variants are known to cause early onset CRC, and disruption of the Wnt signaling pathway is proven causative in e.g., patients with familial adenomatous polyposis (caused by pathogenic variants in the *APC* gene).
- Our findings do not support that a duplication including the *MIR942*-gene (operating within the Wnt signaling pathway) is a monogenetic cause of CRC in a 24-year-old male.

What is the implication, and what should change now?

- Further studies should investigate whether this duplication is a risk factor for CRC in combination with other genetic- and non-genetic risk factors for CRC, or whether it is an incidental finding.

Genetics

In parallel with the patient's treatment, he was referred for genetic counselling. This included mapping of the family pedigree (*Figure 1A*) and germline genetic testing. An in-house gene panel consisting of 17 CRC/polyposis predisposing genes was analyzed. The gene panel included the following genes: *APC*, *AXIN2*, *BMPR1A*, *EPCAM*, *GREM1*, *MLH1*, *MSH2*, *MSH3*, *MSH6*, *MUTYH*, *NTHL1*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *SMAD4*, and *STK11*. No pathogenic variants were identified. Thus, a mosaic screening of variants in *APC* and additional germline genetic testing of variants in *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, and *TP53* was initiated. This did not reveal any pathogenic genetic variants either, resulting in risk assessment for the patient's

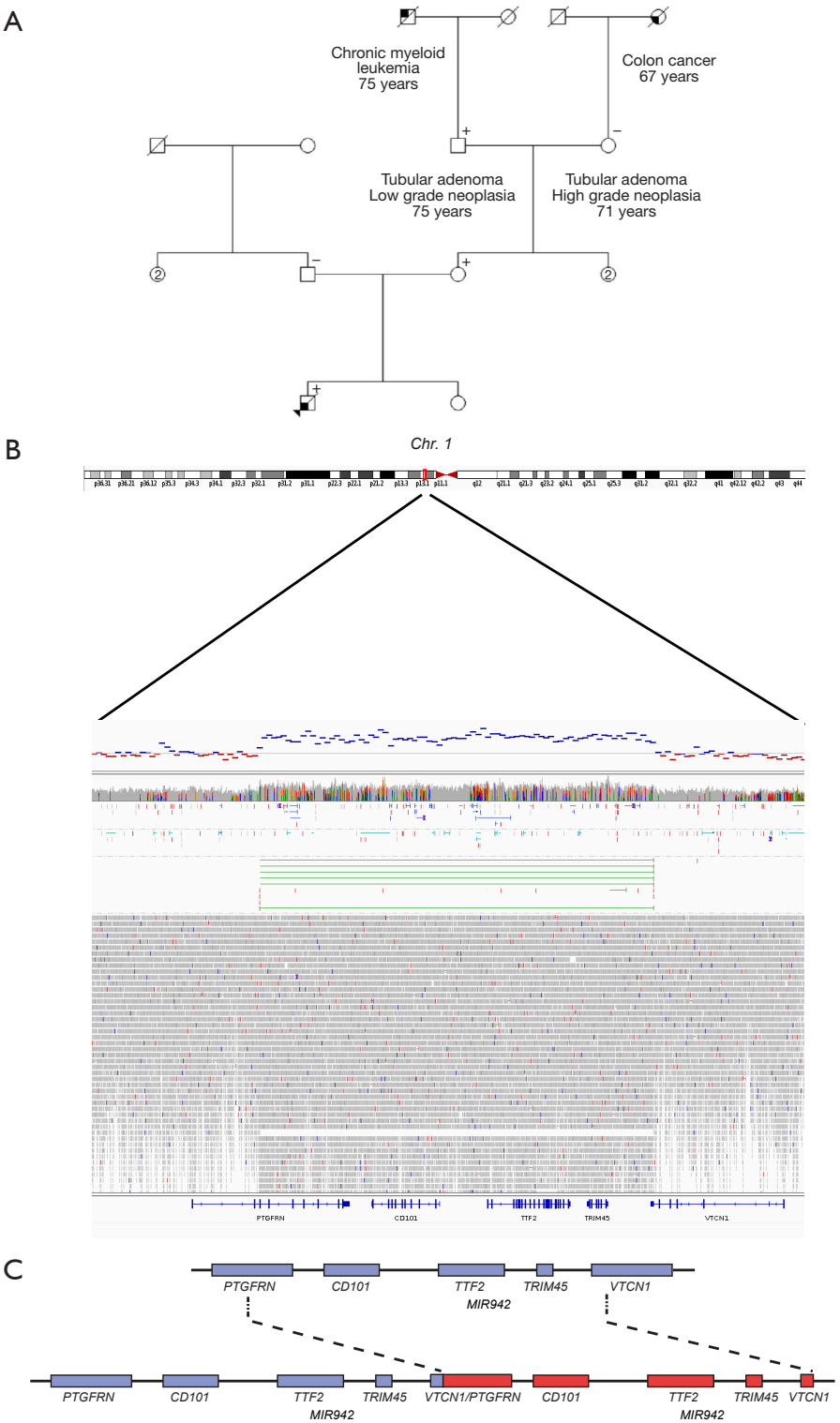

Figure 1 Visualization of the family pedigree, the location of the duplication and the genes included in the duplication. (A) Family pedigree. Square: male; circle: female; arrow: index patient; "+": carrying the chromosome 1 duplication; "–": not carrying the chromosome 1 duplication; line crossing square/circle: indication that the family member has passed away. (B) Chromosomal visualization of the duplicated area on chromosome 1 in integrative genomics viewer. (C) Visual presentation of the duplicated genes and their location in tandem.

Table 1 Other genetic variants identified through germline whole genome sequencing of the patient

Chromosome: position	Reference/ alteration	Variant allele frequency	Gene	HGVS c. (clinically relevant)	HGVS p. (clinically relevant)	GnomAD v.2.1.1. (for non-Finnish Europeans) [N]
8:30948045	A/G	0.785714	*WRN*	NM_000553.6: c.1717A>G	NP_000544.2: p.(Thr573Ala)	0.19186% [247]
11:1263400	A/G	0.481481	*MUC5B*	NM_002458.3: c.5290A>G	NP_002449.2: p.(Arg1764Gly)	0.080569% [103]
2:47641458	A/T	1.0	*MSH2*	NM_000251.3: c.843A>T	NP_000242.1: p.(Ser281=)	0.0046643% [6]
1:235894366	A/C	0.411765	*LYST*	NM_000081.4: c.8913T>G	NP_000072.2: p.(Asn2971Lys)	0.44919% [580]
1:235875386	T/C	0.384615	*LYST*	NM_000081.4: c.9896A>G	NP_000072.2: p.(Tyr3299Cys)	0.019941% [16]
7:148524327	A/G	0.468085	*EZH2*	NM_004456.5: c.657T>C	NP_004447.2: p.(Pro219=)	0.075923% [98]
10:50732202	T/G	0.318182	*ERCC6*	NM_000124.4: c.1274A>C	NP_000115.1: p.(Asp425Ala)	0.29267% [371]
11:71146886	C/G	0.45283	*DHCR7*	NM_001360.3: c.964-1G>C	p. (?)	0.60784% [722]
22:29085143	G/C	0.404255	*CHEK2*	NM_007194.4: c.1522C>G	NP_009125.1: p.(Leu508Val)	0.0027606% [3]
13:103498672	C/T	0.479167	*ERCC5*	NM_000123.4: c.56C>T	NP_000114.3: p.(Pro19Leu)	0.10878% [139]
17:63554469	G/A	0.418182	*AXIN2*	NM_004655.4: c.270C>T	NP_004646.3: p.(Asp90=)	0.12314% [159]

HGVS, Human Genome Variation Society; c., nucleotide change; p., amino acid change.

first-degree relatives based on the family pedigree.

A few months after the patient died, his mother and sister were referred for genetic counselling. They had not accompanied the patient when he underwent genetic testing and wanted to know their risk of developing CRC. The family was offered whole genome sequencing (WGS) using DNA from the patient. WGS revealed that the patient carried a duplication on chromosome 1 [Chr1(hg19):g.117487504_117687735dup]. The duplication was classified as a variant of unknown significance (VUS, class 3). The duplication on chromosome 1 spans a region of 200 kb and covers the genes *CD101*, *TTF2*, *MIR942*, *TRIM45*, and parts of the genes *PTGFRN* and *VTCN1*, and was shown to be located in tandem (*Figure 1B,1C*). The duplication had not previously been described in gnomAD or in the literature. However, a similar duplication covering an overlapping area (including *TTF2*, *MIR942*, and *TRIM45*) had previously been reported in another family with CRC and was considered a likely cause of CRC in the family (9). Segregation analysis revealed that the duplication was maternally inherited. On the maternal side of the family, there had been one case of a tubular adenoma with high-grade neoplasia at 71 years of age in the patient's maternal grandmother and one case of CRC at 67 years of age in her mother (the patient's great-grandmother). The patient's maternal grandfather had a tubular adenoma with low-grade neoplasia at 75 years of age (and his father had chronic myeloid leukemia at 75 years of age). This led to genetic testing of the patient's maternal grandparents. The duplication proved to be inherited from the patient's maternal grandfather, who had never had CRC or the removal of polyps with high-grade neoplasia.

Moreover, gene panel analysis identified 11 variants (*Table 1*) in the patient using a gene panel of 390 known and suspected cancer predisposing genes and an allele frequency ≤1%. The most interesting variant in relation to CRC was a relatively rare synonymous *MSH2* variant [c.843A>T, p.(Ser281=)] and a rare missense variant in

CHEK2 [c.1522C>G, p.(Leu508Val)]. The *MSH2* variant is reported 6 times in gnomAD (v.2.1.1) in heterozygote form. *In silico* analysis indicates that it has no effect on splicing. Moreover, the variant is reported 11 times in the ClinVar database as likely benign (variation ID: 237412). Interestingly, the variant was identified in homozygous form in our patient. However, based on the current knowledge we also classify the variant as likely benign. The variant in *CHEK2* is reported 3 times in gnomAD v.2.1.1 in the European (non-Finnish) population. The variant changes a weakly conserved amino acid, and *in silico* analysis accordingly indicates that the variant was unlikely to be pathogenic. Functional analysis showed that the variant had an intermediate effect in a CHEK2 activity assay but behaved as wild-type in a KAP1 activity assay (10). Based on these data the variant was classified as a VUS. The nine other variants are regarded as being too common based on allele frequency or not relevant for CRC. We were unable to examine for *de novo* variants, as the parents only agreed to data analysis of the chromosome 1 duplication. Subsequently, we calculated PRS for CRC in our patient using 95 single nucleotide polymorphisms (SNPs) correlated to the risk of CRC. The methodology employed is described in detail elsewhere (11). The calculated PRS for our patient was 7.87, indicating an average risk of developing CRC compared to other individuals with CRC. This suggests that our proband's risk of CRC, based on the PRS score, falls within the typical range, neither being particularly elevated nor reduced.

Discussion

Genetic predisposition to CRC is well-known with Lynch syndrome and familial adenomatous polyposis, most commonly caused by pathogenic variants in the mismatch repair genes or by deletions in EPCAM and the *APC* gene respectively (12). In recent years more genes have been linked to an increased risk of developing CRC (with or without polyposis)—among them are *MLH3*, *MSH3*, *MUTYH*, *GREM1*, *POLE*, *POLD1*, *RNF43*, *RPS20* and *NTHL1* (12). Furthermore, a combination of common genetic variants and a family history of CRC, can be used in the calculation of a PRS that can predict an individual's risk of CRC (13). Additionally, copy number variations (CNV) of genes relevant for CRC have been proven to increase the risk of CRC, e.g., duplications in *GREM1* (14) and deletions in *EPCAM* (15). In this case, we did not identify any pathogenic variants in well-established CRC-associated genes, nor did we find a particularly high PRS. We did, however, identify a duplication on chromosome 1. The duplication identified in our patient overlaps with a duplication previously identified in two brothers who developed CRC at the ages of 52 and 61, respectively (9). Both duplications covered the *TTF2*, *MIR942*, and *TRIM45* genes. Franch-Expósito *et al.* performed whole exome sequencing (WES) in 71 patients from 38 families with a family history of CRC. WES data was analyzed for variants in known CRC causative genes, and subsequently assessed for CNVs if no germline single nucleotide variants (SNV) were found. After identifying the duplication on chromosome 1 they performed an expression analysis on RNA from blood which showed an upregulation of the *TTF2* transcript which was not found in controls, while no significant change was observed for *TRIM45*. This finding was confirmed by the authors through a real-time quantitative polymerase chain reaction (PCR) analysis, and tumor gene expression analysis found that *MIR942* also proved upregulated (9). It is worth mentioning that the duplication did not segregate fully in the family described by Franch-Expósito *et al.* as the two brother's mother (CRC 84 years old) did not carry the variant. However, the risk of CRC increases with increasing age—so the mother's CRC is not necessarily suspected of being attributed to a genetic predisposition. *MIR942* has been found to be involved in the regulation of the Wnt signaling pathway, which will lead to CRC development when it is disrupted (16-18). These studies were the reason for investigating the duplication further when identified in our patient. However, as the duplication did not segregate with CRC in our family, we cannot say that our findings support pathogenicity. Whether the duplication could play a role if occurring alongside other genetic and non-genetic risk factors is still unknown, although the PRS calculated for our patient did not put him at an increased risk of CRC.

Conclusions

We did not identify a monogenetic cause of the early onset and aggressive CRC in our patient. Further studies are needed to elucidate whether the duplication on chromosome 1 may play a role in CRC risk either alone or in combination with other risk factors.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-148/rc

Peer Review File: Available at available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-148/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-148/coif). K.W. reports a speaking engagement at Seagen Denmark ApS for which she received payment. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the index patient's family for the publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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