Received: 9 July 2023 | Revised: 18 October 2023 | Accepted: 6 November 2023

DOI: 10.1002/ccr3.8229

CASE REPORT

Clinical Case Reports Open Access WILEY

Monoallelic deleterious MUTYH mutations generate colorectal cancer: A case report

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Key clinical message

Here we reported a particular case of MUTYH-associated polyposis (MAP) that had only one rare heterozygous variant, but some particular clinical manifestations contributed to occur in this male patient by only one defective MUTYH allele were worth of further investigation. We reported a case of MAP. It is about a 33-year-old man with chief complaints of hematochezia who had multiple polyps that were found in his colon via colonoscopy. He followed his doctor's advice and performed a genetic analysis examination. Germline test was positive for a major heterozygous variant: chr1:45800165 on the MUTYH gene. MUTYH gene sequence analysis confirmed the following heterozygous variant: c.55CT (p.R19X) in exon 2 (ClinVar NM_001128425). Unfortunately, his mother and daughter have the ILK variant according to genetic analysis. However, this variant at the site was not detected in his father. Various types of polyps were found on repeated colonoscopy, which tended to become latent cancerous in the future. This case indicated that awareness of the risk of carcinogenesis of polyps in carriers of monoallelic variants might accordingly increase, and our understanding of the type of genetically related disease will be enhanced by us.

KEYWORDS

colorectal cancer, hereditary colorectal cancer, MUTYH, polyposis

1 | BACKGROUND

Familial adenomatous polyposis (FAP), a rare autosomal dominant inherited disease, is generally considered to be related to the APC gene.[1] However, there is a special type of APC-negative but MUTYH-positive called MUTYH-associated polyposis (MAP). MAP includes both monoallelic variants and biallelic variants.[2] Of course, biallelic variants lead to an increased risk of colorectal cancer. But patients with biallelic variants are a minority, and heterozygous variants are more common. It is still unclear whether only one MUTYH variant is of clinical importance or not. Recently, more and more research has focused on the risk of colorectal cancer caused by monoallelic variants.[3] Previously, a number of studies showed that monoallelic MUTYH had little to do with CRC. Whether heterozygous variants increase the risk of colorectal cancer is still under debate.[4] Interestingly, what happens in the gut deserves

further investigation if there is another variant associated with colorectal polyps. In this report, we describe the rare genetic variant, which were unusual genetic variants that improve our awareness and understanding of the disease.

2 | CASE DESCRIPTION

A 33-year-old man was taken for counseling after discovering genetic variants. Firstly, on March 21, 2022, the patient went to Anhui Provincial Hospital for treatment with chief complaint of hematochezia for several months. He then underwent a colonoscopy which was showed that a 3.5-cm-long pedunculated polyp could be seen in the descending colon at a distance of 55 cm from the edge of the anus. And then a 0.8-cm-size polyp was detected near it. In addition, another larger polyp, about 6 cm in size, was found at the junction of the sigmoid and descending colon. It was worth noting that this distinct sessile polyp with a lobulated surface and varicose veins of the surrounding mucosa almost blocked the intestinal lumen. Several polyps ranging in size from 0.5 cm to 1 cm were also found in the rest of the colon. Pathologic findings after biopsy confirmed that the maximal polyp is a tubulovillous adenoma with moderate dysplasia. A computed tomography of the abdomen, performed half a month later, documented multiple lesions in the splenic flexion of the colon and in the sigmoid, considering the larger one, which is local with intussusception proximal to the sigmoid (Figure 1). Genetic analysis revealed a deleterious single-allele heterozygous germline variant. MUTYH gene sequence analysis confirmed the following heterozygous variant: c.55CT (p.R19X) in exon 2 (ClinVar NM_001128425). In addition, the LHX4 variant: c.256G > A (p.G86S) in exon 3 (ClinVar NM_033343) also was notable. The electrophoretic sequence of MUTYH exon 2 revealing variants is shown in Figure 2. This genetic analysis confirmed that the MUTYH variant was a single-allele heterozygous variant. A diagnosis of MAP was then confirmed. His mother and daughter have the same MUTYH gene variant, however, while no particular genetic variations occurred in his father. Interestingly, this MUTYH variant carrier had a family history consistent with dominant inheritance. His daughter currently has no tumor-related clinical manifestations, and his mother and siblings have no history of endometrial cancer, colon cancer, or other tumors. When he was admitted to another Class A tertiary hospital on May 2, 2022, he underwent endoscopic mucosal resection surgery. Pathological analysis showed that cystic fibrosis located 25 cm from the margin of anus was a microvillous tubular adenoma with high-grade intraepithelial neoplasia and local carcinogenesis. Specifically, cancerous tissue at the site has infiltrated into the 3 mm submucosal layer, but the vertical and lateral margins were both negative. The surgeon

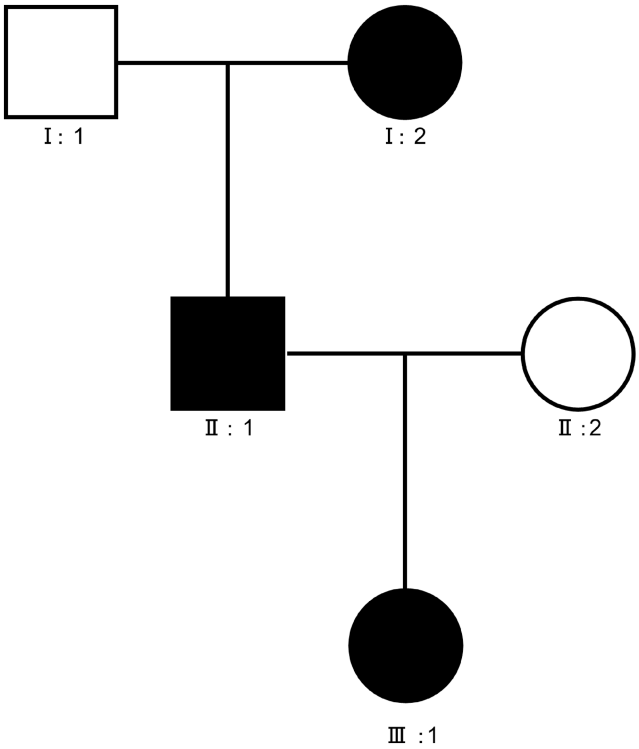

FIGURE 1 Family tree of patient. The proband's age at onset of the polyposis (33 years). The patient's father was unaffected, but his mother and daughter had a heterozygous mutation (without colonoscopy).

recommended abdominal surgery for the patient but failed. Almost about 22 days later, the patient sought further endoscopic treatment and came to our hospital. An abdominal enhancement CT was later performed, documenting multiple mass lesions of the colonic splenic curvature and sigmoid colon. The next day, the patient underwent colorectal EMR and ESD (Figure 3). Lesions between 5 mm and 6 cm are found during surgery. The largest tissue sample with dissociative tissue pieces was a villous tubular adenoma consisting of large low-grade and rarely high-grade intraepithelial neoplasia. In addition, a lesion grows nearby, the pathology of which was a villous tubular adenoma with low-grade intraepithelial neoplasia. The splenic flexure and sigmoid also have several similar polyps. Some hyperplastic polyps were detected in the rectum. All pathologically confirmed lesion strains were negative. Immunohistochemistry analysis was added showing that the junction of the descending colon with the sigmoid, sigmoid, and splenic flexure showed similar results: all polyps were sent for investigation and manifested as Desmin (mucosal muscle+), CEA (+), and P53 (+), including wild-type and partially mutant and various grades of Ki67 (+).

Three months ago, he came to our hospital for colonoscopy surveillance. And the positron emission tomography (PET-CT) scan was unremarkably normal. When he was hospitalized this time, his bowel preparation was

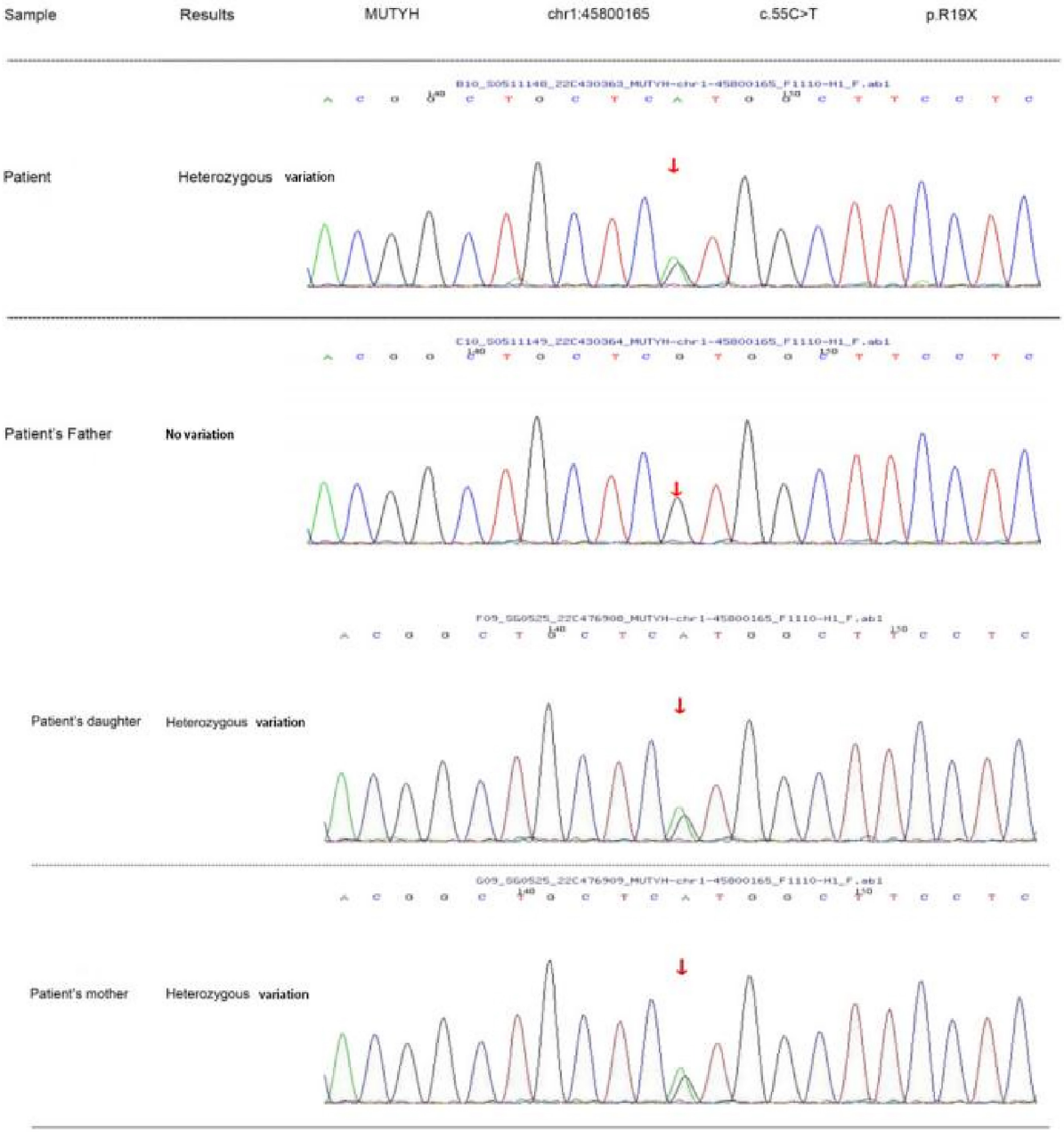

FIGURE 2 Partial chromatogram of the junction sequencing MUTYH gene sequence analysis confirmed the following heterozygous mutation: c.55CT (p.R19X) in exon 2 (ClinVar NM_001128425). In contrast to the patient, his mother and his daughter, the patient's father does not carry a heterozygous variant.

not fairly satisfactory as a large amount of feces remained in the bowel (Figure 4). Many polyps were found again after the colonoscopy. Tubular adenomas and hyperplastic polyps were removed with the technique of a cold snare. Considering the poor bowel preparation, he was instructed to repeat the colonoscopy after 3 months. At present, he went to our hospital again for a colonoscopy. During this process, several newly emerged polyps were found in the colon and were removed via conventional EMR. These polyps remain concentrated in the distal colon, including the descending colon, sigmoid colon, and rectum (Figure 5). In order to avoid unnecessary risks, we also arranged an additional CT examination for him, and this time there were no signs of intussusception and other potential malignant changes.

3 | DISCUSSION

According to relevant research, the particular genetic variant has been reported only in Asian regions, in contrast to MUTYH-related common gene variants in

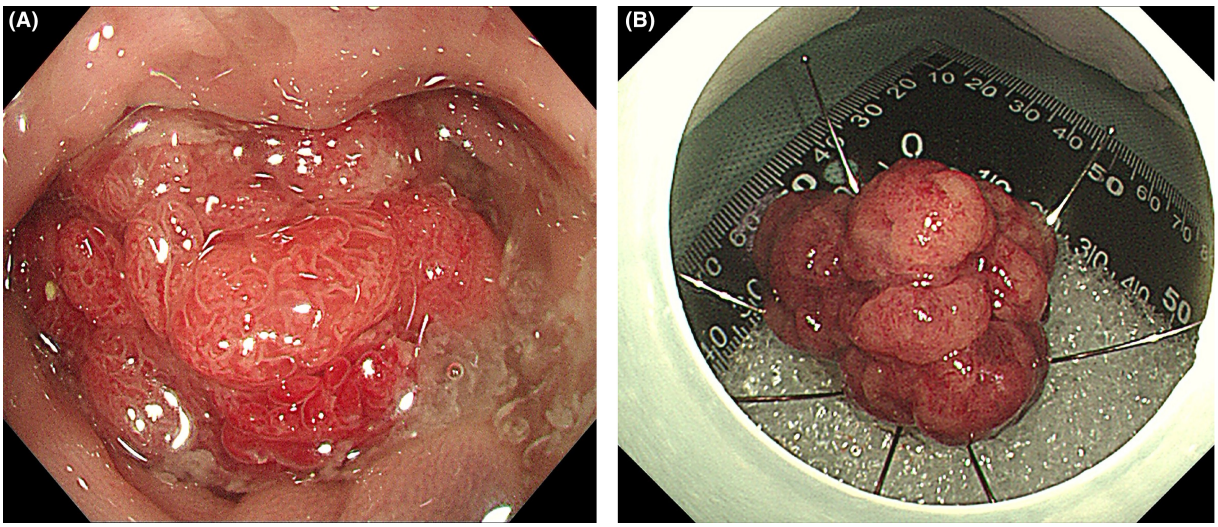

FIGURE 3 First colonoscopy in our hospital. (A) A huge mass can be seen at the junction of the descending colon and the sigmoid colon. (B) This is the specimen of the lesion that was removed. The pathology indicates that it is a villous tubular adenoma, most of which are accompanied by low-grade intraepithelial neoplasia, and a small number of high-grade intraepithelial neoplasia on the surface of the adenoma.

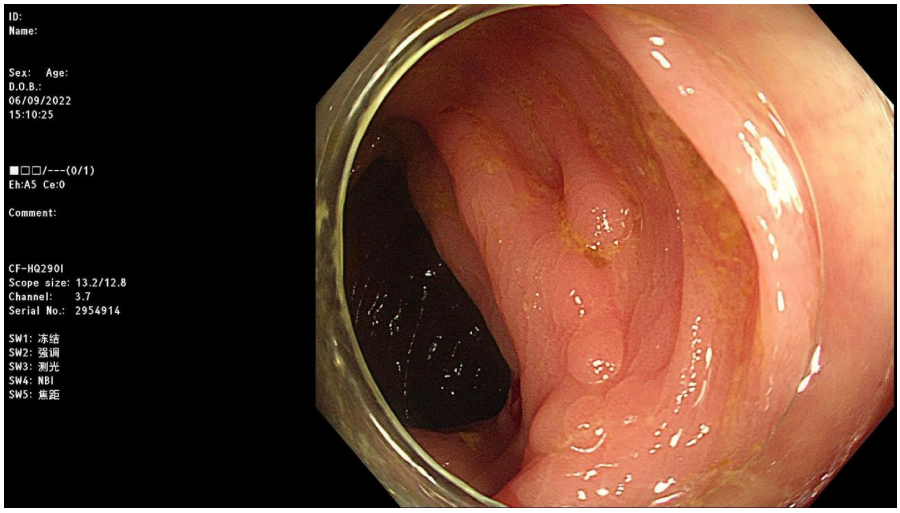

FIGURE 4 Second colonoscopy in our hospital. The intestinal mucosa was not completely exposed because the intestinal preparation was not good and only a few polyps were seen this time. As shown in the image, there are polyp-like growths in the descending colon.

Caucasians.[5–8] MUTYH-associated familial intestinal polyposis caused by this gene is also attenuated compared to regular MAP. MAP occurred mainly in the proximal colon, and polyps are mainly tubular adenomas, some tubular villous adenomas, and occasionally hyperplastic polyps.[9] Interestingly, the vast majority of polyps in this patient were located in the left colon, in contrast to MAP, which occurred in the right colon. However, recent literature has shown that patients associated with MUTYH deficiency resulting in hyperplastic polyps are not uncommon and present in a condition where hyperplastic polyps coexisted with adenomatous polyps.[9,10] This is consistent with the pathologic features of polyps in this patient, with proliferative polyps, tubular adenomas, and choriotubular adenomas growing together.

He has a heterozygous variant in the MUTYH gene, which is a monoallelic variant. The clinical severity is low; however, caused by this monoallelic heterozygous variant has not yet been reported in any relevant case. Unlike biallelic variants, which could accelerate the development of adenomas in subsequent years, according to previous literature and ESGE guidelines, patients with uniallelic variants rarely developed adenomatous polyposis or had only a slightly increased risk of developing CRC.[4,11] As mild as the description in the literature is, his immunohistochemical results predicted that the tumor had a strong invasive and metastatic capacity. In accordance with the pathological observations revealing infiltration into the submucosal layer, it is reasonable to classify the MUTHY variant c.55C>T as potentially pathogenic. This aligns with a T1N0M0 classification.

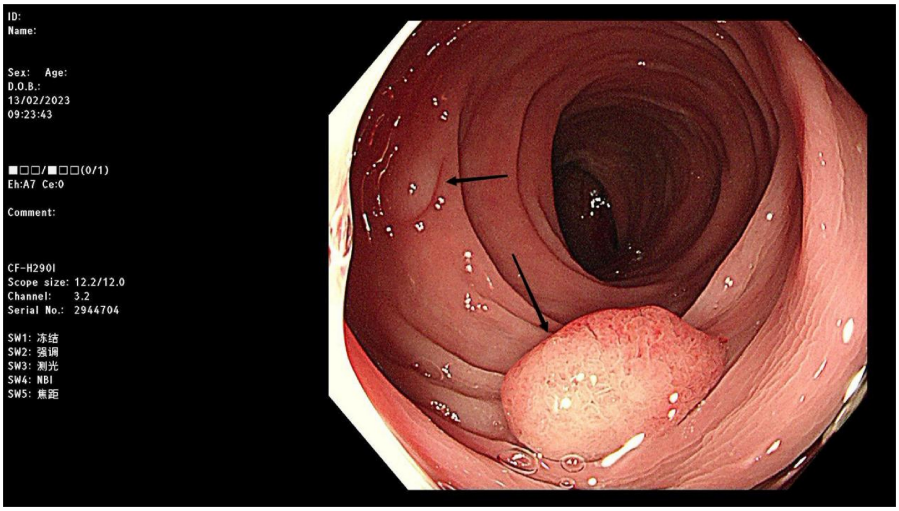

FIGURE 5 Third colonoscopy in our hospital. This time colonoscopy found many flat (0-IIa and 0-IIb) polyps. It is worth noting that larger lesions missed at the last colonoscopy were also seen in the rectum and at the sigmoid junction. Not surprisingly, Polyps remain concentrated in the left colon.

This might indicate the need for closer follow-up care. As understanding increases, there is also a growing body of literature showing that even patients with single allelic variants have a higher risk of cancer than other normal people.[12,13,15] Tumorigenesis is a mechanism of functional heterozygous somatic deletion of the MUTYH allele in tumors due to monoallelic pathogenic MUTYH germline variants. And the carriers of the monoallelic pathogenic germline variant MUTYH have a higher risk of developing tumors, particularly those with frequent events of loss of heterozygosity.[13]

According to the family study, just like the patient in our report, the Clinvar database categorizes his gene as causative, and his mother and daughter have the same gene variant site, and their colorectal cancer risk was more than approximately threefold.[14–16] And depending on the genetic make-up of mother and daughter, it is more like an autosomal dominant inheritance. In addition, family genealogy analyses can be used to better evaluate the common variants in Asian populations in order to better assess and intervene in colorectal cancer hazard in monoallelic carriers.[15]

It was worth mentioning that he has another variant in LHX4, but the genetic report does not explicitly mention the association with colorectal cancer. At present, the expression pattern of LHX gene in colorectal cancer is still unclear. The literature posits that LHX4 upregulates β-catenin levels in colorectal cancer cell lines, and LHX4-associated variants or deletion disrupted the direct LHX4-β-catenin interaction, as well as significantly reduced the capability of LHX4 to both combine and trans-increase target gene promoters. Importantly, deletion or variant of LHX4 also abolished its tumor-promoting function, suggesting that its mediated LHX4-catenin interaction was crucial for LHX4's tumor suppressor functions.[17] It is unknown whether the progression of colon polyps is balanced when the two genetic variants are present at the same time. In clinical work, we must pay more attention to the results of patients' genetic examinations to prevent rare reported gene variants from being overlooked and carry out individual follow-up protocols to study in detail the clinical manifestations caused by polygenic variants.

Despite the fact that MUTHY c. 55C>T/(p. R19Ter) has been mentioned in a number of databases thus far, and each of them offers a unique justification for its pathogenicity. This might be as a result of different final interpretations resulting from small sample sizes and the lack of distinct database data sources. Thus, it is important to us that caution should be exercised when dealing with rare variants in clinical practice. Further functional studies and clinical evidence may be necessary to establish their pathogenicity conclusively.

Malignant tumors accounted for up to 90% of adult intussusception, so if adult intussusception is present, the possibility of tumorigenesis cannot be overlooked, and endoscopy should be considered for surveillance screening and regular follow-up.[18]

In our case report, patients should appropriately lengthen and shorten the endoscopic follow-up time according to the bowel preparation and whether the pathology is prone to cancer, and individualize the endoscopic polypectomy plan so that the patient's lesions do not develop as much as possible.

4 | CONCLUSIONS

At present, colon cancer triggered by homozygous variants in the MUTYH gene was no longer surprising, and serious lesions caused by heterozygous variants have rarely been reported. Our results underscored the need for closer follow-up when patients with this gene variant are present, and we recommended that family

members of patients should be included in the follow-up population.

AUTHOR CONTRIBUTIONS

Bei Zhao: Investigation; writing – original draft. **Wenqi Sun:** Validation. **Yunrong Wang:** Investigation. **Xinrong Wu:** Software. **Yifan Li:** Investigation. **Weiwei Wang:** Software. **Muhan Ni:** Writing – review and editing. **Peng Yan:** Software. **Xiaotan Dou:** Data curation; investigation. **Lei Wang:** Writing – review and editing. **Min Chen:** Investigation; writing – review and editing.

ACKNOWLEDGMENTS

None.

FUNDING INFORMATION

No funding was obtained for this study.

CONFLICT OF INTEREST STATEMENT

All the authors declared that they had no conflicts of interest or financial ties to disclose.

DATA AVAILABILITY STATEMENT

The data that support the study findings are available upon reasonable request from the corresponding authors (Min Chen).

CONSENT

Written informed consent was obtained from the patient for inclusion in this case report. The case was approved by the institutional review board of the affiliated Drum Tower Hospital of Nanjing University, Medical School (2023-CR002-01).

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How to cite this article: Zhao B, Sun W, Wang Y, et al. Monoallelic deleterious MUTYH mutations generate colorectal cancer: A case report. *Clin Case Rep*. 2023;11:e8229. doi:10.1002/ccr3.8229