



SPECIAL ARTICLE

MSH3-related adenomatous polyposis in a patient with the negative family history of colorectal polyps

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Abstract Recently, biallelic *MSH3* germline pathogenic/likely pathogenic variants have been recognized as a rare cause of adenomatous polyposis. We present a 49-year-old woman who was admitted to our high-risk colorectal cancer clinic after incidental detection of a biallelic *MSH3* (likely) pathogenic variant when tested for the germline (likely) pathogenic variants in hereditary breast and ovarian cancer related genes. The focus of this case report is to describe the genotype and phenotype of our patient with *MSH3*-related adenomatous polyposis. More than half of the polyps (13/19) were located in the right colon. In addition, benign and malignant extraintestinal lesions may be common as our patient had simple liver and kidney cysts and two basal cell skin carcinomas.

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PALABRAS CLAVE

MSH3;
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Poliposis adenomatosa relacionada con MSH3 en un paciente con antecedentes familiares negativos de pólipos colorrectales

Resumen Recientemente, las variantes patogénicas/probablemente patogénicas de la línea germinal bialélica de *MSH3* han sido reconocidas como una causa rara de poliposis adenomatosa. Presentamos a una mujer de 49 años que ingresó en nuestra clínica de cáncer colorrectal de alto riesgo después de la detección incidental de una variante patógena probable de la línea germinal *MSH3* bialélica cuando se analizó la línea germinal variantes patogénicas/probablemente patogénicas en genes hereditarios relacionados con el cáncer de mama y de ovario. El objetivo

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de este informe de caso es describir el genotipo y el fenotipo de nuestro paciente con poliposis adenomatosa relacionada con MSH3. Más de la mitad de los pólipos (13/19) se localizaron en el colon derecho. Además, las lesiones extraintestinales benignas y malignas pueden ser comunes, ya que nuestra paciente tenía quistes hepáticos y renales simples y dos carcinomas cutáneos de células basales.

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Adenomatous polyposis syndromes of the colorectum are precancerous conditions¹ characterized by the presence of dozens to thousands of adenomatous polyps. Autosomal-dominant familial adenomatous polyposis (FAP), caused by heterozygous germline likely pathogenic variants (L)PV in the *APC* gene, and autosomal-recessive *MUTYH*-associated polyposis (MAP) which is caused by biallelic germline (L)PV in the gene *MUTYH*, are two major inherited monogenic predispositions for colorectal adenomatous polyposis.² In 2016, compound-heterozygous loss-of-function germline (L)/PV in the mismatch-repair gene *MSH3* was identified and reported for the first time.³ The mode of inheritance is autosomal-recessive. The authors recognized biallelic *MSH3* germline (L)/PV as a rare cause of adenomatous polyposis.³ The tumor spectrum in these four individuals included colorectal and duodenal adenomas, colorectal cancer, gastric cancer and early onset astrocytoma. This is a rare polyposis predisposition which, to our knowledge, has only been reported in a few families only.^{4,5}

The main aim of this report is to describe the genotype and phenotype of a case of *MSH3*-related adenomatous polyposis treated at our center.

We present a 49-year-old woman who was admitted to our high-risk colorectal cancer clinic due to the incidental detection of a biallelic *MSH3* germline (likely) pathogenic variant (L)PV when tested for the germline (L)PV in hereditary breast and ovarian cancer (HBOC) related genes.

Due to a diagnosis of breast cancer before the age of 45 (she was diagnosed at the age of 40), a patient was referred for genetic counseling at Department of Clinical Cancer Genetics. Prior to genetic testing, the patient signed an informed consent form allowing germline genetic testing and the use of her pseudonymised data for research purposes before submitting her blood sample. She was also counseled and opted to be informed of possible secondary findings, in case medically actionable variants in genes unrelated to the indication for testing were detected.

Next-generation sequencing for germline (L)PV in HBOC related genes of peripheral blood DNA sample was performed on Illumina's MiSeqDx Sequencing System using the TruSight Hereditary Panel (Illumina, San Diego, CA, USA) targeting 113 genes. To enrich and sequence all translated exons and ± 25 bp flanking intronic regions of all investigated genes, bioinformatics and copy number analysis were performed as described by our group previously.^{6,7} The presence of deletions/duplications was analyzed with SeqPilot, module SeqNext (JSI Medical Systems).⁸ A virtual HBOC gene panel included the following genes: *ATM*, *BARD1*, *BRCA1*,

BRCA2, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11* and *TP53* gene.

No germline (L)PV was detected in HBOC related genes. A secondary finding of a biallelic (likely) pathogenic variant in the *MSH3* gene was reported, i.e. a homozygous deletion of exon 16 (NM_002439.4 (*MSH3*): c.(2255+1_2254-1).(2318+1_2319-1)del p.(?)). The variant was classified for its clinical importance according to ACMG/AMP guidelines^{9,10} and is described according to HGVS v20.05 nomenclature.¹¹ Deletion of exon 16 has previously been reported in ClinVar as probably pathogenic. It is a gross deletion of the genomic region encompassing exon 16 of the *MSH3* gene. This deletion is out-of-frame, and is expected to create a premature termination codon and result in an absent or disrupted protein product.

The patient's medical history was notable for a diagnosis of breast cancer at the age of 40 (invasive ductal carcinoma, estrogen and progesterone receptor positive, human epidermal growth factor receptor 2 negative). She underwent surgery and received hormone therapy with letrozole. She also underwent successful excision of a basal cell carcinoma on the right lower extremity at the age of 43, and another on the neck at the age of 49.

She attended our high-risk colorectal cancer clinic at the age of 47 following referral from the Department of Clinical Cancer Genetics, due to genetic findings. Her family history was negative for colorectal neoplasia and colorectal polyps. Her mother was the only family member (among first- and second-degree relatives) diagnosed with cancer (mature T-cell lymphoma diagnosed at the age of 56) (Fig. 1). She also did not report any consanguinity in the family. At the age of 47, our patient had never undergone upper and lower endoscopy and was therefore referred for colonoscopy and oesophagoduodenoscopy (EGD).

At the first colonoscopy (October 2021) a large 40 mm $\times$ 45 mm polyp was identified in the cecum (LST-G, Olla, NICE 2). The appendiceal orifice and the valve of the Bauhinii were not involved, hence patient was referred for the piecemeal endoscopic mucosal resection (pEMR) (Fig. 2). During the same colonoscopy three small adenomas from the right hemicolon and three from the left hemicolon were removed, all with low grade dysplasia.

Histological analysis after pEMR (March 2022) of the large cecal polyp revealed a tubulovillous adenoma with focal serrated component with low grade and focal high grade dysplasia. The surveillance colonoscopy at six months showed no evidence of recurrence (Fig. 3). In addition, nine small

Family tree

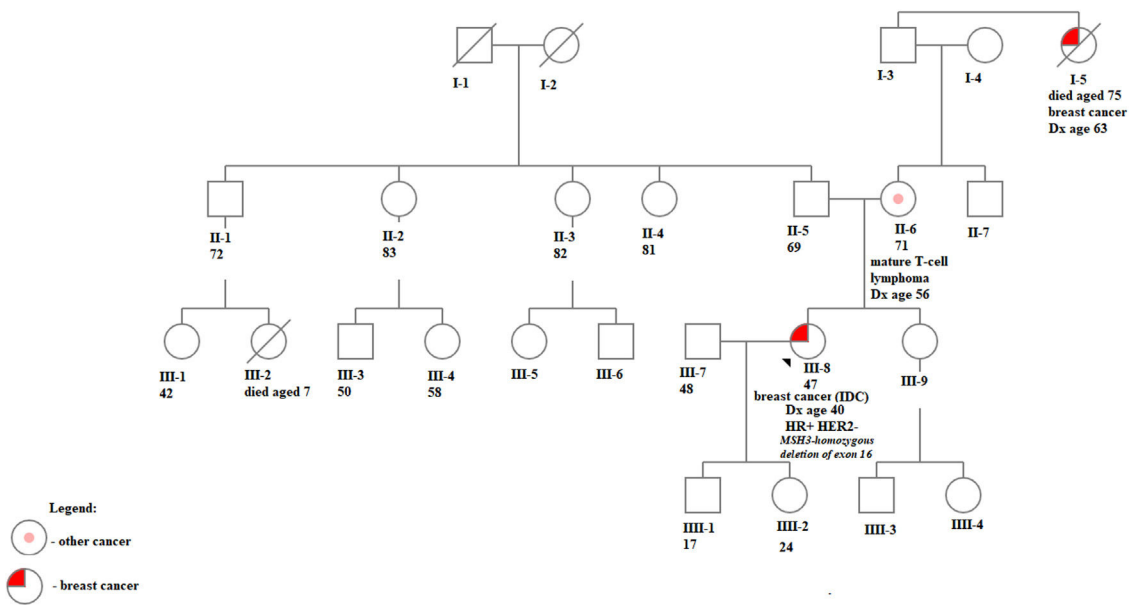


Figure 1 Four-generation pedigree of identified carrier of biallelic likely pathogenic variant in the *MSH3* gene (a homozygous deletion of exon 16). Dx: diagnosis, BCC: basal cell skin carcinoma, H+: estrogen and progesterone receptor positive, HER+: human epidermal growth factor receptor 2 negative.

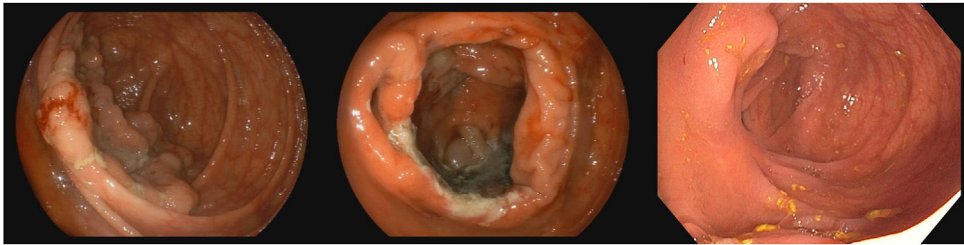


Figure 2 40 mm × 45 mm LST-G, OIIa, NICE 2 in the cecum. Piecemeal endoscopic mucosal resection of the LST-G in the cecum on the left and the scar after the piecemeal endoscopic mucosal resection in cecum without signs of recurrence as seen during the surveillance colonoscopy.

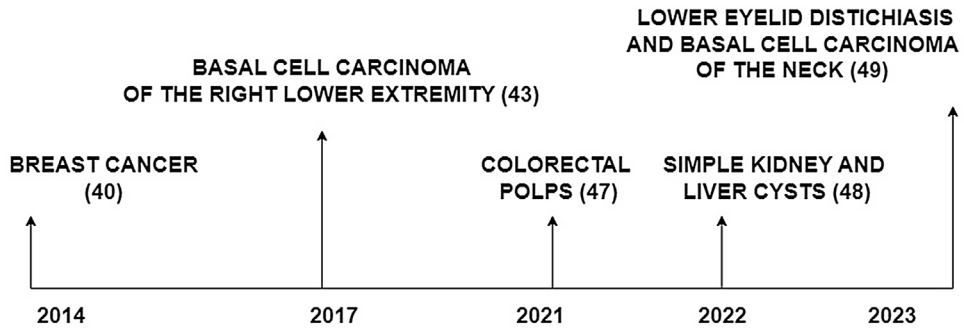


Figure 3 A retrospective chronological phenotypic description of our patient.

polyps were removed from the right hemicolon and three from the left hemicolon, all of which were adenomas with low grade dysplasia. A total of 19 polyps were removed in three colonoscopies over 43 weeks. The patient underwent an abdominal ultrasound which identified simple liver

and simple kidney cysts. She was scheduled for surveillance colonoscopy after one year, as recommended by the NCCN guidelines,¹² and also underwent EGD, during which we did not find adenomas of the stomach or duodenum. Papilla of the Vater was normal. Due to the limited data on effective

cancer screening in biallelic carriers of (L)PV in the *MSH3* gene, and a report of astrocytoma in *MSH3* (L)PV carriers, a magnetic resonance scan of the brain was also performed, but no pathological findings were reported. Her sister was offered genetic counseling and testing at the Cancer Genetics Clinic, but she has not yet opted for testing.

She reported eye irritation in her right eye and was referred to an ophthalmologist. She was diagnosed with lower eyelid distichiasis, a rare condition in which a primary epithelial germ cell destined to differentiate into the meibomian glands of the tarsus develops into a complete (cilia and glandular structure) pilosebaceous unit.¹³ Aberrant lashes were removed by epilation and ocular lubricants were prescribed. There were no other cases of eyelid distichiasis in her family.

To our knowledge, our report is the clinical presentation of one of the very few cases of *MSH3*-associated polyposis reported to date. Similar to the reports in the literature, polyps in our patient were predominantly located in the right colon (68% of all polyps in our patient). In addition to colorectal polyps, our patient had a history of HER-2 negative breast cancer, basal cell carcinoma of the skin, and simple liver and kidney cysts. This is consistent and in concordance with the recent report of a large family with *MSH3*-polyposis,⁴ where three of four affected individuals had multiple liver cysts and one had bilateral kidney cysts. However, (L)PV in the *MSH3* gene has not been reported to be associated with cyst formation. In addition, one affected family member had breast cancer in the ectopic axillary breast tissue. None of the family members in the report⁴ had a history of basal cell carcinoma.

Adam et al.³ reported that colorectal cancer and adenomatous polyps from the affected individuals had absence of the *MSH3* protein on immunohistochemical (IHC) staining and elevated microsatellite alterations at selected tetranucleotide repeats (EMAST). We also plan to perform IHC staining for the loss of *MSH3* expression and a test for elevated microsatellite alterations at selected tetranucleotide repeats on tumor tissue of our patient (breast cancer tissue and adenomas), to further elaborate on possible tumor risks of biallelic carriers of germline (L)PV of *MSH3* gene, preferably/if possible within a bigger European cohort of *MSH3*-related polyposis patients.

In conclusion, (L)PV in the *MSH3* gene are associated with the adenomatous polyposis, with polyps predominantly in the right colon and an age of diagnosis in the 40s. In addition, benign and malignant extraintestinal lesions may be common, particularly in the stomach, brain, liver and skin.

Authors' contributions

All authors contributed equally to the work presented in this paper. All authors have read and approved the paper.

Conflict of interest

The authors have no potential financial or funding conflict of interest.

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