https://doi.org/10.33878/2073-7556-2020-19-1-107-116

DIAGNOSTIC DIFFICULTIES IN *MutYH*-ASSOCIATED POLYPOSIS (case report)

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MutYH-associated polyposis (MAP) is hereditary syndrome with autosomal recessive inheritance, caused by biallelic mutation in MutYH gene and characterized by presence of multiple (20 and more) polyps in the bowel and increased life-time risk of colorectal cancer. At the same time finding 2 heterozygous mutations in MutYH gene (by Sanger method) doesn`t mean the diagnosis of MAP because of need to confirm their biallelic location. This case-report demonstrates difficulties in diagnostic of MAP caused by inability to investigate parent DNA samples and our options for solution of this problem.

[Key words: MutYH-associated polyposis, colorectal cancer, biallelic mutations]

For citation: Tsukanov A.S., Pikunov D.Yu., Toboeva M.K., Kuzminov A.M., Majnovskaya O.A., Kashnikov V.N., Shubin V.P. Diagnostic difficulties in *MutYH*-associated polyposis (case report). *Koloproktologia.* 2020; v. 19, no. 1 (71), pp. 107-116

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Among hereditary forms of colorectal cancer, adenomatous polyposis syndromes play a significant role, the most common of which are familial adenomatous polyposis and *MutYH*-associated polyposis [1].

The role of selecting and monitoring patients with these syndromes is due to the high risk (up to 100%) of developing cancer in them against the background of the presence of tens and hundreds of polyps in the colon [2,3]. At the same time, despite the fact that the syndromes have similar clinical manifestations, the genetic basis that cause their occurrence are significantly different.

Thus, familial adenomatous polyposis is most often a consequence of a monoallelic hereditary mutation in the *APC* gene, which plays a key role in the WNT pathway, as well as in cell adhesion, apoptosis and transcription regulation [4]. At the same time, the detection of a germ line mutation in the *APC* gene in a patient is a sufficient criterion for a diagnosis and determining treatment approach.

The situation is somewhat different in the diagnosis of *MutYH*-associated polyposis, which has an autosomal recessive type of inheritance [5,6].

For the manifestation of the clinical picture, it is necessary to have 2 mutations in both alleles of the *MutYH* gene *(MYH),* i.e. in both chromosomes of the first pair (1p34.1). Such a genotype can occur only when a child

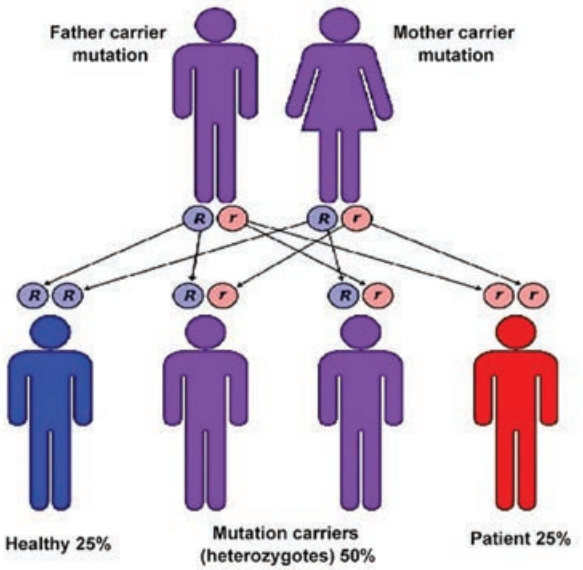

Figure 1. *Scheme of inheritance of autosomal recessive trait and its manifestation in the disease*

is transmitted one mutation from each parent (Fig. 1). But even the detection of 2 heterozygous mutations in the *MutYH* gene in a patient during molecular genetic study does not make it possible to unambiguously establish a diagnosis. This is because due to technological features, the 1st generation sequencing method (by Sanger) does not allow to determine the identity of the detected mutations to one or different alleles, resulting in the variant with the location of both mutations on one allele may be erroneously recognized as pathogenic (Fig. 2).

Thus, *MutYH*-associated polyposis of the colon is a rarer syndrome compared to familial adenomatous polyposis, and therefore not all questions concerning molecular genetic causes, clinical picture and treatment approachin such patients have clear decisions [7,8].

It was the presence of difficulties in diagnosis that prompted us to present our own clinical and genetic observation of a patient with *MutYH*-associated polyposis.

Female patient B. of 42 years old was admitted to the clinic with complaints of periodic discharge of blood and mucus with stools. The disease had history of several months. A total colonoscopy revealed the presence of about 20 polyps in all parts of the colon up to 2.5 cm in diameter.

Endoscopic removal of 2 of the largest of them was performed (according to histological study, the tumors were represented by tubular adenomas with severe epithelial dysplasia).

For further treatment, the patient was recommended to contact our clinic.

Colonoscopy revealed 20 polyps of 0.2-0.7 cm, some of which when viewed in white light and i-Scan mode were adenomas (Kudo IIIL type, Sano-II), the rest-as hyperplastic (0-IIa).

In addition, 2 laterally spreading tumors (LST-G) of 2 cm and 3 cm in diameter, respectively, towering above the mucosa level by 3 mm were detected in the caecum and ascending colon (when viewed in white light and i-Scan mode, the epithelium fossa of Kudo IIIS-Vi type, Sano-II).

CT of the chest, abdomen and pelvis revealed no pathological changes.

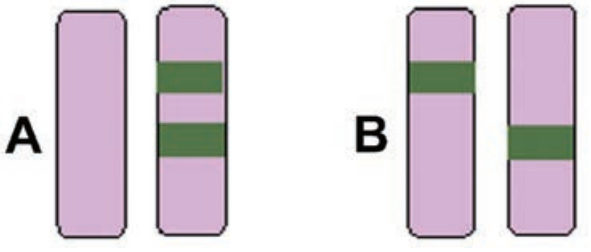

Figure 2. *Heterozygous mutations in the MutYH gene: A – monoallelic option, B – biallelic (pathogenic) variant*

Since the colonoscopy in a 42-year-old female patient revealed the presence of more than 20 polyps, she was suspected for a genetically-caused disease.

To establish hereditary causes, it was necessary to investigate carefully family history, as well as to make a molecular genetic study.

Of the features of family history, it is worth noting the lack of reliable data on the presence of the patient's closest blood relatives' complaints indicating the detection of intestinal polyps, malignant tumors of various locations.

The only exception is her maternal uncle, who had stomach cancer at the age of 60.

However, it is important to note that many relatives died at a young age from unrelated bowel disease causes: her sister died at the age of 36 years old (an accident), her brother died at the age of 40 years old (an accident); the patient's mother died at the age of 42 years old septic complications after tooth extraction), the father died at the age of 54 years old (cirrhosis).

The patient has 2 children: a son of 15 years old and a daughter of 7 years old, and their fathers are different.

Thus, taking into account the absence of explicit indications for the presence of tumors in the intestine in the nearest blood relatives, the number of polyps detected, their structure, the age of the patient, it was decided to make a molecular genetic study. It was advisable to start DNA diagnostics with the study of the *MutYH* gene [8].

The study found 2 heterozygous mutations with unclear localization on one or different alleles: p. R231H and p. G382D.

Variant p.G382D (Fig. 3A) is one of the two most common pathogenic mutations found in Caucasians [9].

Pathogenic value of p.R231H mutation (Fig. 3B) was established earlier in the work by Grasso F. [10]. Nevertheless, for the final diagnosis of *MutYH*-associated polyposis it was necessary to establish if these mutations are in a biallelic state (on different chromosomes) or in monoallelic (one chromosome) (Fig. 2).

The easiest way to find out is the DNA study of the patient's parents, but this was not possible because they are not alive.

In this regard, the son and the daughter of our patient were examined. As a result of the molecular genetic study of the son, it was found that he has both these mutations (p.R231H and p.G382D), which indicates rather their localization on chromosome1, which could be inherited from the mother.

However, it was impossible to exclude the possibility that one mutation he received from his mother, and the second from his father. At the same time, only 1

mutation of p.G382D was detected in the daughter. This mutation could also be transmitted to the daughter, both from the mother and from the father.

In this regard, it was decided to examine the fathers of the son and the daughter. The children had different fathers.

It turned out that the father of the elder son died at the age of 36 years old (the reason was not established), and to obtain blood samples of his parents was not possible. The blood of the second husband of our patient (the father of the younger daughter) was taken and when performing DNA diagnostics of the *MutYH* gene, it turned out that there were no mutations in it. Thus, only after the examination of the father of the second child, the genetic picture of the mother and the daughter finally cleared up: the daughter version of p.G382D was transmitted from the mother, whose mutations were on different chromosomes, and the normal allele – from the father. Consequently, the elder son also inherited only one of the mutations from his mother and the other from his father (Fig. 4). In this regard, the son was also diagnosed with *MutYH*-associated polyposis.

Despite the seemingly complete clinical and genetic picture, unresolved issues in this family still remained: it is unknown which of the mutations p.R231H and p.G382D the son inherited from his mother, and which one from his father, and the second question is how many mutations (one or two) were his father's. After all, if the father also had 2 mutations in the *MutYH* gene, then it is possible that the cause of his death could be *MutYH*-associated polyposis. On the other hand, the probability of meeting in a population of 2 people with the same hereditary syndromes caused by biallelic mutations is significantly lower than the meeting of one patient with biallelic mutations and a person with only one mutation in the same gene.

In any case, this will not influence the further tactics of clinical monitoring of the elder son of our patient. He is prescribed to undergo endoscopic examination

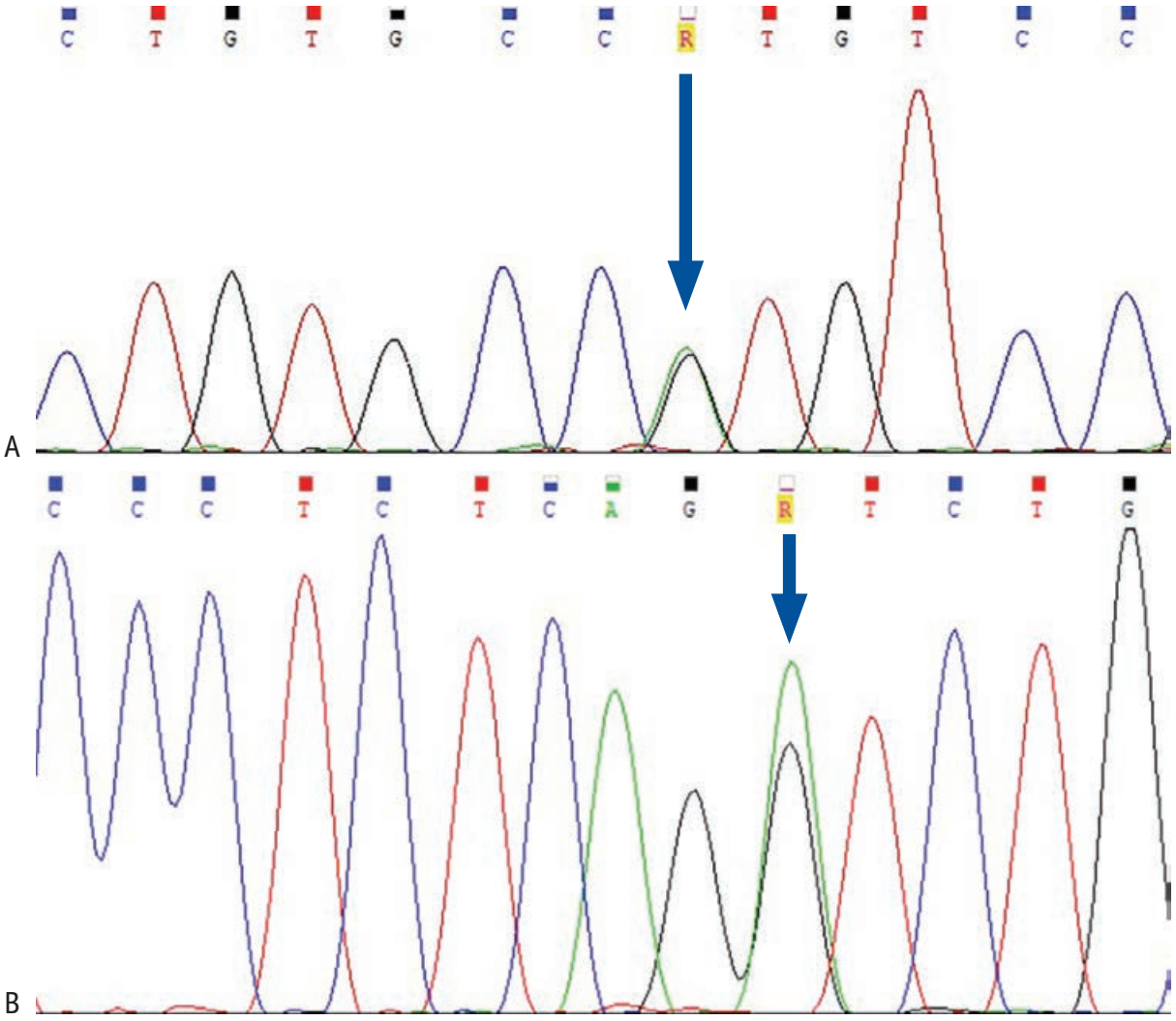

Figure 3. *Sequences of MutYH gene fragments. Arrows indicate hereditary missense mutations of p.R231H (A) and p.G382D (B)*

of the colon from the age of 25 years old every 1-2 years like any other patient with *MutYH*-associated polyposis [11].

In relation to the described patient B. with an established diagnosis of *MutYH*-associated polyposis and an extremely high risk of colorectal cancer, it was decided to perform preventive surgery in the volume of colectomy with the ileorectal anastomosis.

When studying the removed specimen, it was revealed that in the left colon there were multiple (8) polyps with a diameter of 0.5-0.7 cm on wide bases, with smooth surfaces of gray-pink color, elastic consistency. In the transverse colon, there were four polyps with a diameter of 0.5-0.7 cm on wide bases of a similar type; in the right colon, nine polyps with a diameter of 0.5 to 2.5 cm on wide and narrowed bases were detected.

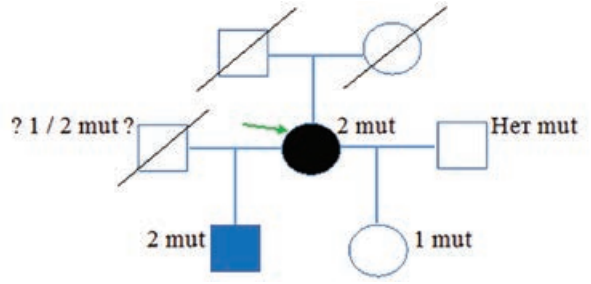

Figure 4. *Pedigree of the female patient (indicated by arrow) with MutYH-associated polyposis*

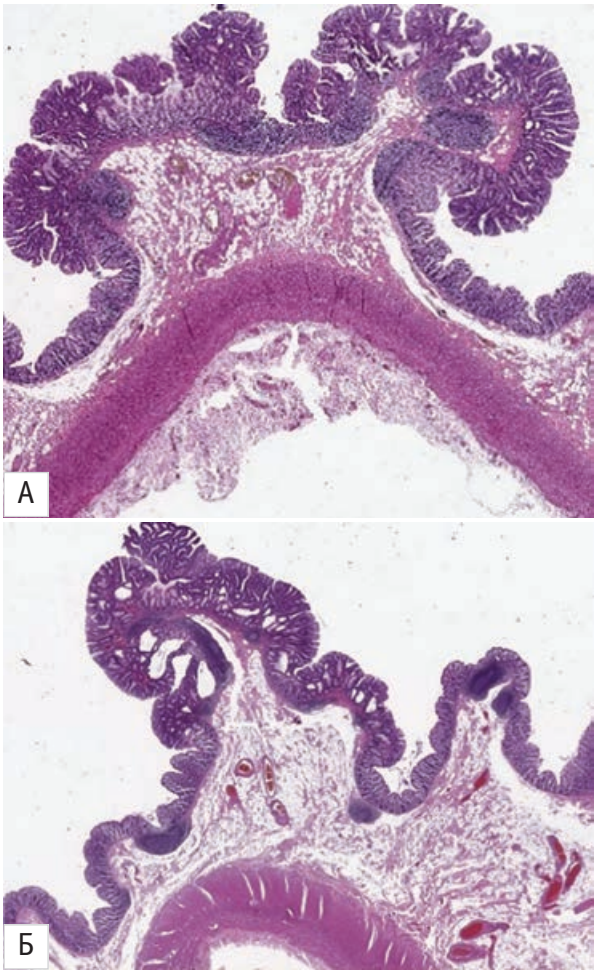

Figure 5. *Histological structure of colon polyps (A-descending colon polyp, B-ascending colon polyp), hematoxylin and eosin staining, X6 increase*

According to the morphological study, all macroscopically described formations in the large intestine were represented by tubular adenomas, in the transverse colon, descending and sigmoid intestine, tubular adenomas with slight epithelial dysplasia-were found, in the right colon – tubular adenomas with intraepithelial neoplasia of a high degree were found (Fig. 5).

Sixty-two lymph nodes of the mesentery had a normal structure.

No unfavorable events occurred postoperatively. The first stools were on the 3rd day. There were no significant deviations in laboratory parameters.

On the 9th day the patient was discharged from the hospital. In the future, it is planned to make lifelong clinical monitoring in the Registry of hereditary forms of colorectal cancer.

In conclusion, it should be noted that the clinical and genetic study has shown that *MutYH*-associated polyposis is not a simple disease, as well as the fact that to sort out its related complex issues it is necessary to examine not only all the patient's blood relatives (parents/children), but also the other family members (husbands/wives) – mutation carriers.

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The authors declare no conflict of interest.

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Received – 30.10.2019 *Revised – 10.12.2019* *Accepted – 10.01.2020*