https://doi.org/10.33878/2073-7556-2022-21-2-25-33

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# Juvenile polyposis in a family with «familial adenomatous polyposis» — an accidental find or a natural phenomenon?

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**ABSTRACT** *Hereditary polyposis syndromes are genetically determined conditions characterized by multiple polyps observed in patients throughout the gastrointestinal tract. The most common is familial adenomatous polyposis. At the same time, the juvenile polyposis syndrome found under it can be considered the most common in hamartomous polyposis syndromes, however, according to the endoscopic picture, it often causes one of the forms of adenomatous polyposis. A clinical case of the family with suspected familial adenomatous polyposis for years, and only complete exome sequencing revealed juvenile polyposis syndrome. A previously unknown pathogenic mutation in the SMAD4 gene was detected — c .705dupA (p.Gly236ArgfsTer28).*

**KEYWORDS:** *juvenile polyposis, adenomatous polyposis syndrome, familial adenomatous polyposis, hamartomatous polyposis syndrome, SMAD4, whole-exome sequencing*

**CONFLICT OF INTEREST:** *the authors declare no conflict of interest*

**FOR CITATION:** Pikunov D.Yu., Loginova A.N., Kuzminov A.M., Toboeva M.Kh., Barinov A.A., Tsukanov A.S. Juvenile polyposis in a family with «familial adenomatous polyposis» — an accidental find or a natural phenomenon? *Koloproktologia.* 2022;21(2):25–33. (in Russ.). https://doi.org/10.33878/2073-7556-2022-21-2-25-33

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*Received — 04.02.2022* *Revised — 24.03.2022* *Accepted for publication — 21.05.2022*

## INTRODUCTION

Hereditary polyposis syndromes are a whole group of genetically determined conditions characterized by the development of multiple polyps in patient throughout the gastrointestinal tract. In addition, patients with this pathology have an increased risk of developing both colorectal cancer and tumors of extra-intestinal sites. Thus, malignant tumors of the large intestine caused by the presence of hereditary polyposis syndrome account for up to 2–3% in the general statistics of colorectal cancer [1,2]. According to the nature of polyps formed in the gastrointestinal tract, polypous syndromes are divided into adenomatous and hamartomic [3]. The most common and most studied in this group of diseases is familial adenomatosis poliposis (FAP) — a syndrome with an autosomal dominant type of inheritance due to the presence of a mutation in the *APC* gene and characterized by the appearance of multiple (from several tens to several thousands) adenomatous polyps in the colon. According to generally accepted data, the risk of developing colorectal cancer in FAP reaches 70–100% [2], thus familial colon adenomatosis can be considered an obligately precancerous condition.

It is important to note that according to various authors, the frequency of detection of mutations in the *APC* gene in FAP is 70–85% [4, 5]. At the same time, in some cases, with a peculiar clinical picture, a genetic study indicates the absence of mutations in the *APC* and *MutYH* genes responsible for the manifestations of adenomatous polyposis syndrome.

Such a situation requires the continuation of the diagnostic search with the inclusion of other rare hereditary polyposis syndromes in the differential series. One of

the diseases masquerading as the FAP can be considered juvenile polyposis syndrome (JPS), which refers to hamartomic polyposis syndromes; however, according to the endoscopic picture, it often resembles one of the forms of adenomatous polyposis syndrome [6].

Juvenile polyposis syndrome (OMIM # 174900) is a rare disease with an autosomal dominant type of inheritance, which is characterized by the presence of multiple juvenile polyps in the gastrointestinal tract. Polyps are found mainly in the large intestine (98%), stomach (14%), duodenum (7%), jejunum and ileum (7%) [7]. The number of detected polyps is very variable: in some patients, there may be only four or five of them in their entire life; in the other members of the same family, it can reach 100 or more [8]. In addition to juvenile polyps, patients may have adenomatous polyps, which greatly complicates the diagnosis of the disease [6]. At the same time, the term 'juvenile polyp' defines its histological structure, and not the age of appearance of polyps. Thus, the presence of single juvenile polyps is not considered as belonging to a hereditary JPS and can be detected in 2–3% of children and adolescents [9]. Another peculiar feature of the JPS is an increased risk of developing malignant neoplasm of the large intestine and stomach cancer in patients, which reaches 40–50% and 20%, respectively [9,10].

The prevalence of the JPS ranges from 1:100,000 to 1:160,000 people [11]. In 60% of cases, the molecular genetic cause of the JPS is the presence of a hereditary mutation in one of the genes: *SMAD4*, localized on chromosome 18q21, or *BMPR1A*, located on chromosome 10q22.

Both genes are involved in the signaling cascade of the TGFß family, which plays a key role in suppressing cell growth and apoptosis [12]. At the same time, about 25% of newly diagnosed cases are sporadic and are associated with *de novo* mutations [7,12]. According to one of the most comprehensive databases on mutations in the human genome, HGMD Professioanal 2021.1, only 141 pathogenic variants in the *SMAD4* gene and 160 in the *BMPR1A* gene have been described in the world.

Due to the highly variable clinical picture and the rare occurrence, the diagnosis of the JPS is often difficult. In this paper, we present a clinical case of a family in which the presence of familial adenomatosis polyposis was suspected for several years, and only a full-exome study helped to reveal a juvenile polyposis syndrome, while a new pathogenic variant in the *SMAD4* gene, not previously described in the literature, was identified in the patients.

***Clinical Case***

The first member of R.'s family who applied to the RNMRCof Coloproctology was patient III.1 (Fig. 1).

In 2019, at the age of 59, she was consulted in an outpatient unit of the Center. From the history of the disease it became known that from the age of 13 she noted the blood in stools, she was examined at the place of residence, a large polyp of the sigmoid colon was detected during colonoscopy, as a result of which a resection of the sigmoid colon was performed in 1975. During a control examination 3 years after the surgery, in the patient polyps in the right colon were detected. She was sent to the RNMRC of Coloproctology, where, based on the presence of multiple polyps in the large intestine with a predominant location in the right colon, the young age of the patient who applied, she was diagnosed with FAP. Due to the treatment approach applied at that time, based on the clinical picture of the disease, in 1980 the patient underwent a right hemicolectomy. Follow-up at the place of residence showed new polyps in the remaining parts of the large intestine, as well as growth of polypoid tumors in the stomach, in connection with which in 1986, 1996, 2006, 2007, 2011, their endoscopic removal was performed.

In 2012 due to the uncontrolled growth of polyps in the patient's stomach, laparoscopically assisted Billroth Ire section of

2/3 of the stomach was done. Follow-up showed the growth of polyps in the stump of the stomach, and in 2014 the removal of the stomach stump with Roux-en-Y anastomosis was done.

Colonoscopy in 2019 in the RNMRC of Coloproctology, revealed 2 polyps of 1.5cm and 2.5cm without endoscopic signs of malignancy in the remaining part of the large intestine. Taking into account the patient's history, the previously established diagnosis of FAP (however, without genetic verification due to the lack of technical feasibility of the study), the patient's family history was carefully reassembled, and a molecular genetic study was done, in which mutations in the *APC* and *MutYH* genes were not detected.

Taking into account the peculiarities of the family history, as well as the clinical picture of the disease in the patient herself, which is somewhat unusual for FAP, it was decided to make a full-exome sequencing. As a result of the test, the variant c.705dupA (p.Gly236ArgfsTer28) in exon 6 of the *SMAD4* gene, previously not described in the world literature, was found.

The presence of the detected mutation was confirmed by sequencing using the Sanger method (Fig. 2). No mutations were detected in the other genes, changes in which led to the polyps in the gastrointestinal tract. Thus, the genetic test made it possible to detect in patient III.1 the juvenile polyposis syndrome.

The patient underwent endoscopic removal of the neoplasms, according to histology, the polyps had the structure of tubular and tubulo-villous adenoma of the large intestine with low grade dysplasia. No complications occurred in the postoperative period, in the future regular follow-up was recommended.

The patient has a 41-year-old son (IV.1). Given the hereditary nature of the disease in the mother, he also underwent a genetic study aimed at finding a mutation in the *SMAD4* gene. According to the results of the study, the sought-for mutation was not detected.

The conducted comprehensive endoscopy (gastro-, colonoscopy) also revealed no lesions in the stomach and large bowel.

With careful collection of the family history, the closest relatives of the patient with a similar clinical picture were identified (Fig. 1).

So, her own older sister (patient III.2) underwent gastric resection twice at the age of 35 and 39 due to uncontrolled growth of

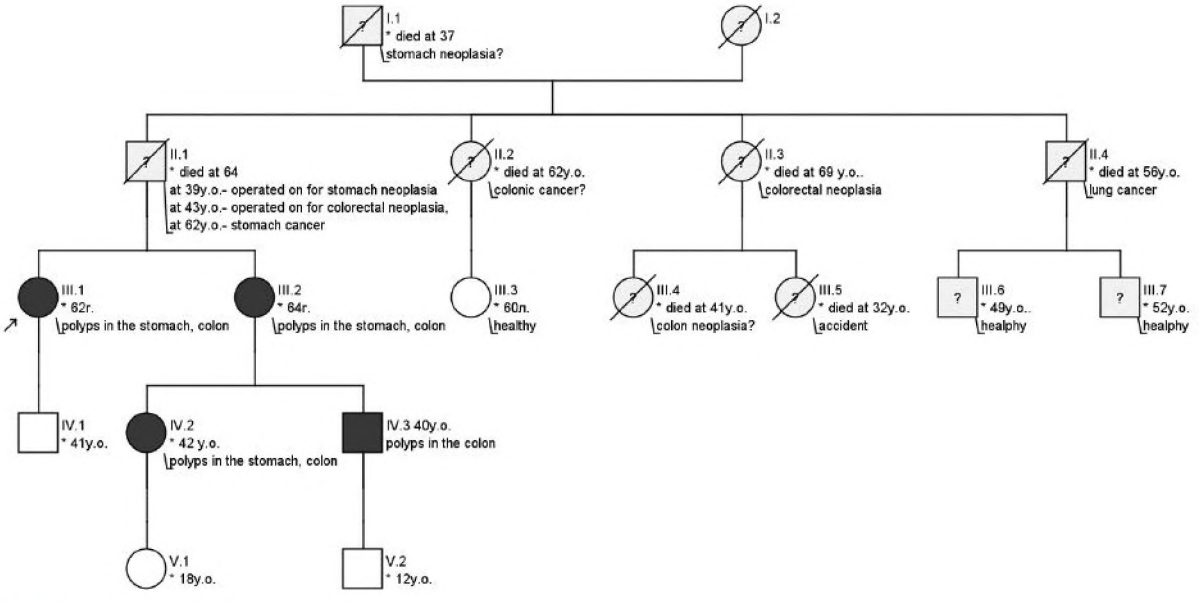



**Figure 1.** *The R. family tree*

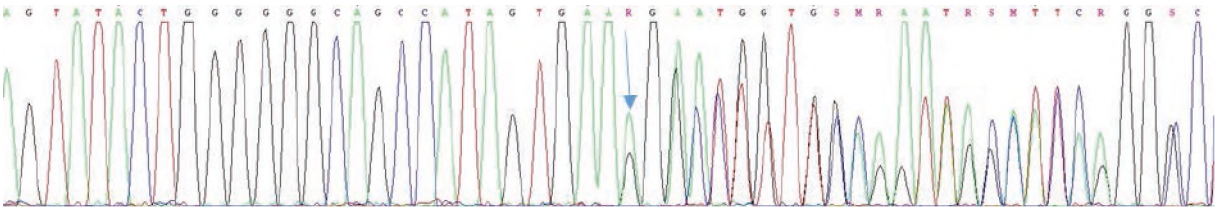


**Figure 2.** *Sanger sequencing of SMAD4 gene. The beginning of c.705dupA mutation is indicated by an arrow*

polyps in the stomach. Subsequently, 4 polyps of up to 3.5 cm in length were found in the large intestine; an endoscopic polypectomy was done at the age of 46. The histology of the removed polyps, unfortunately, are unknown. The patient was invited to the RNMRC of Coloproctology for examination. The endoscopy of the upper gastrointestinal tract revealed no growth of polyps. Colonoscopy revealed a 10 polyps 0.3–1.0 cm in the large intestine throughout, on broad bases, with a fibrin on the surface (Fig. 3), with an endoscopic picture corresponding to juvenile polyps. As planned, the largest polyps were endoscopically removed. The histology showed juvenile polyps.

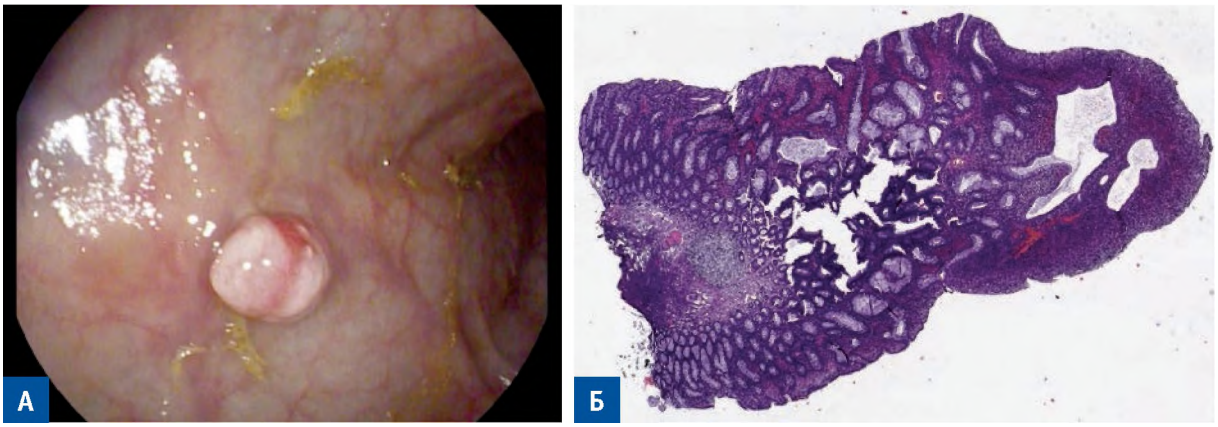
A genetic study confirmed the mutation in the *SMAD4* gene.

In turn, patient III.2 has two children, who were invited for examination within the framework of the Register of patients with hereditary forms of colorectal cancer, functioning in the RNMRCof Coloproctology [13]. It should be noted that in both children, a genetic study also revealed the presence of a mutation in the *SMAD4* gene. When analyzing history of the disease, it turned out that the daughter (patient IV.2) at the age of 16 underwent endoscopic removal of 6 colon polyps of up to 1.5 cm in length (the histology is unknown). At the age of 18, multiple gastric polyps, detected with gastroscopy, were not amenable to endoscopic removal, as a result of which subtotal resection of the stomach was performed. Further, no significant changes were detected during the periodic check-up. A colonoscopy in the Center showed several polyps in the large intestine: in the descending colon — a polypoid neoplasm 0.5 cm in length with an indeterminate pit pattern (Fig. 4.a), in the sigmoid colon — 3 polypoid neoplasms up to 1.0 cm, on a one infiltrated pedicle, with a pit pattern corresponding to type IIIL-IV by Kudo (Fig. 4.b).

Endoscopic removal of the identified polyps was done. The histology showed the morphological picture of a juvenile polyp in the descending colon and a tubular-villous adenoma with low grade epithelial dysplasia in the sigmoid colon (Fig. 5).

Gastroscopy revealed two polyps of up to 1.0 cm in the area of gastro-jejunal anastomosis, subjected to endoscopic removal.

In the son of patient III.2 (patient IV.3) at the age of 14 years old, 15 polyps of up to




**Fugure 3.** *Juvenile colon polyp of patient III.2: А — endoscopic picture, Б — micro-specimen (staining with hematoxylin and eosin, ×40)*

3.5 cm were detected in the colon at the place of residence; their endoscopic removal was performed (histological structure is unknown). In the future, for more than 20 years, the patient was not checked-up anywhere. Colonoscopy in the Center revealed 4 polyps of up to 0.4 cm in the caecum with an endoscopic picture corresponding to juvenile polyps (Fig. 6). No pathological formations were detected during gastroscopy. Given the small size of the colon polyps, it was decided to refrain from their endoscopic removal; follow-up was recommended to the patient.

It should be noted that in the children of patients IV.2 and IV.3 (aged 18 and 12 years old, respectively) no mutation of the *SMAD4* gene was detected.

It also follows from the family history that the father of proband (patient II.1) at the age of 39 underwent a sigmoid resection (the reason for the surgery is unknown), and at the age of 43, he underwent a Billroth II resection (the reason for the surgery is also unknown). At the age of 64, stomach stump cancer with distant metastases was detected, which was the cause of his death. In addition, in his own 2 sisters and 1 brother (subjects II.2, II.3 and II.4) according to his relatives, presumably malignant tumors of various sites (colorectal cancer, lung cancer) were found, which caused the death of the patients aged 62, 69 and 56 years old, respectively.

In addition, Proband's paternal grandfather (subject I.1) at the age of 37 underwent

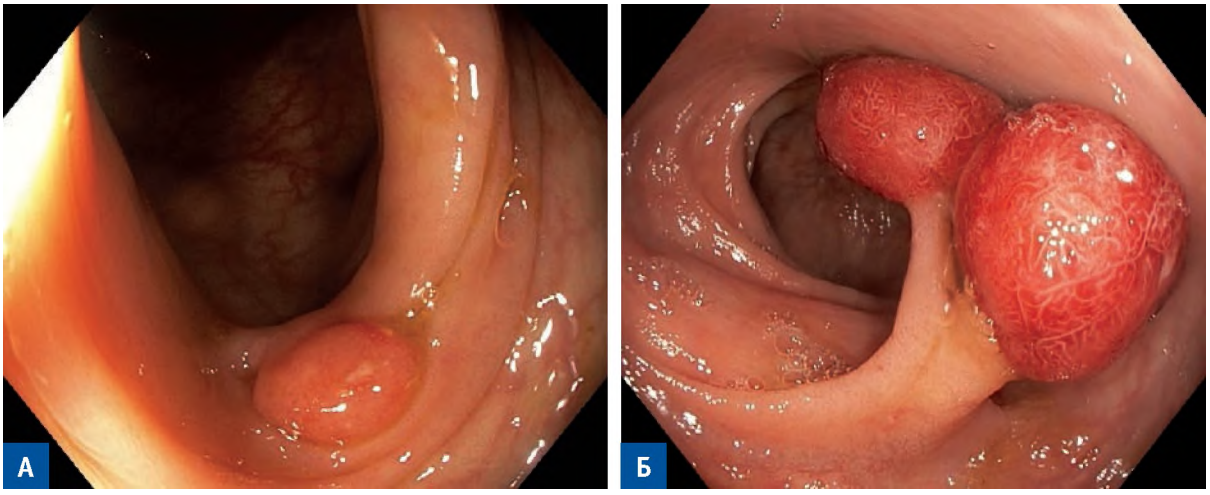



**Figure 4.** *Colonoscopy in patient IV.2: А — juvenile polyp of 0.5 cm in the descending colon; Б — adenomatous polyps of the sigmoid colon*

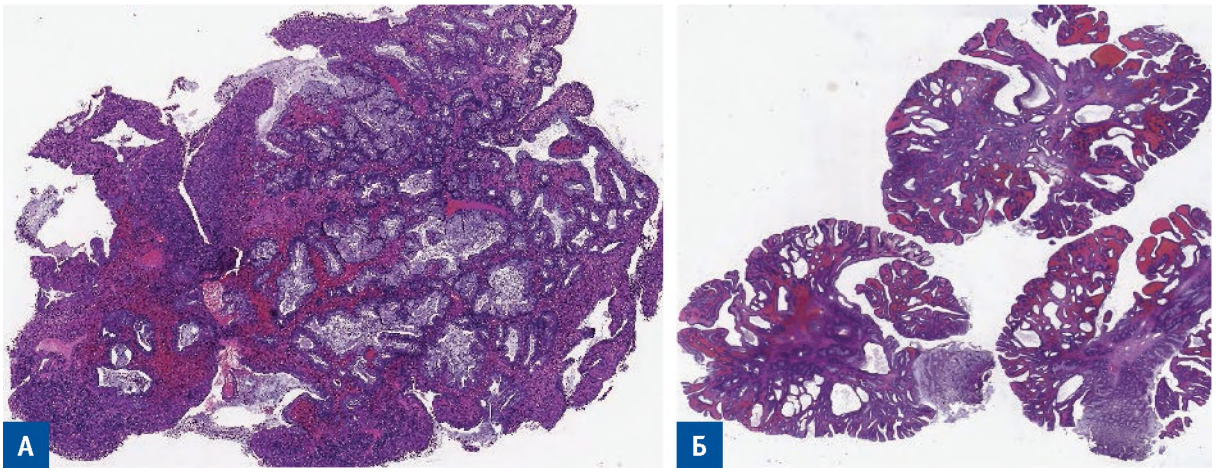



**Figure 5.** *Micro-specimens of patient IV.2: А — juvenile polyp of the descending colon (×40); Б — tubular villous adenomas of the sigmoid colon (×20). Stained with hematoxylin and eosin*

gastric surgery, the cause of which was presumably a tumor (the removal extent is unknown). A few months after the surgery, he died (the cause of the death also remained unknown).

## DISCUSSION

Juvenile polyposis syndrome is a rare disease. In accordance with generally accepted criteria, the diagnosis can be established when patient confirms one of the following signs: 1) the presence of 5 or more juvenile polyps in the large intestine; 2) the presence of multiple juvenile polyps throughout the gastrointestinal tract; 3) any number of juvenile polyps in the presence of the JPS in a family history [7,14]. According to these criteria, patient III.1, who applied to the Center, had no reasons for the diagnosis of the JPS: the 2 large neoplasms identified at that time in the large intestine had the structure of tubular and tubulo-villous adenoma; there were no indications of the presence of juvenile polyps throughout the gastrointestinal tract, as well as accurate information about the JPS in the family history. Moreover, the clinical data could well correspond to the previously established diagnosis of the FAP. And only a genetic study, which made it possible to exclude the presence of mutations in the *APC* and *MutYH* genes in patient III.1, as well as to identify a pathogenic variant in the *SMAD4* gene, made it possible to establish a diagnosis of juvenile polyposis in the family. Despite the fact that the variant c.705dupA (p.Gly236ArgfsTer28) in exon 6 of the *SMAD4* gene has not been previously described in the literature, its pathogenicity is not in doubt, since the mutation is represented by a duplication of one nucleotide, which leads to a shift in the reading frame, causing the formation of a premature stop codon. The phenotypic picture of the carriers of the mutation in R.'s family confirms the data of various authors testifying to a significantly more often lesion with juvenile polyps of the upper gastrointestinal tract when a mutation in the *SMAD4* gene is detected compared with carriers of mutations in the *BMPR1A* gene [6,9,15].

So, Blatter, R. et al., as a result of a retrospective assessment of literature data on over 600 patients with juvenile polyposis syndrome, state about 39% vs.13% ($p$ = 0.001) of the detection rate of juvenile polyps in the stomach, as well as a more clinically severe manifestation of the disease in carriers of the mutation in the *SMAD4* gene compared with carriers of the mutation in the *BMPR1A* gene, respectively [16]. And indeed, in R.'s family almost each patient with a confirmed mutation had a stomach lesion, which led primarily to the need for its resection, and only after that there were indications for surgeries in the other parts of the gastrointestinal tract. At the same time, the checked-up members of R.'s family did not have another symptom most characteristic of carriers of the mutation in the *SMAD4* gene — the presence of hereditary hemorrhagic teleangioectasias [17], which can manifest only when *SMAD4* is affected (they are detected in 34% of patients) and are not described in the presence of the mutation in the *BMPR1A* gene [16].

By the nature of neoplasms formed in the gastrointestinal tract, juvenile polyposis refers to hamartomic polyposis syndromes [18]. Wherein, hamartomic intestinal polyps are formed from normal intestinal wall tissues in their unusual combination with a violation of the ratio of tissue elements and the predominance of stroma, while in adenomatous polyps, the pathological process affects only the epithelial layer [18,19]. In R.'s family we are observing, colorectal adenomatous polyps prevailed checked-up patients at the time of endoscopy, which made diagnosis complicated. When analyzing literature data, the unusual,at first glance, presence of adenomatous polyps in patients with the JPS found its explanation. Back in 1994, Subramony, S. et al. noted that juvenile polyps of less than 1 cm in size had a

morphology of a hamartomic polyp; however, with an increase in size from 1 to 2.9 cm, the occurrence of epithelium with mild or moderate dysplasia increased, and with a polyp size exceeding 3 cm, most juvenile polyps were covered mainly with dysplastic epithelium, visually masquerading as an adenoma [20]. In addition, a number of authors confirm the fairly often occurrence of other types of polyps in patients with the JPS [21]; some even single out a separate type of polyposis syndrome — hereditary mixed polyposis syndrome (HMPS), while noting its conditionality by mutations in the *BMPR1A* gene [22,23]. For example, Blatter R. et al. have given data on 37.6–82.2% of patients with the JPS, who had the presence of other types of polyps (mainly adenomas and hyperplastic polyps), however, with relatively the same incidence of mutations in the *SMAD4* and *BMPR1A* genes [16].

In R.'s family we have presented, three relatives allegedly had colorectal cancer, which caused the death at the ages of 41, 62 and 69, and two family members were diagnosed with stomach cancer at the ages of 37 and 64. Among the 8 family members checked-up in the Center (4 of whom are carriers of the first detected mutation in the *SMAD4* gene) at the age of 12–64 years, none of them had malignant tumors. According to literature data, the risk of colorectal cancer in patients with the JPS is 17–22% by the age of 35, and the lifetime risk of stomach and duodenal cancer is 10–21% [3]. Unlike FAP, which is an obligate precancerous disease, the JPS does not have such a high oncological risk, as a result of which less invasive methods are used as treatment, depending on the degree of clinical manifestations. Thus, the main method of treatment is endoscopic removal of detected polyps, and the reason for surgery is only uncontrolled growth of polyps and/or their malignancy [7,8].

## CONCLUSION

The study of the unusual disease in a family with a previous diagnosis of FAP, a pathogenic mutation c.705dupA (p.Gly236ArgfsTer28) in exon 6 of the *SMAD4* gene, previously not described in world literature, was revealed. Thanks to this, it became possible to diagnose juvenile polyposis syndrome, which nominally refers to hamartomic hereditary polyposis syndromes and has a wide phenotypic variability. At the same time, the probability of detection in the large intestine, in addition to juvenile polyps, also adenomatous and hyperplastic polyps mask the disease and creates prerequisites for diagnostic errors. This indicates the possibility of including in the diagnostic search in patients with a clinical picture of adenomatous polyposis syndrome, genetic study not only for the presence of mutations in the *APC* and *MutYH* genes, but also *SMAD4* and *BMPR1A*.

**AUTHORS CONTRIBUTION**

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