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Large Rearrangements in Genes Responsible for Familial Adenomatous Polyposis, *MUTYH*-Associated Polyposis and Peutz—Jeghers Syndrome in Russian Patients

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Aim: to reveal the rate of large rearrangements in the genes responsible for familial adenomatous polyposis, *MUTYH*-associated polyposis and Peutz–Jeghers syndrome.
Materials and methods. The MLPA method was used for identification of large rearrangements. A total number of 135 patients was included in the study: 83 patients with a clinical diagnosis of "familial adenomatous polyposis", 18 — with suspected *MUTYH*-associated polyposis, and 34 — with a clinical diagnosis of "Peutz–Jeghers syndrome".
Results. Seven large deletions and one large duplication in the *APC* gene were identified in 83 patients with classic familial adenomatous polyposis, with rate of large rearrangements 9.6 % (8/83). In 18 patients with suspected *MUTYH*-associated polyposis, no large rearrangements were found in the *MUTYH* gene. Four large deletions in the *STK11* gene (12 %, 4/34) were detected in 34 patients with Peutz–Jeghers syndrome.
Conclusion. For the first time, the expediency of including the method of detecting large rearrangements in routine DNA test list for Russian patients with various hereditary polyposis syndromes is demonstrated. Routine use of MLPA method makes it possible to increase the total frequency of detection of pathogenic variants in the *APC* and *STK11* genes above 90 %. At the same time, the need for searching of large rearrangements in the *MUTYH* gene were not justified.
Keywords: familial adenomatous polyposis, *MUTYH*-associated polyposis, Peutz–Jeghers syndrome, large gene rearrangements, MLPA method
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Протяженные перестройки в генах, ответственных за развитие семейного аденоматоза толстой кишки, *MUTYH*-ассоциированного полипоза и синдрома Пейтца–Егерса у российских пациентов

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Цель исследования: поиск протяженных перестроек в генах, ответственных за развитие семейного аденоматоза толстой кишки, *MUTYH*-ассоциированного полипоза и синдрома Пейтца—Егерса.
Материалы и методы. Для исследования крупных перестроек использовали метод MLPA. Общее число пациентов составило 135 человек (83 — пациенты с клиническим диагнозом «семейный аденоматоз толстой кишки», 18 — с подозрением на *MUTYH*-ассоциированный полипоз, 34 — с клиническим диагнозом «синдром Пейтца—Егерса»).
Результаты. Среди 83 пациентов с диагнозом классической формы семейного аденоматоза толстой кишки в гене *APC* обнаружено 7 крупных делеций и 1 крупная дупликация, что составило 9,6 % (8/83). У 18 пациентов с подозрением на наличие *MUTYH*-ассоциированного полипоза крупных перестроек в гене *MUTYH* не обнаружено. Среди 34 пациентов, страдающих синдромом Пейтца—Егерса, выявлены 4 крупные делеции, что составило 12 % (4/34).
Выводы. Впервые показана целесообразность включения в рутинную ДНК-диагностику российских пациентов с различными наследственными полипозными синдромами метода детекции крупных перестроек,

что позволит поднять суммарную частоту обнаруженных патогенных вариантов в генах *APC* и *STK11* выше 90 %. При этом необходимость поиска протяженных делеций/дупликаций в гене *MUTYH* неоправданна.
Ключевые слова: семейный аденоматоз толстой кишки, *MUTYH*-ассоциированный полипоз, синдром Пейтца—Егерса, крупные генные перестройки, метод MLPA
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

Colorectal cancer (CRC) is currently the third most common cancer in the world (second in men) and the second largest in terms of mortality [1, 2]. In recent years, a significant younger age of patients at detection of colorectal cancer causes reasonable concern of specialists [3]. Approximately 90 % of CRC cases develop sporadically, and only a small part (< 10 %) is genetically determined [4]. The most common hereditary polyposis syndromes leading to CRC include familial adenomatous polyposis, *MUTYH*-associated polyposis and Peutz–Jeghers syndrome.

Familial adenomatous polyposis is a syndrome with an autosomal dominant inheritance, characterized by a large number of colorectal polyps (from 100 to several thousand). The first manifestations of the disease appear at the age of 20 years [5]. The prevalence of familial adenomatous polyposis is less than 1 % of all cases of colorectal cancer [4]. Polyps occur throughout the large intestine, which inevitably leads to cancer in the absence of timely surgical treatment. There are classical and attenuated forms of familial adenomatous polyposis. The attenuated form characterized by a milder course and fewer number of polyps (less than 100) [4]. The cause of familial adenomatous polyposis in most cases is the presence of a germline pathogenic variant in the *APC* gene, which is a tumor suppressor gene and participates in the regulation of the Wnt-pathway [6, 7]. Recently, the HGMD database [8] includes 2,099 different hereditary variants in the *APC* gene, of which the main share consists of small deletions — 799 (38 %), missense/nonsense — 587 (28 %), small inserts/duplications — 343 (16 %), large deletions — 146 (7 %), variants of the splicing site — 125 (6 %), large duplications — 20 (1 %), etc.

***MUTYH*-associated polyposis syndrome** has an autosomal recessive type of inheritance, characterized by a significant number (from 20 to several hundred) of adenomatous polyps in the large intestine [9]. In addition to adenomatous polyps, serrated, hyperplastic and mixed polyps may occur in *MUTYH*-associated polyposis [10]. Cases with a large number of polyps, or their complete absence, also described. The average age of diagnosis of colorectal cancer in patients with *MUTYH*-associated polyposis is 48 years, while cases of duodenal, ovarian, bladder, breast and endometrial cancers are possible as well [10–12]. The cause of *MUTYH*-associated polyposis is biallelic pathogenic variants in the *MUTYH* gene. This gene encodes a DNA glycosylase involved in the repair of oxidative DNA damage [13]. Currently, 220 pathogenic variants are described. Of these, 145 (66 %) are missense/nonsense variants, 32 (15 %) are mutations of the splice site variants, 18 (8 %) are small deletions, 8 (4 %) are large deletions, 5 (2 %) are substitutions causing regulatory violations, 5 (2 %) are small inserts/duplications, 1 (0.5 %) — large insertion/duplication, etc. [8].

Peutz–Jeghers syndrome has an autosomal dominant type of inheritance, and is characterized by a combination of polyposis of the gastrointestinal tract with mucocutaneous pigmentation, as well as a predisposition to the cancer [14, 15]. Hamartomatous polyps developing in Peutz–Jeghers syndrome are most often found in the small intestine, but can also occur in the stomach, large intestine and other hollow organs [14]. Polyps can cause serious complications, including intussusception, intestinal obstruction, and rectal prolapse, as well as severe gastrointestinal bleeding with secondary anemia. The age of onset of symptoms varies, so in some children complaints appear already during the first few years of life [14, 15]. The diagnosis of "Peutz–Jeghers syndrome" based on clinical data, and the identification of a heterozygous pathogenic variant in the *STK11* gene using molecular genetic testing confirms this diagnosis. The *STK11* gene is a tumor suppressor gene and encodes the protein serine-threonine kinase 11, which participates in the regulation of cell polarity, apoptosis and angiogenesis [14, 16]. Recently, 577 pathogenic variants in the *STK11* gene were described. They include missense/nonsense variants — 245 (42 %), also small deletions — 103 (18 %), large deletions — 98 (17 %), small inserts/duplications — 60 (10 %), splice site variants — 45 (8 %), large duplications — 4 (0.7 %) and others [8].

At the moment, there are practically no scientific papers in Russia devoted to the search for extended deletions/duplications in patients with familial adenomatous polyposis, *MUTYH*-associated polyposis, as well as Peutz–Jeghers syndrome. In this regard, the aim of our study was to assess the need of inclusion of additional test for identification of large rearrangements in *APC*, *MUTYH* and *STK11* genes in

the routine protocol of DNA tests for patients with different polyposis syndromes.

Materials and methods

Patients

A total number of 135 patients was included in the study: 83 patients with clinical presentation of familial adenomatous polyposis, 18 — suspected for *MUTYH*-associated polyposis, and 34 — with a clinical diagnosis of "Peutz–Jeghers syndrome".

Patients with familial adenomatous polyposis underwent surgical treatment at the Federal State Budgetary Institution "Ryzhikh National Medical Research Center of Coloproctology" of the Ministry of Health of Russia from January 2020 to April 2022. The selection criteria were young age (up to 45 y.o.) and the presence of more than 100 polyps in the bowel [17].

Patients with suspected *MUTYH*-associated polyposis and Peutz–Jeghers syndrome underwent treatment from January 2013 to April 2022 at the same institution. The selection criteria for patients with suspected *MUTYH*-associated polyposis were 20 or more colorectal polyps [17], as well as the absence of pathogenic variants in the *APC* gene. At the same time, four patients had a previously identified monoallel mutation in the *MUTYH* gene.

The selection criteria for patients with Peutz – Jeghers syndrome were the presence of ≥ 2 hamartomatous polyps in the gastrointestinal tract, the family history and/or the presence of specific mucocutaneous pigmentation [15].

All patients underwent a complete checkup, which included family history and history of the disease, esophagogastroduodenoscopy, colonoscopy, abdominal ultrasound and chest and abdominal CT, as well as capsule endoscopy of the small intestine for patients with Peutz–Jeghers syndrome. Informed consent obtained in all cases (Local Ethical Committee Protocol 4a/14, 04.04.2014).

DNA extraction

DNA was obtained from the peripheral blood of patients using the Promega isolation Kit (Wizard (R) Genomic DNA Purification Kit 500 Isolations), the procedure was performed according to the manufacturer's protocol. The DNA concentration was measured using the DeNovix QFX device (Denovix, USA), using the Qubit dsDNA HS assay Kit (ThermoFisher Scientific, USA) to determine the DNA concentration. A DNA concentration of at least 10 ng/uL used for the work.

MLPA Method

Traditional Sanger sequencing cannot detect large DNA deletions/duplications. In our study, we used the most common method for detecting of large rearrangements — MLPA (Multiplex Ligation-dependent Probe Amplification).

Table 1. Rate of large gene rearrangements detection in different countries in patients with familial adenomatous polyposis and *MUTYH*-associated polyposis

Таблица 1. Частота выявления протяженных генных перестроек в различных странах у больных с семейным аденоматозом толстой кишки и *MUTYH*-ассоциированным полипозом

Rreference Ссылка	Country Страна	Large del/dup *APC* Протяженные перестройки	Large del/dup *MUTYH* Протяженные перестройки
[19]	Hungary Венгрия	10 % (9/87)	0 %
[20]	Brazil Бразилия	8.7 % (2/23)	4.3 % (1/23)
[21]	Spain Испания	7.3 % (6/82)	0 %
[22]	Sweden Швеция	8.3 % (2/24)	n/d н/д
[24]	Belgium Бельгия	4.7 % (4/85)	n/d н/д
[23]	China Китай	14 % (2/14)	n/d н/д
[28]	Iran Иран	5.8 % (2/34)	n/d н/д
[25]	USA США	2 % (28/1421)	0 %
[26]	Greece Греция	0 % (0/25)	0 % (0/25)

Note. n/d — no data.

Примечание. н/д — нет данных.

Table 2. Clinical characteristics of patients with familial adenomatous polyposis and large alterations in the *APC* gene

Таблица 2. Клинические характеристики пациентов с семейным аденоматозом толстой кишки и крупными перестройками в гене *APC*

Patient number № пациента	Age of diagnosis Возраст диагноза	Large del/dup Протяженные перестройки
A747	33	del 4, 8–15
A834	41	dup 1–10
A836	36	del prB
A846	36	del 8–10
A853	29	del prB
A855	24	del 14
A875	33	del prB
A903	24	del *APC*

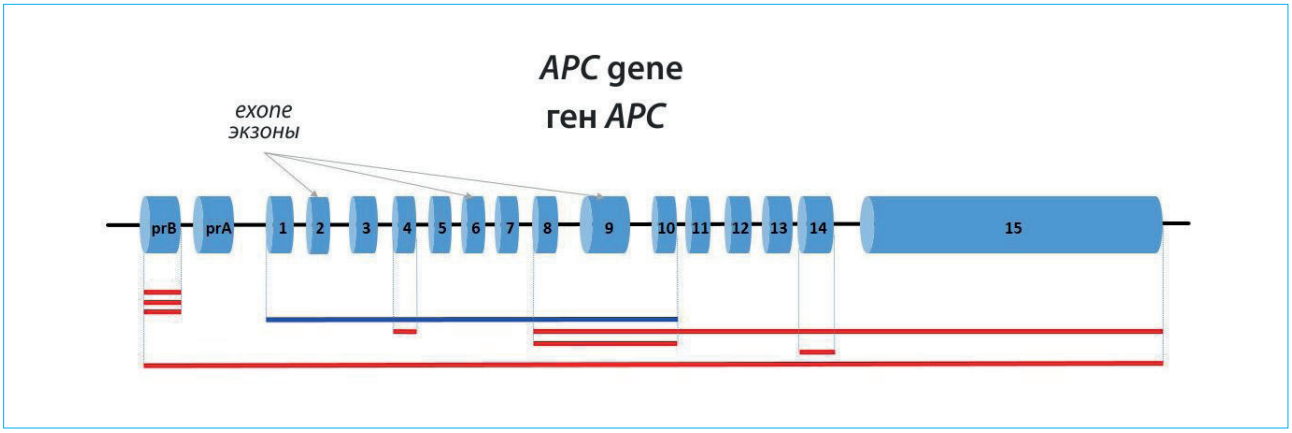

Fig. 1. The layout of large deletions/duplications in the *APC* gene found in the study sample. Deletions represented in red, duplication — in blue

Рис. 1. Схема расположения протяженных делеций/дупликаций в гене *APC*, обнаруженных в исследуемой выборке. Делеции представлены красным цветом, дупликация — синим

Table 3. Rate of detection of large deletions/duplications in patients with Peutz–Jeghers syndrome in various countries

Таблица 3. Частота выявления протяженных делеций/дупликаций у пациентов с синдромом Пейтца — Егерса в различных странах

Reference Ссылка	Country Страна	Large del/dup *STK11* Протяженные перестройки
[32]	Germany Германия	24 % (17/71)
[33]	Australia Австралия	30 % (10/33)
[29]	England Англия	14 % (11/76)
[31]	China Китай	45 % (5/11)
[34]	Hungary Венгрия	38 % (5/13)
[35]	Chile Чили	31 % (4/13)
[30]	Netherlands Нидерланды	13 % (3/23)

We performed the search for large deletions/duplications of *APC*, *MUTYH*, *STK11* genes using a mixture of MRC-Holland (Netherlands) SALSA MLPA Probemix probes P043 — *APC*, P378 — *MUTYH* and P101 — *STK11*, respectively, according to the manufacturer's instructions [18].

Amplification products were separated using fragment analysis on an ABI PRISM 3500 sequencer (ThermoFisher Scientific, USA) using the GeneScan600 LIZ dye Size Standard v2.0 (ThermoFisher Scientific, USA). The obtained results were analyzed using software Coffalyser.Net v.140721.1958 (MRC-Holland, Netherlands).

Statistical processing of the obtained data was carried out using the Statistica 10.0 program.

Results and discussion

Familial adenomatous polyposis

Initially, the samples from all 83 patients with familial adenomatous polyposis were sequenced by Sanger for searching point pathogenic variants in the *APC* gene, which were revealed in 68 (82 %) patients. Then, we used the MLPA method in the remaining 15 patients for searching large rearrangements, and found them in 8/15 cases. Thus, the detection rate of large deletions/duplications

Table 4. Clinical characteristics of patients with large deletions/duplications in the *STK11* gene

Таблица 4. Клинические характеристики пациентов с протяженными делециями/дупликациями в гене *STK11*

Patient number № пациента	Age of diagnosis Возраст диагноза	Clinical features Клинические особенности	Large del/dup Протяженные
Stk11	6	Total polyposis of the gastrointestinal tract. The skin of the lips is pigmented Тотальный полипоз желудочно-кишечного тракта. Кожа губ пигментирована	del 2–10
Stk16	16	Multiple polyps of the jejunum and colon. Pigmentation at the age younger than 40 years Множественные полипы тощей и толстой кишки. Пигментация до 40 лет	del 2–8
Stk26	5	Total polyposis of the gastrointestinal tract. The skin of the lips is pigmented Тотальный полипоз желудочно-кишечного тракта. Кожа губ пигментирована	del 1
Stk40	28	Total polyposis of the gastrointestinal tract. Characteristic pigmentation of the mucous membrane of the lips, cheeks, etc. Тотальный полипоз желудочно-кишечного тракта. Характерная пигментация слизистой оболочки губ, щек и др.	del 1

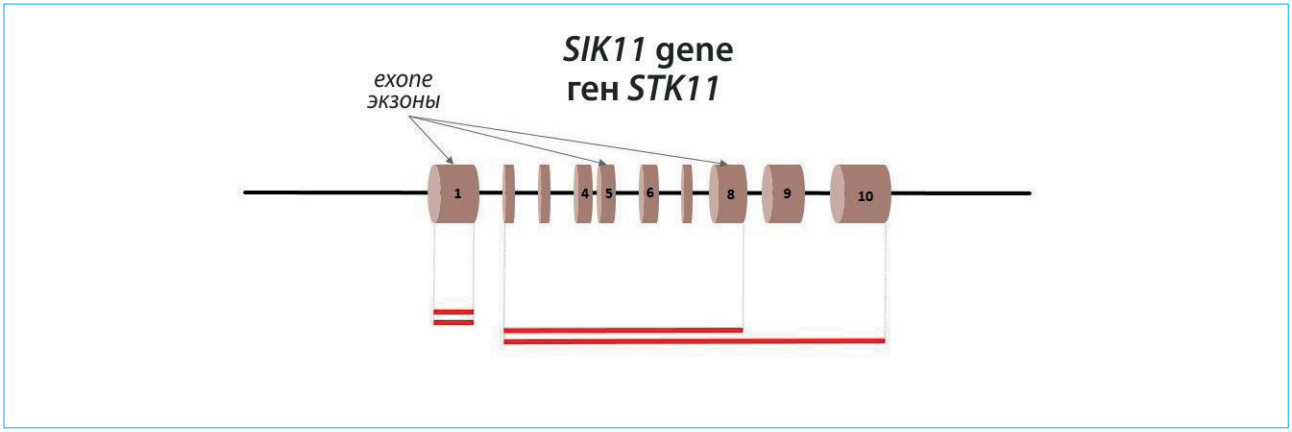

Fig. 2. Layout of large deletions/duplications in the *STK11* gene

Рис. 2. Схема расположения протяженных делеций/дупликаций в гене *STK11*, обнаруженных в исследуемой выборке

in presented group with familial adenomatous polyposis was 9.6 % (8/83). At the same time, the total rate of all pathogenic variants in the *APC* gene reached 91.5 % (76/83).

It should be noted that in comparison with the rate of large rearrangements in patients from other countries, the results obtained in our study are most similar to those of patients with familial adenomatous polyposis from Hungary (10 %) [19], Brazil (8.7 %) [20], Spain (7.3 %) [21] and Sweden (8.3 %) [22] (Table 1). Globally, the maximal rate of large rearrangements was detected in China (14 %) [23], and the lowest — in Belgium (4.7 %) [24] and the USA (2 %) [25]. Moreover, no large deletions/duplications were found in the Greek study [26] (Table 1). At the same time, it is important to note that there was a statistically significant difference in our results only in comparison with the data obtained for patients with familial adenomatous polyposis from the USA ($p < 0.05$), which is due to a very large sample of patients (1421) [25].

Interestingly, in comparison with our earlier paper [27], the percentage of detection of large rearrangements became higher (9.6 % vs. 4.8 %), which may be due to both an increase number of studied patients and their clinical and genetic features, however, these results did not differ statistically ($p > 0.05$).

The main characteristics of patients with large rearrangements are shown in Table 2. The number of polyps in all patients was more than 100, and the average age of onset of the disease was 32 years, which did not differ from the indicator patients with point mutations in the *APC* gene. At the same time, the size of the large deletion/duplication also did not affect the severity of the disease. Thus, patient A855 with deletion of only one exon had the age of diagnosis of 24 years, and patient A846 with deletion of three exons — 36 years. Thus, according to the clinical features of all patients with large rearrangements, the manifestation of the disease corresponded to the classical form of familial adenomatous polyposis and did not differ from patients with point mutations.

Figure 1 schematically shows all the detected large rearrangements in the *APC* gene. In total, seven large deletions and one large duplication revealed. Among the detected variants, the most often was deletion of promoter B (del prB), detected in three patients.

MUTYH-associated polyposis

Among the included 18 patients with suspected *MUTYH*—associated polyposis, no large deletions/duplications revealed. Similar results were obtained in most of the countries whose data we analyzed. However, only in Brazil [20], a single large rearrangement was detected (Table 1).

Recently, only nine large deletions/duplications were described worldwide, which was only 4 % of the whole spectrum of pathogenic variants detected in the *MUTYH* gene [8].

Peutz–Jeghers syndrome

Of the 34 patients included, 27 (79 %) had point mutations in the *STK11* gene. Among the remaining seven patients, four had large deletions of this gene. Thus, the rate of large rearrangements in Russian patients with Peutz–Jeghers syndrome was 12 % (4/34), and the total rate of all pathogenic variants in the *STK11* gene was 91 %.

Analyzing data from other countries, the results obtained in England (14 %) [29] and Netherlands (13 %) [30] were the closest to ours. The highest detection rate of large rearrangements, which significantly differed from ours ($p < 0.05$), was described in China (45 %) [31] (Table 3).

According to the clinical presentation, patients with Peutz–Jeghers syndrome and large deletions/duplications did not differ from patients with point mutations. At the same time, the size of the deletion itself also did not affect the severity of the disease (Table 4).

Figure 2 shows the layout of large deletions/duplications of the *STK11* gene found in the patients with Peutz–Jeghers syndrome. Four large deletions were found. Of these, deletion of the first exon occurred in two patients.

Conclusion

The study demonstrated the feasibility of including the method of detecting large rearrangements in routine DNA diagnostics of Russian patients with familial adenomatous polyposis and Peutz–Jeghers syndrome. Routine use of MLPA method makes it possible to increase the total frequency of detection of pathogenic variants in the *APC* and *STK11* genes above 90 %. At the same time, the need for searching of large rearrangements in the *MUTYH* gene was not justified.

References / Литература

1. *Siegel R.L., Miller K.D., Fedewa S.A., Ahnen D.J., Meester R.G.S., Barzi A., et al.* Colorectal cancer statistics, 2017. CA: a Cancer *Journal for Clinicians*. 2017;67(3):177–93. DOI: 10.3322/caac.21387
2. *Sung H., Ferlay J., Siegel R.L., Laversanne M., Soerjomataram I., Jemal A., et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a Cancer *Journal for Clinicians*. 2021;71(3):209–49. DOI: 10.3322/caac.21660
3. *Stoffel E.M., Murphy C.C.* Epidemiology and Mechanisms of the Increasing Incidence of Colon and Rectal Cancers in Young Adults. *Gastroenterology*. 2020;158(2):341–53. DOI: 10.1053/j.gastro.2019.07.055
4. *Ma H., Brosens L.A.A., Offerhaus G.J.A., Giardiello F.M., de Leng W.W.J., Montgomery E.A.*. Pathology and genetics of hereditary colorectal cancer. Review. *Pathology*. 2018;50(1):49–59. DOI: 10.1016/j.pathol.2017.09.004
5. *Ghadamyari F., Heidari M.M., Zeinali S., Khatami M., Merat S., Bagherian H., et al.* Mutational screening through comprehensive bioinformatics analysis to detect novel germline mutations in the *APC* gene in patients with familial adenomatous polyposis (FAP). *Journal of Clinical* Laboratory Analysis. 2021;35(5):e23768. DOI: 10.1002/jcla.23768
6. *GeneCards.* https://www.genecards.org/cgi-bin/carddisp.pl?gene=*APC*
7. *OMIM.* https://omim.org/entry/175100
8. *HGMD Professional 2022.2.* https://digitalinsights.qiagen.com/products-overview/clinical-insights-portfolio/human-gene-mutation-database/
9. *Цуканов А.С., Шубин В.П., Кузьминов А.М., Тобоева М.Х., Савельева Т.А., Кашников В.Н. и др.* Дифференциальный диагноз *MUTYH*-ассоциированного полипоза и спорадических полипов толстой кишки. *Российский журнал гастроэнтерологии, гепатологии, колопроктологии.* 2018;28(6):51–57. [*Tsukanov A.S., Shubin V.P., Kuzminov A.M., Toboeva M.Kh., Savelyeva T.A., Kashnikov V.N., et al.* Differential diagnosis of *MUTYH*-associated polyposis from sporadic colon polyps. *Russian journal of gastroenterology, hepatology, coloproctology*. 2018;28(6):51–57 (In Russ.)]. DOI: 10.22416/1382-4376-2018-28-6-51-57
10. *Тобоева М.Х., Шелыгин Ю.А., Фролов С.А., Кузьминов А.М., Цуканов А.С. MUTYH*-ассоциированный полипоз толстой кишки. *Терапевтический архив*. 2019;91(2):97–100. [*Toboeva M.Kh., Shelygin Yu.A., Frolov S.A., Kuzminov A.M., Tsukanov A.S. MUTYH*-associated polyposis. *Therapeutic archive*. 2019;91(2):97–100 (In Russ.)]. DOI: 10.26442/00403660.2019.02.000124
11. *OMIM.* https://omim.org/entry/608456
12. *GeneReviews.* https://www.ncbi.nlm.nih.gov/books/NBK107219/
13. *GeneCards.* https://www.genecards.org/cgi-bin/carddisp.pl?gene=*MUTYH*
14. *GeneReviews.* https://www.ncbi.nlm.nih.gov/books/NBK1266/
15. *Савельева Т.А., Пикунов Д.Ю., Кузьминов А.М., Цуканов А.С.* Синдром Пейтца-Егерса: что стало известно за 125 лет изучения? (обзор литературы). *Колопроктология*. 2021;20(2):85-96. [*Savelyeva T.A., Pikunov D.Yu., Kuzminov A.M., Tsukanov A.S.* Peutz – Jeghers syndrome: what has been known for 125 years of research? (review). *Coloproctology*. 2021;20(2):85–96 (In Russ.)]. DOI: 10.33878/2073-7556-2021-20-2-85-96
16. *GeneCards.* https://www.genecards.org/cgi-bin/carddisp.pl?gene=*STK11*
17. *Цуканов А.С.* Стратегия комплексного молекулярно-генетического изучения наследственных форм колоректального рака у российских пациентов: автореф. дис. ... докт. мед. наук. М.: ФГБУ «МГНЦ», 2017. 48 с. [*Tsukanov A.S.* Strategy for a comprehensive molecular genetic study of hereditary forms of colorectal cancer in Russian patients: abstract of the thesis. dis. doc. honey sciences. Moscow: FGBU "MGNTS", 2017. 48 p. (In Russ.)].
18. *MRC Holland.* https://www.mrcholland.com/
19. *Papp J., Kovacs ME., Matrai Z., Orosz E., Kásler M., Børresen-Dale A.-L., et al.* Contribution of *APC* and *MUTYH* mutations to familial adenomatous polyposis susceptibility in Hungary. *Fam Cancer*. 2016;15(1):85–97. DOI: 10.1007/s10689-015-9845-5
20. *Torrezan G.T., da Silva F.C.C., Santos É.M.M., Krepischi A.C,V., Achatz M.I.W., Junior S.A., et al.* Mutational spectrum of the *APC* and *MUTYH* genes and genotype–phenotype correlations in Brazilian FAP, AFAP, and MAP patients. *Orphanet J Rare Dis*. 2013;8:54. DOI: 10.1186/1750-1172-8-54
21. *Gómez-Fernández N., Castellví-Bel S., Fernández-Rozadilla C., Balaguer F., Muñoz J., Madrigal I., et al.* Molecular analysis of the *APC* and *MUTYH* genes in Galician and Catalonian FAP families: a different spectrum of mutations? *BMC Med Genet*. 2009;10:57. DOI: 10.1186/1471-2350-10-57
22. *Meuller J., Kanter-Smoler G., Nygren A.O.H., Errami A., Grönberg H., Holmberg E., et al.* Identification of genomic deletions of the *APC* gene in familial adenomatous polyposis by two independent quantitative techniques. *Genet Test*. 2004;8(3):248–256. DOI: 10.1089/gte.2004.8.248
23. *Sheng J.Q., Cui W.J., Fu L., Jin P., Han Y., Li S.-J., et al. APC* gene mutations in Chinese familial adenomatous polyposis patients. World J Gastroenterol. 2010;16(12):1522 –1526. DOI: 10.3748/wjg.v16.i12.1522
24. *Michils G., Tejpar S., Thoelen R., van Cutsem E., Vermeesch J.R., Fryns J.-P., et al.* Large deletions of the *APC* gene in 15 % of mutation-negative patients with classical polyposis (FAP): A Belgian study. *Hum Mutat*. 2005;25(2):125–134. DOI: 10.1002/humu.20122
25. *Kerr S.E., Thomas C.B., Thibodeau S.N., Ferber M.J., Halling K.C. APC* germline mutations in individuals being evaluated for familial adenomatous polyposis: a review of the Mayo Clinic experience with 1591 consecutive tests. *J Mol Diagn*. 2013;15(1):31–43. DOI: 10.1016/j.jmoldx.2012.07.005
26. *Fostira F., Thodi G., Sandaltzopoulos R., Fountzilas G., Yannoukakos D.* Mutational spectrum of *APC* and genotype-phenotype correlations in Greek FAP patients. *BMC Cancer*. 2010;10:389.
27. *Tsukanov A.S., Zabnenkova V.V., Shubin V.P., Pikunov D.Y., Savelyeva T.A., Kuzminov A.M., et al.* Identification of large deletions in the *APC* gene in Russian patients with familial adenomatous polyposis. *Neoplasma*. 2020;67(6):1343–1348. DOI: 10.4149/neo_2020_191230N1351
28. *Farahani R.K., Haghighi M.M., Aghdaei H.A., Keshavarzi F., Taleghani M.Y., Goodarzi F., et al.* Adenomatous polyposis coli gene large deletions in Iranian patients with familial adenomatous polyposis. *Indian J Cancer*. 2014;51(3):352–7. DOI: 10.4103/0019-509X.146758
29. *Volikos E., Robinson J., Aittomäki K., Mecklin J.-P., Järvinen H., Westerman A.M., et al.* LKB1 exonic and whole gene deletions are a common cause of Peutz – Jeghers syndrome. *J Med Genet*. 2006;43(5):e18. DOI: 10.1136/jmg.2005.039875
30. *De Leng W.W.J., Jansen M., Carvalho R., Polak M., Musler A.R., Milne A.N.A., et al.* Genetic defects underlying Peutz–Jeghers syndrome (PJS) and exclusion of the polarity-associated MARK/Par1 gene family as potential PJS candidates. *Clin Genet*. 2007;72(6):568–73. DOI: 10.1111/j.1399-0004.2007.00907.x
31. *Zheng B., Wang C., Jia Z., Liu Z., Li M., Jin Y., et al.* A Clinical and Molecular Genetic Study in 11 Chinese Children With Peutz–Jeghers Syndrome. J *Pediatr Gastroenterol Nutr*. 2017;64(4):559–64. DOI: 10.1097/MPG.0000000000001316
32. *Aretz S., Stienen D., Uhlhaas S., Loff S., Back W., Pagenstecher C., et al.* High proportion of large genomic

STK11 deletions in Peutz–Jeghers syndrome. Hum Mutat. 2005;26(6):513–9. DOI: 10.1002/humu.20253
33. *Chow E., Meldrum C.J., Crooks R., Macrae F., Spigelman A.D., Scott R.J.* An updated mutation spectrum in an Australian series of PJS patients provides further evidence for only one gene locus. *Clin Genet*. 2006;70(5):409–14. DOI: 10.1111/j.1399-0004.2006.00704.x
34. *Papp J., Kovacs M.E., Solyom S., Kasler M., Børresen-Dale A.-L., Olah E.* High prevalence of germline *STK11* mutations in Hungarian Peutz–Jeghers Syndrome patients. *BMC Med Genet*. 2010;11:169. DOI: 10.1186/1471-2350-11-169
35. *Orellana P., López-Köstner F., Heine C., Suazo C., Pinto E., Church J., et al.* Large deletions and splicing-site mutations in the *STK11* gene in Peutz–Jeghers Chilean families. *Clin Genet*. 2013;83(4):365–9. DOI: 10.1111/j.1399-0004.2012.01928.x

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