https://doi.org/10.33878/2073-7556-2021-20-3-35-42

Genetic and phenotypic characteristics of 60 Russian families with Lynch syndrome

Yuri A. Shelygin[1,2], Sergey I. Achkasov[1,2], Dmitrii A. Semenov[3], Oleg I. Sushkov[1], Dmitry G. Shakhmatov[1,2], Ekaterina M. Romanova[1], Vitaly P. Shubin[1], Alexey S. Tsukanov[1]

[1]Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya str., 2, Moscow, 123423, Russia)
[2]Russian Medical Academy of Postgraduate Education (Barricadnaya str., 2/1-1, Moscow, 125993, Russia)
[3]Medical clinic "K+31" (Lobachevsky st., 42, building 4, Moscow, 119415, Russia

ABSTRACT *AIM: to evaluate the genetic and clinical characteristics of Russian patients with Lynch syndrome.*
PATIENTS AND METHODS: in the period from 2012 to 2019, patients with suspected Lynch syndrome were studied, according to the selection guidelines (Amsterdam II and original criteria). All patients underwent a microsatellite instability test in the tumor, and if it was detected, germline mutations in the genes of MMR system. All patients underwent standard clinical procedures (colonoscopy, gastroscopy, CT, MRI).
RESULTS: Lynch syndrome was genetically confirmed in 60 unrelated patients (30 women was studied, ranging in age from 24 to 68 years). Germline mutations were found in the following genes: MLH1 — 30, MSH2 — 26, MSH6 — 2, PMS1 — 1, PMS2 — 1. For the first time in the world, 12 novel mutations have been described. Clinical features of Russian patients with Lynch syndrome include: the early age of the first cancer — 39.0 years; frequent 45% tumor site in the left colon; high (55%) incidence of poorly differentiated adenocarcinomas. A total of 234 tumors were diagnosed in Russian patients with Lynch syndrome and their relatives. It is also important to note that the stomach cancer is the third most common cancer after colon cancer.
CONCLUSION: Russian patients with Lynch syndrome showed clinical and genetic features, that distinguish them from European and North American population and should be taken into account when treating.

KEYWORDS: *Colorectal cancer, Lynch syndrome, MMR genes, germline mutations, microsatellite instability*

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

FINANCIAL INTERESTS: *The authors have no financial or proprietary interests in any material discussed in this article.*

CONSENT TO PARTICIPATE: *Informed consent was obtained from all individuals included in the study.*

CONSENT FOR PUBLICATION: *Participants consented to publication of de-identified information on the consent to participate. Only de-identified information included.*

ETHICS STATEMENT: *The studies involving human participants were reviewed and approved by Ethics Committee of the Ryzhikh National Medical Research Center of Coloproctology (Moscow, Russia). The patients participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.*

FOR CITATION: Shelygin Yu.A., Achkasov S.I., Semenov D.S., Sushkov O.I., Shakhmatov D.G., Romanova E.M., Shubin V.P., Tsukanov A.S. Genetic and phenotypic characteristics of 60 Russian families with Lynch syndrome. *Koloproktologia*. 2021;20(3):35–42. (in Russ.). https://doi.org/10.33878/2073-7556-2021-20-3-35-42

ADDRESS FOR CORRESPONDENCE: *Dmitrii A. Semenov, Medical clinic "K + 31", Lobachevsky st., 42, building 4, Moscow, 119415, Russia, e-mail: dr.semenov@inbox.ru*

Received — 07.06.2021 *Revised — 21.06.2021* *Accepted for publication — 11.08.2021*

INTRODUCTION

In Russia in 2019, about 77000 new cases of colorectal malignant neoplasms were registered. According to Kaprin A.D., et al., colorectal cancer is second in the morbidity structure [1]. In about 95% of cases, colorectal cancer is sporadic, and in 5% caused by a hereditary predisposition [2].

Lynch syndrome (OMIM 120435) is one of the most common hereditary cancer syndromes [3]. It caused by heterozygous germline mutations in the genes of the mismatch repair nucleotide system and characterized by the occurrence of cancer

[4]. It is believed that 3.6% of all cases of colorectal cancer are due to this [5].

The syndrome caused by mutations in the following genes: *MLH1* (OMIM 120436), *MSH2* (OMIM 609309), *MSH6* (OMIM 600678), *PMS1* (OMIM 600258), *PMS2* (OMIM 600259), *EPCAM* (OMIM 185535) [6]. Moreover, about 90% of hereditary mutations are concentrated in the genes *MLH1*, *MSH2*, *MSH6* [7].

The average age of patients with Lynch syndrome at the onset of the first cancer is significantly lower than in patients with sporadic tumors. According to Sinicrope F.A., the average age of patients with Lynch syndrome is about 45 years, while in the group of patients with sporadic cancer it is 69 years [6].

In 80% of cases, the first colorectal cancer in Europeans with Lynch syndrome occurs in the right colon. In addition, with Lynch syndrome, the risk of developing cancer of the endometrium, prostate, ureters and bladder, ovaries, breast, small intestine and other organs is increased [8].

In a study by Pérez-Cabornero, L. et al. in 2013, it was noted that patients from different populations are characterized by the presence of both clinical and genetic characteristics [9]. This article is devoted to the results of a study of the clinical and genetic characteristics of Russian patients with Lynch syndrome.

PATIENTS AND METHODS

In the period from 2012 to 2019 an observational single-center study was carried out. The research materials were clinical data on 60 probands with genetically confirmed Lynch syndrome. These patients included 30 females and 30 males, aged from 24 to 68 years. Initially, the Amsterdam II criteria used to select patients with colorectal cancer who needed molecular genetic testing [7]. Due to these criteria, we identified 9 patients with Lynch syndrome [10]. A significant disadvantage of the Amsterdam II criteria is the exclusion from the study of patients without a family history of malignant neoplasms. For this reason, since 2014, we have been guided by two independent original criteria [11]:

1. Colorectal cancer in a patient under the age of 43 (sensitivity — 88.9%, specificity — 82.9%)
2. Along with colorectal cancer, 2 or more cases of cancer in the patient or his blood relatives (regardless of age) (sensitivity — 100%, specificity — 64.7%)

Clinical check-up included family history, and history of the disease reviews, as well as colonoscopy with biopsy, gastroduodenoscopy, chest and abdominal CT. Fragment analysis (markers NR21, NR24, NR27, BAT25, BAT26) was performed on an ABI Prism 3500 capillary sequencer (Applied Biosystems, USA) according to the manufacturer's protocol to detect microsatellite instability in a tumor sample. When microsatellite instability detected in a tumor sample, a study carried out to identify germline mutations in the *MLH1* and *MSH2* genes. For this, polyacrylamide gel electrophoresis performed on a Sequi-Gen GT Sequencing Cell (BIO RAD, United States). When the electrophoretic picture of the fragments of studied genes of the particular patient has differed from the control samples, it was sequenced on an ABI PRISM 3500 device according to the manufacturer's protocol. DNA samples from patients whose tumors displayed microsatellite instability, but did not display mutations in the *MLH1* and *MSH2* genes were further studied using high-throughput sequencing on a Junior 454 device (Roche, Switzerland) and NextSeq550 (Illumina, USA), according to the manufacturer's protocols, with subsequent confirmation of detected mutations on the ABI PRISM 3500 genetic analyzer (Applied Biosystems, USA).

RESULTS

The most common germline mutations in Russian patients were found in genes *MLH1* — 30/60 (50,0%), and *MSH2* — 26/60 (43.3%). In the *MLH1* gene, among the 30 germline variants, there were 7 deletions, 3 insertions, 6 missense mutations, 10 splice site mutations, and 4 nonsense mutations. In the *MSH2* gene, 26 hereditary mutations identified: 5 deletions, 2 insertions, 3 missense mutations, 8 splice site mutations, 8 nonsense mutations. Two hereditary mutations were found in the *MSH6* gene, including the missense mutation c.2234T>A, as well as the nonsense mutation c.3577G>T. A nonsense mutation c.829C>T was detected in the

Table 1. *Genetic and phenotypic characteristics of families with Lynch syndrome (including probands)*

Gene	Mutation	Mutation-type	New	Families (*n* = 60)	Cases of a malignant tumor in the family (*n*)											
					Colon	Uterus	Stomach	Breast	Brain	Skin	Ureters	Ovaries	Bladder	Kidneys	Prostate	Pancreas	Thyroid
MLH1																	
	c.2T>G	missense		1	2												
	c.100G>T	nonsense	Yes	1	1												
	c.117-2A>G	splicesite		1	2												
	c.207+2T>A	splicesite	Yes	1	2												
	c.298C>T	nonsense		2	9	1	1		1								
	c.299G>C	missense		1	5												
	c.306+5G>A	splicesite		2	4	1											
	c.350C>T	missense		2	8												
	c.445dupC	insertion	Yes	1	1												
	c.546-2A>G	splicesite		1	5												
	c.677G>T	splicesite		1	5												
	c.947delT	deletion	Yes	1	2												
	c.1225C>T	nonsense		1	4	1											
	c.1520dupT	insertion		1	1												
	c.1668-1G>C	splicesite		1	1		1	1									
	c.1731G>A	splicesite		1	2		2										
	c.1852_1854del	deletion		5	23	2	5	1	1								
	c.1896+1G>C	splicesite		1	5		3	1									
	c.1896+1G>T	splice site		1	3	3	1	2									
	c.1921_1922insC	insertion	Yes	1	3												
	c.2038T>C	missense		1	3	1		1									
	c.2059C>T	missense		1	3												
	c.2073_2074delAT	deletion	Yes	1	4		1			1							
MSH2																	
	c.345_348del4	deletion	Yes	1	3	1		1			1			1			
	c.388_389delCA	deletion		1	5								1				
	c.571_573del	deletion		1	2												
	c.792+2T>C	splicesite		1	2												
	c.942+3A>T	splicesite		4	10	2	2				2		1		1		
	c.942G>A	splicesite		1	2				1								
	c.989T>C	missense		2	4	3										1	
	c.1174A>T	nonsense	Yes	1	3	1	1					1					
	c.1255C>T	nonsense		1	1	1	1										
	c.1288A>T	nonsense		2	5												
	c.1379_1477ins99	insertion	Yes	1	3					1							
	c.1386+1G>T	splicesite		2	3												
	c.1786_1788del3	deletion		1	3							1					
	c.1861C>T	nonsense		1	8	1											
	c.1968C>A	nonsense		1	4												
	c.1968C>G	nonsense		1	2	1											
	c.2038C>T	nonsense		1	1	2											
	c.2086C>T	missense		1	1												
	c.2266_2267delAC	deletion	Yes	1	2	1											
	c.2407dup	insertion	Yes	1	1												
MSH6																	
	c.2234T>A	missense		1	1												
	c.3577G>T	nonsense	Yes	1	1												
PMS1																	
	c.829C>T	nonsense		1	2												1
PMS2																	
	c.1144+1G>A	splicesite		1	1	1	1	1									
					168	23	19	8	3	2	3	2	2	1	1	1	1
Summary					**234**												

PMS1 gene, and a germline mutation of the splice site c.1144+1G>A in the *PMS2* gene. For the first time, 12 hereditary mutations identified: in the *MLH1* gene — 6 (c.100G>T, c.207+2T>A, c.445dupC, c.947delT, c.1921_1922insC, c.2073_2074delAT), in the *MSH2* gene — 5 (c.345_348del4, c.1174A>T, c.1379_1477ins99, c.2266_2267delAC, c.2407dup), in the *MSH6* gene — 1 (c.3577G>T).

Thus, the incidence of mutations in genes *MLH1*, *MSH2*, *MSH6*, *PMS1* and *PMS2* was 50%, 43.3%, 3.3%, 1.7% and 1.7%, respectively (Table 1).

Of the 60 probands with a genetically confirmed diagnosis of Lynch syndrome, 45 (75.0%) patients had relatives with malignant tumors of various organs, and 15 (25.0%) cases did not have family members with cancer.

The average age of the first tumor in Russian patients was 39.0 (24–68) years.

Among the detected mutations in the *MLH1* and *MSH2* genes, repeated variants were detected in patients from different families, which made it possible to analyze the probable presence of a correlation of a certain mutation with its phenotypic manifestation (Table 2).

The c.298C>T mutation in the *MLH1* gene was detected in 2 patients. In both cases, they had a malignant tumor of the right colon.

C.306+5G>A in the *MLH1* gene was also diagnosed in 2 patients. In the first case a cancer of the right colon was found, and in the second case — rectal cancer.

The c.350C>T mutation in the *MLH1* gene was found in 2 more patients with tumor site in the left colon and in the rectum.

Variant c.1852_1854del of the *MLH1* gene detected in 5 patients from unrelated families. Cancer of the right colon — in 3 cases, the left one — in 2 cases. In addition, 1 patient had uterine cancer.

The c.942+3A>T mutation in the *MSH2* gene was found in 4 patients. Malignant neoplasms of the right colon — in 2 cases, of the left — in 1 case, and of the rectum — in 1 patient. It is worth noting that in addition to colorectal cancer, malignant neoplasms of the prostate, uterus and ureters detected as well.

The c.989T>C mutation in the *MSH2* gene was found in 2 patients. In the first case, the tumor site was in the left colon and uterus, in the second case — in the right colon and uterus.

Variants c.1288A>T and c.1386+1G>T in the *MSH2* gene were detected two times. Cancer of the right colon — in 2 cases and rectal one — in 2 cases.

Thus, we did not find a significant correlation between a certain mutation variant and its phenotypic manifestation. In addition, it is worth noting that each of the identified duplicate variants in the InSiGHT database (www.insight-group.org) described in patients from different populations, which indicates the complexity of solving the problem using the “founder effect” approach.

Further, the spectrum of malignant neoplasms in patients with Lynch syndrome was analyzed, depending on the gene in which the mutation has been detected.

In 30 probands and their relatives with mutations in the *MLH1* gene, malignant neoplasms were detected in 6 different organs, namely, 98 cases of colorectal cancer, 14 cases of stomach cancer, 9 — uterine cancer, 6 — breast cancer, 2 — brain tumors, and 1 case of skin cancer. There was also no significant correlation between the hereditary mutation and the tumor site.

The spectrum of malignant neoplasms in families with a mutation in the *MSH2* gene was significantly more diverse than in families with mutations in the *MLH1* gene. In total, 65 cases of colorectal cancer, 13 cases of uterine cancer, 4 — stomach cancer, 3 — ureteral cancer, 2 — ovarian cancer, 2 — bladder cancer, 1 — of prostate cancer, and one case of breast, brain, skin, kidney and pancreas cancer were revealed in patients and their relatives.

Both patients with hereditary mutations in the *MSH6* gene had no relatives with cases of malignant neoplasms, and a molecular genetics study was carried out in them, since the age of development of colorectal cancer in patients was 33 and 41 years, respectively. Thus, the small number of patients with a hereditary mutation in the *MSH6* gene, as well as the absence of tumor-affected relatives in their families, does not allow us to determine any genetic and phenotypic correlations regarding germline mutations in this gene.

A mutation in the *PMS1* gene revealed in one patient, and that patient had no relatives with cases of malignant neoplasms.

Table 2. *The clinical picture of repeated mutations*

Gene	Mutations	Localization					
Patients (*n*)		**Right colon**	**Left colon**	**Rectum**	**Uterus**	**Prostate**	**Ureters**
MLH1							
2	c.298C>T	+					
	c.298C>T	+					
2	c.306+5G>A			+			
	c.306+5G>A	+					
2	c.350C>T		+				
	c.350C>T			+			
5	c.1852_1854del	+					
	c.1852_1854del		+				
	c.1852_1854del		+				
	c.1852_1854del	+					
	c.1852_1854del	+			+		
MSH2							
4	c.942+3A>T	+					
	c.942+3A>T	+				+	+
	c.942+3A>T		+		+		
	c.942+3A>T			+			
2	c.989T>C		+		+		
	c.989T>C	+			+		
2	c.1288A>T			+			
	c.1288A>T	+					
2	c.1386+1G>T	+					
	c.1386+1G>T			+			

In the *PMS2* gene, one patient was found to have the c.1144 + 1G > A mutation. In this case, cancer of the right colon was diagnosed, and the patient had a history of cancer of the uterus and breast. The family history of that patient revealed a stomach cancer.

The most common site of malignant neoplasms in patients with Lynch syndrome in Russia, as well as in patients from other countries, was the colon.

Of 49 primary malignant neoplasms in the colon, in 27 (55.0%) patients cancer was detected in the

right colon and in 22 (45%) cases — in the left, of which in 13 cases the tumor site was the rectum.
Colon cancer stage I was detected in 3 (6%) of 49 patients, stage II — in 6 (12%), stage III — in 36 (74%), and stage IV — in 4 (8%) cases.
Highly differentiated colon adenocarcinoma detected in 1 (2%) of 49 cases, moderately differentiated — in 21 (43%) cases, and poorly differentiated cancer was found in 27 (55.0%) patients.
The second place between tumor sites in Russian patients with Lynch syndrome is uterine cancer.
Primary gastric cancer was detected in 1 (1.6%) of 60 patients. In 1 (1.6%) thyroid cancer was detected; skin cancer was detected in 2 (3.2%) cases.
Recurrence of colorectal cancer occurred in 3 (5%) of 60 patients. All of them underwent curative surgery.
Metachronous colorectal cancer was in 23 (38.3%) patients with Lynch syndrome. The average age at the onset of metachronous colorectal cancer was 49.8 (26-68) years.
Stage I metachronous colorectal cancer was in 6 (26.0%) cases, II — in 11 (48%), III — in 6 (26.0%).
Highly differentiated colon adenocarcinoma was in 2 (9.0%) of 23 cases, moderately differentiated in 6 (26%) cases, and poorly differentiated cancer in 15 (65.0%) patients.
No distant metastases occured in patients with metachronous cancer of the colon and rectum.
Two-hundred-thirty-four tumors diagnosed in Russian patients with Lynch syndrome and their relatives. Most often, malignant tumor site were in the colon — 168 (71.8%) cases, uterine cancer was in the second place — 23 (9.8%) cases, stomach cancer — in the third, it was detected in 19 (8.1%) observations. At the same time, stomach cancer is only in the 6th place between tumor sites in the Western European and North American populations.

DISCUSSION

The most well-known criteria for selecting patients for genetic testing for suspected Lynch syndrome are the Amsterdam II criteria. According to Weissman S., these criteria do not provide 100% detection of patients with Lynch syndrome [12]. We developed our own criteria that are suitable for Russian patients and take into account the shortcomings of Amsterdam II.
The use of these criteria allowed us to identify 60 families with mutations in the genes of the DNA repair system. At the same time, the application of the Amsterdam II criteria would not give us the opportunity to find Lynch syndrome in 15 (25%) out of 60 probands, since they did not have relatives with an oncological history and did not have to undergo molecular genetic tests.
Because of the study, some genetic and phenotypic differences between Russian patient population and European and North American patient populations revealed.
The average age of the first tumor in Russian patients was 39.0 years, which is significantly lower than this average age from the data of the most representative European multicenter study — 45 years [13].
The most frequent mutations in Russian patients found in the *MLH1* gene — 50% (30/60) and *MSH2* — 43.3% (26/60), while mutations in the *MSH2* gene are more often described in the HGMD Professional 2020.3 database.
No correlation between a certain mutation in *MLH1* and *MSH2* genes and a phenotypic manifestation detected; however, patients with a pathogenic mutation in the *MSH2* gene have a significantly greater number of target organs for cancer development than those with a mutation in the *MLH1* gene.
In Russian patients with Lynch syndrome included in the study, left-sided colon tumor found in 45% (22/49) of cases. Interestingly, in 13 out of 49 (26.5%) cases, the tumor found in the rectum, which is also a distinctive feature of patients from Russia. For European and North American populations, approximately 80% of cases characterized by proximal colon cancer [14]. Since a most common tumor site in the left colon and in the rectum in Russian patients, European guidelines for performing colectomy with ileorectal anastomoses are not always justified [15].
Attention drawn to the fact that in Russian patients the third place in terms of incidence is taken by stomach cancer, which was detected in 19 (6.6%) cases from 60 families with a oncological history. At the same time, according to the literature, this

pathology in the United States ranks only sixth in occurrence in Lynch syndrome [8].

CONCLUSION

Lynch syndrome was diagnosed in 60 Russian patients from 60 families. Clinical and genetic features identified in Russian patients that distinguish them from the European and North American populations. Given these features, our criteria improve the identification of patients whose system of mismatch repair needs to be estimated. For the first time in the world, 12 hereditary mutations in the MMR genes identified. The data obtained on germline mutations indicate the advisability (if Lynch syndrome is suspected) of starting a molecular genetics study from the *MLH1* gene, and demonstrate the need to study all coding exons of the DNA repair system genes. At the same time, no correlation "a certain gene mutation — phenotype" was found, but it was shown that the largest spectrum of malignant neoplasms in various organs is characteristic of carriers of a mutation in the *MSH2* gene. The identified clinical features of Russian patients with Lynch syndrome include the early average age of development of the first cancer — 39.0 years; common (45%) tumor site in the left colon; high (55%) incidence of poorly differentiated adenocarcinomas. It is also important to note that the stomach cancer is the third most common cancer after colon cancer.

The identified population clinical features force us to return from the standardized strategy of colorectal cancer surgery on the background of Lynch syndrome to a personalized approach.

AUTHORS CONTRIBUTION

Concept and design of the study: *Alexey S. Tsukanov, Sergey I. Achkasov, Dmitry G. Shakhmatov*

Collection and processing of the material: *Dmitrii A. Semenov, Vitaly P. Shubin, Ekaterina M. Romanova*

Statistical processing: *Dmitrii A. Semenov, Alexey S. Tsukanov*

Writing of the text: *Dmitrii A. Semenov, Alexey S. Tsukanov*

Editing: *Yuri A. Shelygin, Sergey I. Achkasov, Alexey S. Tsukanov, Oleg I. Sushkov*

INFORMATION ABOUT THE AUTHORS (ORCID)

Yuri A. Shelygin — 0000-0002-8480-9362
Sergey I. Achkasov — 0000-0001-9294-5447
Dmitrii A. Semenov — 0000-0001-7680-5911
Oleg I. Sushkov — 0000-0001-9780-7916
Dmitry G. Shakhmatov — 0000-0001-7964-2126
Ekaterina M. Romanova — 0000-0003-3874-6695
Vitaly P. Shubin — 0000-0002-3820-7651
Alexey S. Tsukanov — 0000-0001-8571-7462

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