DOI: 10.21294/1814-4861-2018-17-4-53-58
УДК: 618.19-006.6-056.7-053:575.113:575.24(47+57)

Для цитирования: *Анисименко М.С., Пауль Г.А., Козяков А.Е., Гуткина Н.И., Бердюгина Д.А., Гаранин А.Ю., Буторина А.В., Горностаева Е.В., Хафизов К.Ф., Вяткин Ю.В., Штокало Д.Н., Коваленко С.П.* Спектр мутаций гена *BRCA1* у больных раком молочной железы в молодом возрасте в России. Сибирский онкологический журнал. 2018; 17 (4): 53–58. – doi: 10.21294/1814-4861-2018-17-4-53-58.
For citation: *Anisimenko M.S., Paul G.A., Kozyakov A.E., Gutkina N.I., Berdyugina D.A., Garanin A.Yu., Butorina A.V., Gornostaeva E.V., Khafizov K.F., Vyatkin Yu.V., Shtokalo D.N., Kovalenko S.P.* The spectrum of *BRCA1* gene mutations in early onset breast cancer patients from Russia. Siberian Journal of Oncology. 2018; 17 (4): 53–58. – doi: 10.21294/1814-4861-2018-17-4-53-58.

СПЕКТР МУТАЦИЙ ГЕНА *BRCA1* У БОЛЬНЫХ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ В МОЛОДОМ ВОЗРАСТЕ В РОССИИ

М.С. Анисименко[1,2], Г.А. Пауль[2], А.Е. Козяков[3], Н.И. Гуткина[1], Д.А. Бердюгина[1,2], А.Ю. Гаранин[1,2], А.В. Буторина[1,2], Е.В. Горностаева[1,2], К.Ф. Хафизов[4], Ю.В. Вяткин[5], Д.Н. Штокало[5,6], С.П. Коваленко[1,2,7]

Федеральный исследовательский центр фундаментальной и трансляционной медицины, г. Новосибирск, Россия[1]
Россия, 630117, г. Новосибирск, ул. Тимакова, 2[1]
Лаборатория генодиагностики ООО «Биолинк», г. Новосибирск, Россия[2]
Россия, 630117, г. Новосибирск, ул. Тимакова, 2[2]
Новосибирский областной клинический онкологический диспансер, Новосибирск, Россия. E-mail: jocus@bk.ru[3]
Россия, 630108, г. Новосибирск, ул. Плахотного, 2[3]
Центральный научно-исследовательский институт эпидемиологии Роспотребнадзора, г. Москва, Россия[4]
Россия, 111123, г. Москва, ул. Новогиреевская, 3а[4]
ООО «АкадемДжин», г. Новосибирск, Россия[5]
Россия, 630090, г. Новосибирск, пр. академика Лаврентьева, 6[5]
Институт систем информатики им. А.П. Ершова СО РАН, г. Новосибирск, Россия[6]
Россия, 630090, г. Новосибирск, пр. Академика Лаврентьева, 6[6]
Новосибирский государственный университет, г. Новосибирск, Россия[7]
Россия, 630090, г. Новосибирск, ул. Пирогова, 1[7]

Аннотация

Цель исследования – оценить частоту встречаемости патогенных мутаций в BRCA1 гене у женщин с раком молочной железы, проживающих в России. **Материал и методы.** Проведён анализ полной кодирующей части гена BRCA1 у 445 больных раком молочной железы на ранней стадии (возраст больных до 40 лет), проживающих в Новосибирской области (Россия), с помощью метода таргетного секвенирования на платформе Ion Torrent. Результаты. Выявлено 40 (9 %) носительниц различных патогенных мутаций. У 35 (7,9 %) пациенток обнаружена мутация 5382insC, описанная ранее как «мутация-основателя» в славянской популяции. У 5 (1,1 %) пациенток были выявлены другие различные патогенные мутации, а именно C61G, 462delCC, E143X, 4153delA и IVS18 + 1G> T. Кроме того, 29 генетических вариантов с отсутствующей или неясной клинической значимостью были обнаружены в гене BRCA1 у 445 больных раком молочной железы на ранней стадии. Выводы. Получены данные о частоте генетических вариаций гена BRCA1 у больных раком молочной железы на ранней стадии, проживающих в Новосибирской области (Россия). Доля мутации 5382insC составляет 87,5 % от всех патогенных мутаций в гене BRCA1, обнаруженных у пациенток.

Ключевые слова: ген BRCA1, мутация, рак молочной железы в молодом возрасте, наследственный рак, секвенирование следующего поколения, таргетное секвенирование.

Анисименко Максим Сергеевич, jocus@bk.ru

THE SPECTRUM OF BRCA1 GENE MUTATIONS IN EARLY ONSET BREAST CANCER PATIENTS FROM RUSSIA

M.S. Anisimenko[1,2], G.A. Paul[2], A.E. Kozyakov[3], N.I. Gutkina[1], D.A. Berdyugina[1,2], A.Yu. Garanin[1,2], A.V. Butorina[1,2], E.V. Gornostaeva[1,2], K.F. Khafizov[4], Yu.V. Vyatkin[5], D.N. Shtokalo[5,6], S.P. Kovalenko[1,2,7]

Federal Research Center of Fundamental and Translational Medicine, Novosibirsk, Russia[1]
2, Timakova Street, 630117-Novosibirsk, Russia. E-mail: jocus@bk.ru[1]
BioLink Ltd, Novosibirsk, Russia[2]
2, Timakova Street, 630117-Novosibirsk, Russia[2]
Novosibirsk Regional Oncological Clinic, Novosibirsk, Russia[3]
2, Plahotnogo Street, 630108-Novosibirsk, Russia[3]
Central Research Institute of Epidemiology, Moscow, Russia[4]
3a, Novogireevskaya Street, 111123-Moscow, Russia[4]
AcademGene LLC, Novosibirsk, Russia[5]
6, Academician Lavrentiev Ave., 630090-Novosibirsk, Russia[5]
A.P. Ershov Institute of Informatics Systems, Novosibirsk, Russia[6]
6, Akademika Lavrentieva Ave., 630090-Novosibirsk, Russia[6]
Novosibirsk State University, Novosibirsk, Russia[7]
1, Pirogova Street, 630090-Novosibirsk, Russia[7]

Abstract

Aim of the study. Aim of the study was to estimate the occurrence of pathogenic mutations in the *BRCA1* gene in Russian breast cancer patients. **Material and methods.** Complete coding sequence of the *BRCA1* gene of 445 early onset breast cancer patients (under 40 years) from Novosibirsk region (Russia) were analyzed by targeted Next Generation Sequencing (NGS) using Ion Torrent platform. **Results.** Forty (9%) carriers of various pathogenic mutations were revealed. Thirty five (7,9%) patients carried 5382insC mutation, described earlier as a founder mutation for Slavic population. Five (1.1%) patients carried various pathogenic mutations, namely C61G, 462delCC, E143X, 4153delA, and IVS18+1G>T. Besides, 29 genetic variants with no clinical significance or with unknown clinical significance were detected in *BRCA1* gene among 445 early onset breast cancer patients. **Conclusions.** Data on the frequency of genetic variations in the *BRCA1* gene among early onset breast cancer patients in the Novosibirsk Region (Russia) were obtained. Proportion of the 5382insC mutation is 87.5% of all pathogenic mutations in the *BRCA1* gene found in patients.

Keywords: *BRCA1* gene, mutation, early onset breast cancer, hereditary cancer, NGS, targeted sequencing.

Introduction

Hereditary factors account for up to 10% of all breast cancer cases [1]. A significant part of the hereditary forms of breast cancer is caused by mutations in the *BRCA1* and BRCA2 genes. The likelihood of a malignancy during the lifespan for *BRCA1/2* mutation carriers is very high (up to 90%) [2].

Several studies demonstrated the prevalence of *BRCA1* 5382insC mutation among breast/ovarian cancer patients in Russia [3–5]. Frequency of 185delAG, C61G, and 4153delA mutations is significantly less compared to 5382insC, the frequency of other mutations in *BRCA1* gene remains unexplored [6, 7]. However, there are no exact figures regarding frequency of *BRCA1* mutation in Russian population and among cancer patients, these data can be useful for screening programs and/or for placing objectives on the mutation analysis guidelines. According to our previous results, population study can reveal only frequent mutations (as *BRCA1* 5382insC), only single cases of other frequent mutations can be found even in large (about 8000) population samples [8]. Early onset cancer patient's cohort contains increased proportion of hereditary cancer cases, so analysis of this group can provide information on the spectrum and frequencies of pathogenic mutations in population. This information can be of value for the guidelines for the analysis of mutations among Russian citizens. In this study, we analyzed a complete coding sequence of *BRCA1* gene of 445 early onset breast cancer patients from Novosibirsk region with the aim to estimate the occurrence of pathologic mutations in the *BRCA1* gene in Russia.

Material and Methods

Blood samples were collected from 445 breast cancer patients of the Novosibirsk Regional Oncology Clinic between April 2013 and June 2016. The age of the patients at the time of diagnosis was from 19 to 40 years.

DNA was isolated from the blood samples using RealBest extraction 100 Kit (Vector-Best, Russia).

Analysis of the complete coding sequence of the

Table 1

Genetic variants found in early onset breast cancer patients in the Novosibirsk region

Exon/ Intron	HGVS genomic (GRSh37 assembly)	Mutation type	Base change	Designation	HGVS cDNA	HGVS protein	dbSNP	Clinical importance (BIC)	Number of homozygous carriers	Homozygous carriers frequency	Number of heterozygous carriers	Heterozygous carriers frequency	Allele frequency	Allele frequency (ExAC)	Allele frequency (1000 genomes)
In 2	*41267810G>A*	*IVS*	*C>T*	*IVS2-14C>T*	*c.81-14C>T*	-	*rs80358006*	*Unknown*	*0*	*0*	*1*	*0.0022*	*0.0011*	*0.0005*	-
Ex 5	**41258504A>C**	**Missense**	**T>G**	**C61G**	**c.181T>G**	**p.Cys61Gly**	**rs28897672**	**Yes**	**0**	**0**	**1**	**0.0022**	**0.0011**	**0.00007**	**-**
In 5	41258417T>A	IVS	A>T	IVS5+56A>T	c.212+56A>T	-	-	-	0	0	1	0.0022	0.0011	-	-
Ex 7	**41256236_41256237delGG**	**Frameshift**	**delCC**	**462delCC**	**c.343_344delCC**	**p.Pro115Terfs**	**-**	**-**	**0**	**0**	**1**	**0.0022**	**0.0011**	**-**	**-**
Ex 7	**41256153C>A**	**Nonsense**	**G>T**	**E143X**	**c.427G>T**	**p.Glu143Ter**	**rs80356991**	**Yes**	**0**	**0**	**1**	**0.0022**	**0.0011**	**0.0001**	**-**
In 7	41251931G>A	IVS	C>T	IVS7-34C>T	c.442-34C>T	-	rs799923	No	11	0.0247	139	0.3124	0.1809	0.1738	0.0986
Ex 8	*41251803T>C*	*Missense*	*A>G*	*Y179C*	*c.536A>G*	*p.Tyr179Cys*	*rs56187033*	*Unknown*	0	0	3	0.0067	0.0034	0.0003	0.0002
In 8	41251778delC	IVS	delG	IVS8+14delG	c.547+14_547+14delG	-	rs273902771	Unknown	0	0	1	0.0022	*0.0011*	*0.0001*	-
Ex 9	41249263G>A	Synonymous	C>T	710C>T	c.591C>T	p.Cys197=	rs1799965	No	0	0	1	0.0022	0.0011	0.0015	0.0004
Ex 11	41246481T>C	Missense	A>G	Q356R	c.1067A>G	p.Gln356Arg	rs1799950	Unknown	2	0.0045	37	0.0831	0.0461	0.0441	0.0218
Ex 11	41246298T>C	Missense	A>G	N417S	c.1250A>G	p.Asn417Ser	rs80357113	Unknown	0	0	1	0.0022	0.0011	-	-
Ex 11	*41246092A>G*	*Missense*	*T>C*	*F486L*	*c.1456T>C*	*p.Phe486Leu*	*rs55906931*	*Unknown*	0	0	1	0.0022	0.0011	0.0003	0.0002
Ex 11	41245900T>G	Missense	A>C	N550H	c.1648A>C	p.Asn550His	rs56012641	Unknown	0	0	3	0.0067	*0.0034*	*0.0003*	*0.0002*
Ex 11	41245471C>T	Missense	G>A	D693N	c.2077G>A	p.Asp693Asn	rs4986850	No	0	0	32	0.0719	0.0360	0.0568	0.0335
Ex 11	41245466G>A	Synonymous	C>T	2201C>T	c.2082C>T	p.Ser694=	rs1799949	No	31	0.0697	193	0.4337	0.2865	0.3483	0.3365
Ex 11	41245237A>G	Synonymous	T>C	2430T>C	c.2311T>C	p.Leu771=	rs16940	No	27	0.0607	221	0.4966	0.3090	0.3420	0.3353
Ex 11	*41244952G>A*	*Missense*	*C>T*	*R866C*	*c.2596C>T*	*p.Arg866Cys*	*rs41286300*	*No*	*0*	*0*	*1*	*0.0022*	*0.0011*	*0.0001*	-
Ex 11	41244936G>A	Missense	C>T	P871L	c.2612C>T	p.Pro871Leu	rs799917	No	26	0.0584	223	0.5011	0.3090	0.4100	0.4561
Ex 11	41244435T>C	Missense	A>G	E1038G	c.3113A>G	p.Glu1038Gly	rs16941	No	23	0.0517	152	0.3416	0.2225	0.3429	0.3357
Ex 11	41244429C>T	Missense	G>A	S1040N	c.3119G>A	p.Ser1040Asn	rs4986852	Unknown	0	0	4	0.0090	0.0045	0.0132	0.0098
Ex 11	41244029A>C	Missense	T>G	S1173R	c.3519T>G	p.Ser1173Arg	-	-	0	0	1	0.0022	0.0011	-	-
Ex 11	41244000T>C	Missense	A>G	K1183R	c.3548A>G	p.Lys1183Arg	rs16942	No	30	0.0674	174	0.3910	0.2629	0.3490	0.3526
Ex 11	**41243513delT**	**Frameshift**	**delA**	**4153delA**	**c.4035_4035delA**	**p.Glu1345=fs**	**rs80357711**	**Yes**	**0**	**0**	**1**	**0.0022**	**0.0011**	**0.00004**	**-**
Ex 11	41243509T>C	Missense	A>G	R1347G	c.4039A>G	p.Arg1347Gly	rs28897689	Unknown	0	0	4	0.0090	0.0045	0.0040	0.0006
Ex 13	41234470A>G	Synonymous	T>C	4427T>C	c.4308T>C	p.Ser1436=	rs1060915	No	25	0.0562	214	0.4809	0.2966	0.3431	0.3363
Ex 15	41226488C>A	Missense	G>T	S1512I	c.4535G>T	p.Ser1512Ile	rs1800744	No	0	0	1	0.0022	0.0011	0.0022	0.0006
Ex 16	41223094T>C	Missense	A>G	S1613G	c.4837A>G	p.Ser1613Gly	rs1799966	No	25	0.0562	226	0.5079	0.3101	0.3496	0.3558
Ex 16	*41223048A>G*	*Missense*	*T>C*	*M1628T*	*c.4883T>C*	*p.Met1628Thr*	*rs4986854*	*Unknown*	*0*	*0*	*5*	*0.0112*	*0.0056*	*0.0015*	*0.0026*
Ex 16	41222975C>T	Missense	G>A	M1652I	c.4956G>A	p.Met1652Ile	rs1799967	Unknown	0	0	22	0.0494	0.0247	0.0176	0.0112
Ex 17	*41219694C>A*	*Missense*	*G>T*	*A1669S*	*c.5005G>T*	*p.Ala1669Ser*	*rs80357087*	*Unknown*	*0*	*0*	*2*	*0.0045*	*0.0022*	*0.00005*	-
In 17	41216021G>A	IVS	C>T	IVS17-53C>T	c.5075-53C>T	-	rs8176258	No	0	0	9	0.0202	0.0101	-	0.0110
In 18	**41215890C>A**	**IVS**	**G>T**	**IVS18+1G>T**	**c.5152+1G>T**	**-**	**rs80358094**	**Yes**	**0**	**0**	**1**	**0.0022**	**0.0011**	**-**	**-**
In 18	41215825C>T	IVS	G>A	IVS18+66G>A	c.5152+66G>A	-	rs3092994	No	31	0.0697	149	0.3348	0.2371	-	0.3425
Ex 20	**41209082_41209083insG**	**Frameshift**	**insC**	**5382insC**	**c.5263_5264insC**	**p.Gln1756Profs**	**rs80357906**	**Yes**	**0**	**0**	**35**	**0.0787**	**0.0393**	**-**	**-**
In 20	41208991C>T	IVS	G>A	IVS20+78G>A	c.5277+78G>A	-	rs80358107	Unknown	0	0	3	0.0067	0.0034	-	0.0002

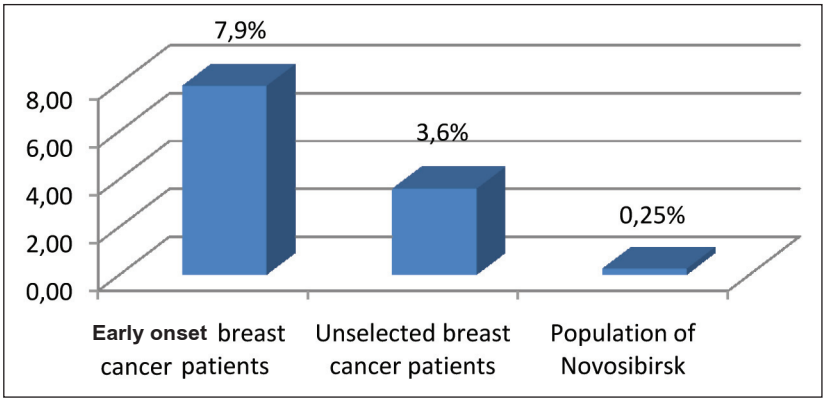

Figure 1. Frequency of the *BRCA1* 5382insC mutation in early onset breast cancer patients, unselected breast cancer patients, and in general population of Novosibirsk city

BRCA1 gene (22 exons, 5592 bp) was performed by targeted sequencing on IonTorrent platform. All exons with adjacent intron regions (20–80 bp) were completely covered with 68 amplicons (140–190 bp). Primers were designed by using Ion AmpliSeq Designer and Primer 3 software. The primer pairs were combined into 3 pools. Three multiplex PCR reactions were used to amplify the 68 selected fragments. Multiplex reaction products were combined and purified using Agencourt AMPure XP magnetic beads (Beckman Coulter, USA). The amplicons were ligated with bar codes and A/P1 adapters. Then enrichment was carried out with the primer pair complementary to adapters A and P1. Concentration of the purified enriched amplicons was measured using Qubit dsDNA HS Assay kit on the Qubit 3.0 fluorimeter (Life Technologies, USA). The normalized DNA libraries were then amplified by emulsion PCR using Ion PGM Hi-Q OT2 kit and sequenced using Ion PGM instrument (Life Technologies, USA) according to the manufacturer's instructions.

Bioinformatic analysis of the raw data was based on PRINSEQ technique [9]. The nucleotide sequences obtained in the analysis were compared with the reference sequence of the human genome GRCh37/hg19 using the BWA-MEM software version 0.7.5 [10]. The search for genetic variants was carried out using the SAM tools software version 0.1.19 [11].

Results and discussion

Analysis of 445 early onset breast cancer patients revealed 35 genetic variants in *BRCA1* gene. Results of the study are presented in Table 1.

We detected 40 carriers (9%) of various pathogenic mutations, including 35 carriers (7.9%) of 5382insC mutation. *BRCA1* 5382 insC was described as founder mutation for Slavic population [5]. Five patients (1.1%) carried pathogenic mutations C61G, 462delCC, E143X, 4153delA, and IVS18+1G>T (each particular mutation was found in a single patient in a heterozygote state). All pathogenic mutations are depicted in bold in Table 1. According to our previous results, the frequency of the 5382insC mutation among residents of Novosibirsk city is 0.25% [8], the frequency of this mutation among unselected breast cancer patients in the Novosibirsk region is 3.6% [12]. Figure 1 shows the frequency of the 5382insC mutation among unselected breast cancer patients and in the cohort of early onset breast cancer patients in comparison with the frequency of this mutation in general population.

Remarkably, allele frequency of 9 genetic variants is at least twice higher than the frequency provided in the database for general population (ExAC or/and 1000 genomes), these variants are marked in italics in Table 1.

The frequency of three genetic variants has not assigned in dbSNP yet and are not specified in Table 1. Two of these variants were undisclosed for the first time. Ermolenko N.A. et al. found the 462delCC (p.Pro115Terfs) mutation in Russian breast cancer patients [13].

The obtained data on *BRCA1* mutation frequencies can be the basis for the guidelines for mutation analysis in various cohort of breast cancer patients (patients with family history, early onset breast cancer patients etc.). Indeed, our data indicate the absence of hot-spot mutation except *BRCA1* 5382insC, but a very strong prevalence of this mutation in early onset cancer patients (87.5 % of all found *BRCA1* mutations). A frequency of the *BRCA1* 5382insC mutation among non-selected breast cancer patients in Russia was reported in several studies [4, 12, 14]. Similar frequency of the *BRCA1* 5382insC mutation was reported for Ukranian breast cancer patients [15].

In spite of the high frequency of the *BRCA1* 5382insC mutation among unselected cancer patients in Poland [16] the mutation occurrence is more than two times less than in Russia (1.9 %) and just slightly higher than the frequency of the mutation C61G (1.2 %). A frequency of *BRCA1* 5382insC mutation in Germany among unselected breast cancer patients is even less (1%) [17].

Thus, the frequency of the *BRCA1* 5382C mutation among unselected breast cancer patients from Europe is maximal in Russia (3.6–4 %), intermediate in Poland

and Germany (1.9 % and 1.0 %, correspondingly) and quite rare in France [18] and in Spain [19].

So, this data leads to the logical considerations regarding the workflow of the *BRCA1* gene mutations analysis specifically for Russia. The frequencies of *BRCA1* gene mutations in Russia dictates the need to analyze *BRCA1* 5382insC mutation as the first step of analysis and, if not found, to analyze a complete coding region of *BRCA1* gene. This workflow is in contrast with the accepted idea to analyze 4–8 mutations which were ever found in cancer patients with family history. Moreover, due to the low cost and relative simplicity analysis of the *BRCA1* 5382insC mutation can be offered to all breast cancer patients with and without family history since a number of publications demonstrate a limited significance of family history in the present study.

Conclusion

As a result of the study, data on the frequency of genetic variations in the *BRCA1* gene among early onset breast cancer patients in the Novosibirsk Region were obtained. Important, that the proportion of the 5382insC mutation is 87.5 % of all pathogenic mutations in the *BRCA1* gene found in patients. Frequency of the 4153delA mutation, which was previously characterized as a founder mutation for Russian breast/ovarian cancer patients is not higher than frequency of other pathogenic mutations found for *BRCA1* mutations appearance [16].

ЛИТЕРАТУРА/REFERENCES

1. *Mavaddat N., Antoniou A.C., Easton D.F., Garcia-Closas M.* Genetic susceptibility to breast cancer. Mol Oncol. 2010 Jun; 4(3): 174–91. doi: 10.1016/j.molonc.2010.04.011.

2. *Fischer C., Kuchenbäcker K., Engel C., Zachariae S., Rhiem K., Meindl A., Rahner N., Dikow N., Plendl H., Debatin I., Grimm T., Gadzicki D., Flöttmann R., Horvath J., Schröck E., Stock F., Schäfer D., Schwaab I., Kartsonaki C., Mavaddat N., Schlegelberger B., Antoniou A.C., Schmutzler R. German Consortium for Hereditary Breast and Ovarian Cancer.* Evaluating the performance of the breast cancer genetic risk models BOADICEA, IBIS, BRCAPRO and Claus for predicting *BRCA1/2* mutation carrier probabilities: a study based on 7352 families from the German Hereditary Breast and Ovarian Cancer Consortium. J Med Genet. 2013 Jun; 50(6): 360–7. doi: 10.1136/jmedgenet-2012-101415.

3. *Gayther S.A., Harrington P., Russell P., Kharkevich G., Garkavtseva R.F., Ponder B.A.J.* Frequently occurring germ-line mutations of the *BRCA1* gene in ovarian cancer families from Russia. Am J Hum Genet. 1997 May; 60(5): 1239–42.

4. *Sokolenko A.P., Mitiushkina N.V., Buslov K.G., Bit-Sava E.M., Iyevleva A.G., Chekmariova E.V., Kuligina E.Sh., Ulibina Y.M., Rozanov M.E., Suspitsin E.N., Matsko D.E., Chagunava O.L., Trofimov D.Y., Devilee P., Cornelisse C., Togo A.V., Semiglazov V.F., Imyanitov E.N.* High frequency of *BRCA1* 5382insC mutation in Russian breast cancer patients. Eur J Cancer. 2006 Jul; 42(10): 1380–84. doi: 10.1016/j.ejca.2006.01.050.

5. *Sokolenko A.P., Rozanov M.E., Mitiushkina N.V., Sherina N.Y., Iyevleva A.G., Chekmariova E.V., Buslov K.G., Shilov E.S., Togo A.V., Bit-Sava E.M., Voskresenskiy D.A., Chagunava O.L., Devilee P., Cornelisse C., Semiglazov V.F., Imyanitov E.N.* Founder mutations in early onset, familial and bilateral breast cancer patients from Russia. Familial Cancer. 2007; 6(3): 281–6. doi: 10.1007/s10689-007-9120-5.

6. *Kwon J.S., Gutierrez-Barrera A.M., Young D., Sun C.C., Daniels M.S., Lu K.H., Arun B.* Expanding the criteria for BRCA mutation testing in breast cancer survivors. J Clin Oncol. 2010 Sep; 28(27): 4214–20. doi: 10.1200/JCO.2010.28.0719.

7. *Iyevleva A.G., Suspitsin E.N., Kroeze K., Gorodnova T.V., Sokolenko A.P., Buslov K.G., Voskresenskiy D.A., Togo A.V., Kovalenko S.P., Stoep N.V., Devilee P., Imyanitov E.N.* Non-founder *BRCA1* mutations in Russian breast cancer patients. Cancer Lett. 2010 Dec 8; 298(2): 258–63. doi: 10.1016/j.canlet.2010.07.013.

8. *Anisimenko M.S., Mitrofanov D.V., Chasovnikova O.B., Voevoda M.I., Kovalenko S.P. BRCA1* gene mutations frequency estimation by allele-specific real-time PCR of pooled genomic DNA samples. Breast. 2013 Aug; 22(4): 532–6. doi: 10.1016/j.breast.2012.12.007.

9. *Schmieder R., Edwards R.* Quality control and preprocessing of metagenomic datasets. Bioinformatics. 2011 Mar 15; 27(6): 863–4. doi: 10.1093/bioinformatics/btr026.

10. *Li H., Durbin R.* Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics. 2009 Jul; 25(14): 1754–60. doi: 10.1093/bioinformatics/btp324.

11. *Li H., Handsaker B., Wysoker A., Fennell T., Ruan J., Homer N., Marth G., Abecasis G., Durbin R.; 1000 Genome Project Data Processing Subgroup.* The Sequence Alignment/Map format and SAMtools. Bioinformatics. 2009 Aug 15; 25(16): 2078–9. doi: 10.1093/bioinformatics/btp352.

12. *Paul G.A., Matyash N.A., Pisareva E.E., Anisimenko M.S., Kozyakov A.E., Kovalenko S.P.* Detection of mutations related to hereditary cancer in relatives of breast cancer patients. Siberian Journal of Oncology. 2017; 16(4): 84–88. doi: 10.21294/1814-4861-2017-16-4-84-88. [in Russian]

13. *Ermolenko N.A., Boyarskikh U.A., Kechin A.A., Mazitova A.M., Khrapov E.A., Petrova V.D., Lazarev A.F., Kushlinskii N.E., Filipenko M.L.* Massive Parallel Sequencing for Diagnostic Genetic Testing of BRCA Genes - a Single Center Experience. Asian Pac J Cancer Prev. 2015; 16(17): 7935–41. doi: 10.7314/APJCP.2015.16.17.7935.

14. *Bermisheva M.A., Zinnamullina G.F., Gantsev Sh.Kh., Kochanova V.A., Popov O.S., Dörk T., Khusnutdinova E.K.* Frequency of 5382insC mutation of the *BRCA1* gene. Vopr Onkol. 2008; 54(1): 31–3.

15. *Gorodetska I., Serga S., Levkovich N., Lahuta T., Ostapchenko L., Demydov S., Anikusko N., Cheshuk V., Smolanka I., Sklyar S., Polenkov S., Boichenko O., Kozeretska I.* The frequency of *BRCA1* founder mutation c.5266dupC (5382insC) in breast cancer patients from Ukraine. Hered Cancer Clin Pract. 2015 Oct; 13: 19. doi: 10.1186/s13053-015-0040-3.

16. *Brozek I., Ratajska M., Piatkowska M., Kluska A., Balabas A., Dabrowska M., Nowakowska D., Niwinska A., Rachtan J., Steffen J., Limon J.* Limited significance of family history for presence of *BRCA1* gene mutation in Polish breast and ovarian cancer cases. Fam Cancer. 2012 Sep; 11(3): 351–4. doi: 10.1007/s10689-012-9519-5.

17. *Backe J., Hofferbert S., Skawran B., Dörk T., Stuhrmann M., Karstens J.H., Untch M., Meindl A., Burgemeister R., Chang-Claude J., Weber B.H.* Frequency of *BRCA1* mutation 5382insC in German breast cancer patients. Gynecol Oncol. 1999 Mar; 72(3): 402–6. doi: 10.1006/gyno.1998.5270.

18. *Muller D., Bonaiti-Pellié C., Abecassis J., Stoppa-Lyonnet D., Fricker J.P. BRCA1* testing in breast and/or ovarian cancer families from northeastern France identifies two common mutations with a founder effect. Fam Cancer. 2004; 3(1): 15–20. doi: 10.1023/B:FAME.0000026819.44213.df.

19. *de Juan Jiménez I., García Casado Z., Palanca Suela S., Esteban Cardeñosa E., López Guerrero J.A., Segura Huerta Á., Chirivella González I., Sánchez Heras A.B., Juan Fita M.J., Tena García I., Guillen Ponce C., Martínez de Dueñas E., Romero Noguera I., Salas Trejo D., Goicoechea Sáez M., Bolufer Gilabert P.* Novel and recurrent *BRCA1/BRCA2* mutations in early onset and familial breast and ovarian cancer detected in the Program of Genetic Counseling in Cancer of Valencian Community (eastern Spain). Relationship of family phenotypes with mutation prevalence. Fam Cancer. 2013 Dec; 12(4): 767–77. doi: 10.1007/s10689-013-9622-2.

Received 29.06.18

Accepted 01.08.18

Funding

This study required no funding.

Conflict of interest

The authors declare that they have no conflict of interest.

ABOUT THE AUTHORS

Maxim S. Anisimenko, Junior research fellow, Federal Research Center of Fundamental and Translational Medicine (Novosibirsk, Russia). E-mail: jocus@bk.ru. Researcher ID (WOS): I-3226-2017. Author ID (Scopus): 36514172600.
Galina A. Paul, MD, Head of laboratory, laboratory physician, BioLink Ltd (Novosibirsk, Russia). E-mail: galapaul@mail.ru. Author ID (Scopus): 56417221700.
Anton E. Kozyakov, Head of division, oncologist, Novosibirsk Regional Oncological Clinic (Novosibirsk, Russia). E-mail: dr-anton72@mail.ru. Author ID (Scopus): 56418702200.
Nadezhda I. Gutkina, PhD, Senior researcher, Federal Research Center of Fundamental and Translational Medicine (Novosibirsk, Russia). E-mail: gutkina.nadezhda@gmail.com. Author ID (Scopus): 6701374482.
Daria A. Berdyugina, Junior research fellow, Federal Research Center of Fundamental and Translational Medicine (Novosibirsk, Russia). E-mail: kostyakovada1993@yandex.ru.
Alexander Yu. Garanin, Laboratory assistant, Federal Research Center of Fundamental and Translational Medicine (Novosibirsk, Russia). E-mail: chemistry1992sasha@mail.ru.
Anna V. Butorina, Laboratory assistant, Federal Research Center of Fundamental and Translational Medicine (Novosibirsk, Russia). E-mail: anechkaustina1991@mail.ru.
Elena V. Gornostaeva, Junior research fellow, Federal Research Center of Fundamental and Translational Medicine (Novosibirsk, Russia). E-mail: phys.lena@gmail.com.
Kamil F. Khafizov, PhD, Head of scientific group, Central Research Institute of Epidemiology (Moscow, Russia). E-mail: kkhafizov@gmail.com. Researcher ID (WOS): E-5368-2011. Author ID (Scopus): 26536043300. ORCID: 0000-0001-5524-0296.
Yuri V. Vyatkin, Head of Department of Bioinformatic technologies, AcademGene LLC (Novosibirsk, Russia). E-mail: yuri@nprog.ru. Researcher ID (WOS): E-8027-2018. Author ID (Scopus): 55651086400. ORCID: 0000-0002-9056-8796.
Dmitry N. Shtokalo, PhD, Senior researcher, A.P.Ershov Institute of Informatics Systems (Novosibirsk, Russia). E-mail: shtokalod2@gmail.com. Researcher ID (WOS): H-3351-2016. Author ID (Scopus): 14219725900. ORCID: 0000-0003-3716-2794.
Sergei P. Kovalenko, PhD, Head of laboratory, Federal Research Center of Fundamental and Translational Medicine (Novosibirsk, Russia). E-mail: sp_kovalenko@yahoo.com. Author ID (Scopus): 7101988072.

СВЕДЕНИЯ ОБ АВТОРАХ

Анисименко Максим Сергеевич, младший научный сотрудник, Федеральный исследовательский центр фундаментальной и трансляционной медицины (г. Новосибирск, Россия). E-mail: jocus@bk.ru. SPIN-код: 7751-0277. Researcher ID (WOS): I-3226-2017. Author ID (Scopus): 36514172600.
Пауль Галина Александровна, кандидат медицинских наук, заведующий лабораторией, врач-лабораторный генетик, ООО «Биолинк» (г. Новосибирск, Россия). E-mail: galapaul@mail.ru. Author ID (Scopus): 56417221700.
Козяков Антон Евгеньевич, заведующий отделением, врач-онколог, Новосибирский областной клинический онкологический диспансер (г. Новосибирск, Россия). E-mail: dr-anton72@mail.ru. SPIN-код: 9596-0420. Author ID (Scopus): 56418702200.
Гуткина Надежда Игоревна, кандидат биологических наук, старший научный сотрудник, Федеральный исследовательский центр фундаментальной и трансляционной медицины (г. Новосибирск, Россия). E-mail: gutkina.nadezhda@gmail.com. SPIN-код: 6170-9570. Author ID (Scopus): 6701374482.
Бердюгина Дарья Алексеевна, младший научный сотрудник, Федеральный исследовательский центр фундаментальной и трансляционной медицины (г. Новосибирск, Россия). E-mail: kostyakovada1993@yandex.ru. SPIN-код: 4870-4030.
Гаранин Александр Юрьевич, лаборант, Федеральный исследовательский центр фундаментальной и трансляционной медицины (г. Новосибирск, Россия). E-mail: chemistry1992sasha@mail.ru.
Буторина Анна Владимировна, лаборант, Федеральный исследовательский центр фундаментальной и трансляционной медицины (г. Новосибирск, Россия). E-mail: anechkaustina1991@mail.ru.
Горностаева Елена Викторовна, младший научный сотрудник, Федеральный исследовательский центр фундаментальной и трансляционной медицины (г. Новосибирск, Россия). E-mail: phys.lena@gmail.com.
Хафизов Камиль Фаридович, кандидат биологических наук, руководитель научной группы, Центральный научно-исследовательский институт эпидемиологии Роспотребнадзора (г. Москва, Россия). E-mail: kkhafizov@gmail.com. SPIN-код: 9082-5749. Researcher ID (WOS): E-5368-2011. Author ID (Scopus): 26536043300. ORCID: 0000-0001-5524-0296.
Вяткин Юрий Викторович, руководитель отдела биоинформационных технологий, ООО «АкадемДжин» (г. Новосибирск, Россия). E-mail: yuri@nprog.ru. Researcher ID (WOS): E-8027-2018. Author ID (Scopus): 55651086400. ORCID: 0000-0002-9056-8796.
Штокало Дмитрий Николаевич, кандидат физико-математических наук, старший научный сотрудник, Институт систем информатики им. А.П. Ершова СО РАН (г. Новосибирск, Россия). E-mail: shtokalod2@gmail.com. SPIN-код: 2745-4217. Researcher ID (WOS): H-3351-2016. Author ID (Scopus): 14219725900. ORCID: 0000-0003-3716-2794.
Коваленко Сергей Петрович, доктор биологический наук, заведующий лабораторией, Федеральный исследовательский центр фундаментальной и трансляционной медицины (г. Новосибирск, Россия). E-mail: sp_kovalenko@yahoo.com. SPIN-код: 2272-6747. Author ID (Scopus): 7101988072.

Финансирование
Авторы данной статьи подтвердили отсутствие финансовой поддержки.
Конфликт интересов
Авторы объявляют, что у них нет конфликта интересов.

Поступила 29.06.18
Принята в печать 01.08.18