DOI: 10.21294/1814-4861-2024-23-5-35-46
УДК: 618.19-006.6:575.224:572.9(571.1/.5)



Для цитирования: *Гервас П.А., Молоков А.Ю., Бабышкина Н.Н., Иванова Ф.Г., Николаева Т.И., Тихонов Д.Г., Чойнзонов Е.Л., Чердынцева Н.В.* Применение экзомного секвенирования для поиска мутаций, ассоциированных с наследственными формами рака молочной железы, в этнических группах Сибири. Сибирский онкологический журнал. 2024; 23(5): 35–46. – doi: 10.21294/1814-4861-2024-23-5-35-46
For citation: *Gervas P.A., Molokov A.Yu., Babyshkina N.N., Ivanova F.G., Nikolaeva T.I., Tikhonov D.G., Choynzonov E.L., Cherdyntseva N.V.* Whole exome sequencing: the search for mutations associated with hereditary breast cancer in ethnic groups of Siberia. Siberian Journal of Oncology. 2024; 23(5): 35–46. – doi: 10.21294/1814-4861-2024-23-5-35-46

# WHOLE EXOME SEQUENCING: THE SEARCH FOR MUTATIONS ASSOCIATED WITH HEREDITARY BREAST CANCER IN ETHNIC GROUPS OF SIBERIA

**P.A. Gervas[1], A.Yu. Molokov[1], N.N. Babyshkina[1], F.G. Ivanova[2], T.I. Nikolaeva[2], D.G. Tikhonov[3], E.L. Choynzonov[1], N.V. Cherdyntseva[1]**

[1]Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences
5, Kooperativny St., Tomsk, 634009, Russia
[2]Yakut Republican Cancer Center
89, Petra Alekseeva St., Yakutsk, 677000, Russia
[3]Medical Institute, M.K. Ammosov North-Eastern Federal University
58, Belinsky St., Yakutsk, 677000, Russia

**Abstract**

Hereditary breast cancer (HBC) is a heterogeneous disease caused by mutations in genes characterized by ethnic specificity. The clinical heterogeneity of this disease significantly complicates its diagnosis. The use of high-throughput sequencing is one of the approaches that allow the search for genes and their variants associated with the development of HBC. The purpose of the study was to search for new genes associated with HBC in the understudied ethnic groups of Siberia by using whole exome sequencing (WES). **Material and Methods.** WES was performed on a cohort of 16 probands with BC (Tuvan, Yakut, Altai ethnos). The study material was genomic DNA isolated from peripheral blood leukocytes. Libraries were prepared using a BGI Optimal DNA Library Prep kit. An Agilent SureSelect Human All Exon V6 kit was used for hybridization. High-throughput sequencing was performed on a DNA nanoball sequencing platform (DNBSeq-G400). **Results.** In the overall group of patients with signs of HBC, pathogenic variants were detected in 12.5 % of cases (2/16). For the first time, *BRCA1* (rs80357635) pathogenic variant was identified in a young patient with metachronous BC (Yakut ethnic group). A pathogenic variant of the ATM gene (rs780619951 NM_000051:exon16:c.C2413T:p.R805X) was identified in a young patient with BC (Tuvinian ethnic group). A pathogenic variant of the *TDP2* c.G4T:p.E2X, rs770844602 gene (DNA repair gene) was identified for the first time in a Tuvan BC patient (metachronous) with a family history, but its contribution to HBC remains to be proven. The *TDG* gene variant (rs764159587 NM_001363612:exon7:c.536dupA:p.E179fs) found in the Tuvan ethnic group and affecting splicing (SpliceAI: 0.580) requires special attention. **Conclusion.** This report is the first to describe the germinal variant in the *BRCA1* (rs80357635) gene in the Yakut ethnic group. Further studies are required to confirm pathogenicity of germinal variants in non-well studied genes *TDP2, TDG* in ethnic BC patients.

**Key words: exome sequencing, germline mutations, breast cancer, ethnic groups, Yakuts, Tuvans.**

**Гервас Полина Анатольевна,** pgervas@yandex.ru

# ПРИМЕНЕНИЕ ЭКЗОМНОГО СЕКВЕНИРОВАНИЯ ДЛЯ ПОИСКА МУТАЦИЙ, АССОЦИИРОВАННЫХ С НАСЛЕДСТВЕННЫМИ ФОРМАМИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ, В ЭТНИЧЕСКИХ ГРУППАХ СИБИРИ

**П.А. Гервас[1], А.Ю. Молоков[1], Н.Н. Бабышкина[1], Ф.Г. Иванова[2], Т.И. Николаева[2], Д.Г. Тихонов[3], Е.Л. Чойнзонов[1], Н.В. Чердынцева[1]**

[1]Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук
Россия, 634009, г. Томск, пер. Кооперативный, 5
[2]ГБУ РС(Я) «Якутский республиканский онкологический диспансер»
Россия, 677000, г. Якутск, ул. Петра Алексеева, 89
[3]Медицинский институт, Северо-Восточный федеральный университет им. М.К. Аммосова
Россия, 677000, г. Якутск, ул. Белинского, 58

**Аннотация**

Наследственный рак молочной железы (нРМЖ) представляет собой гетерогенное онкологическое заболевание, обусловленное мутациями ряда генов, характеризующихся этноспецифичностью. Клиническая гетерогенность данного заболевания существенно осложняет его диагностику. Применение метода высокопроизводительного секвенирования является одним из возможных подходов, позволяющих проводить поиск генов и их вариантов, приводящих к формированию нРМЖ. **Целью исследования** явился поиск новых генов и их вариантов, связанных с нРМЖ в этнических группах Сибири, с использованием метода секвенирования экзома. **Материал и методы**. В исследование включено 16 пациенток с РМЖ (тувинки, якутки, алтайки). Материалом исследования служила геномная ДНК, выделенная из лейкоцитов периферической крови. Библиотеки были подготовлены с использованием набора BGI Optimal DNA Library Prep. Для гибридизации использовался набор Agilent SureSelect Human All Exon V6. Высокопроизводительное секвенирование было выполнено на платформе DNBSeq-G400. Данные секвенирования экзома были обработаны с использованием DRAGEN Bio-IT v.3.9.5 (Illumina) и выровнены на референсный человеческий геном hg38. Качество данных секвенирования контролировалось с помощью программного обеспечения MultiQC v.1.11. **Результаты**. В общей группе пациенток с признаками нРМЖ патогенные варианты были обнаружены в 12,5 % (2/16). Патогенный вариант гена *BRCA1* (c.3087_3088del: p.R1029fs, rs80357635) был выявлен у молодой пациентки с метахронным РМЖ (этническая группа якуты). Патогенный вариант гена *ATM* (rs780619951 NM_000051:exon16:c.C2413T:p.R805X) был выявлен у молодой пациентки с РМЖ (этническая группа тувинцы). Патогенный вариант гена репарации ДНК *TDP2* c.G4T: p.E2X, rs770844602 был впервые выявлен у тувинки с метахронным РМЖ и с семейным анамнезом. Вклад гена репарации ДНК *TDP2* в патогенез РМЖ еще предстоит изучить. Вариант гена *TDG* (rs764159587 NM_001363612:exon7:c.536dupA:p.E179fs), обнаруженный в тувинском этносе и влияющий на сплайсинг (SpliceAI: 0.580), требует особого внимания. **Заключение.** Впервые описан герминальный вариант в гене *BRCA1* (c.3087_3088del: p.R1029fs, rs80357635), связанный с РМЖ, в этнической группе якутов. Необходимы дальнейшие исследования для изучения роли герминальных вариантов генов *TDP2, TDG* при РМЖ.

**Ключевые слова: полноэкзомное секвенирование, наследственные мутации, этнические группы, рак молочной железы, якутки, тувинки.**

## Introduction

Hereditary breast cancer (HBC) is a heterogeneous disease with diverse genomic profile which determines the morphology, response to therapy, likelihood to relapse and overall survival. The major type of BC is found to be sporadic, and about 5 % to 10 % of all BC cases are classified as hereditary. Early detection and diagnosis of HBC improves health outcomes (prophylactic mastectomy improved survival by 0.4 to 2.6 years) [1]. HBC screenings have been implemented for healthy woman with family history of BC. However, molecular diagnostics of HBC poses a challenge. One of the challenges of molecular diagnostics for HBC is the high degree of genetic heterogeneity. According to GeneReviews, an international point-of-care resource, BC can be caused by various hereditary syndromes (*BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer, Li-Fraumeni syndrome, Bloom syndrome, Fanconi anemia, Peltz-Jegher syndrome, *PTEN*-hamartoma syndrome, ataxia-telangiectasia, etc.) [2]. The syndromic diagnosis is often used in resource-poor settings where laboratory diagnosis is limited. Moreover, every population/ethnic group has a specific spectrum of mutations in its gene pool

and diverse phenotypic and clinical presentations of malignancies. For some racial/ethnic groups, such as the Ashkenazi Jews variant *BRCA1* c.5266dup (5382insC), *BRCA1* c.68_69del (185delAG) and *BRCA2* c.5946del (6174delT); the Icelandic founder variant *BRCA2* c.771_775del (999del5); the French Canadian variant *BRCA1* c.4327C>T (C4446T), *BRCA2* c.8537_8538del (8765delAG); the *BRCA1* variant c.181T>G, and c.4034delA in Central-Eastern Europe; the *BRCA1* c.548-4185del in Mexico; the *BRCA2* variant c.9097dup in Hungary and others, have been identified. The mutations listed above represent the majority of mutations observed in these populations [3, 4]. Recurrent mutations have been identified in other populations (Scandinavian, Dutch, French, Italian, Hispanic/Mexican, African-American, Middle Eastern, and Asian populations), but they have not been characterized as true founder mutations [3]. Due to the genetic heterogeneity and phenotypic overlap, HBC is well suited to the strengths of next-generation sequencing (gene panels or whole exome sequencing). The technology of whole-exome sequencing (WES) allowed expansion of the spectrum of variants in genes that were not previously associated with BC pathogenesis [5]. The purpose of the study was to search for new genes associated with HBC in the understudied ethnic groups of Siberia by using whole exome sequencing (WES).

## Material and Methods

Our study included 16 patients with early-onset BC (range, 22 to 52 years). Fifty percent of patients were diagnosed with BC prior to age 40. Twenty fife percent of patients (4/16) were diagnosed with synchronous or metachronous BC. Our study included patients diagnosed with BC who belonged to ethnic groups of Siberia: Tuvans, Yakuts, Altaians. The nationality of the patients was determined using a questionnaire. Clinical information was based on the clinical documentation. The diagnosis was morphologically verified. All patients signed informed consent to participate in this study.

The study material was genomic DNA isolated from peripheral blood leukocytes. We used a combined, two-step strategy, based on targeted gene panel as a first NGS screening (n=150) (data not shown), followed by WES in still unsolved cases (n=16). Libraries were prepared using a BGI Optimal DNA Library Prep kit. An Agilent SureSelect Human All Exon V6 kit was used for hybridization. High-throughput sequencing was performed on a DNA nanoball sequencing platform DNBSeq-G400 (depth of coverage is 103.9x, Q30 reflects a base call accuracy of 95 %). The quality of sequencing data was controlled using the MultiQC v.1.11 software. Exome sequencing data were processed using the DRAGEN Bio-IT platform v.3.9.5 (Illumina) and aligned to the hg38 reference human genome. All found variants passed the filtering ($p < 0.005$). Additionally, pathogenic variants were verified by Sanger sequencing (Fig. 1–3).

## Results

In the current study we used WES to search for new genes associated with hereditary BC in the ethnic groups of Siberia. In the overall group of patients with signs of HBC, pathogenic variants were detected in 12.5 % of cases (2/16). Table 1 presents WES data in a group of young Yakut women with BC. A pathogenic variant of the *BRCA1* gene (rs80357635, NM_007297: exon9: c.3087_3088del: p.R1029fs, frameshift dele-

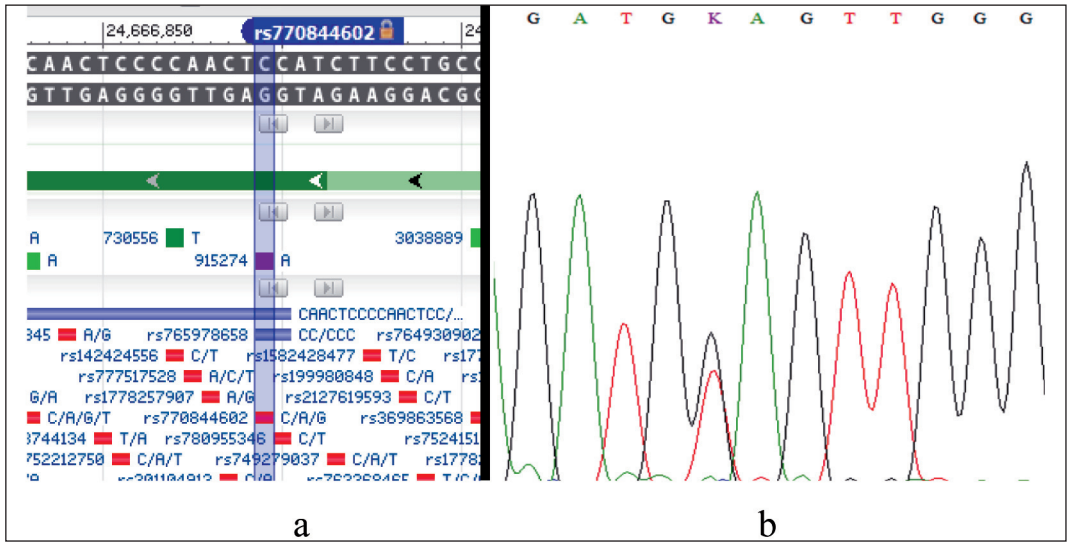


Fig. 1. Detection of the TDP2 repair gene variant (rs770844602 NM_016614:exon1:c.G4T:p.E2X) by Sanger sequencing. Notes: a – is the location of the TDP2 gene (rs770844602) variant according to dbSNP PubMed; b – is the positive sample, the reverse sequence (c.G4T); created by the authors

Рис. 1. Выявление варианта гена репарации TDP2 (rs770844602 NM_016614:exon1:c.G4T:p.E2X) методом секвенирования по Сэнгеру. Примечания: а – расположение варианта гена TDP2 (rs770844602) согласно dbSNP PubMed; б – положительный образец, обратная последовательность (c.G4T); рисунок выполнен авторами

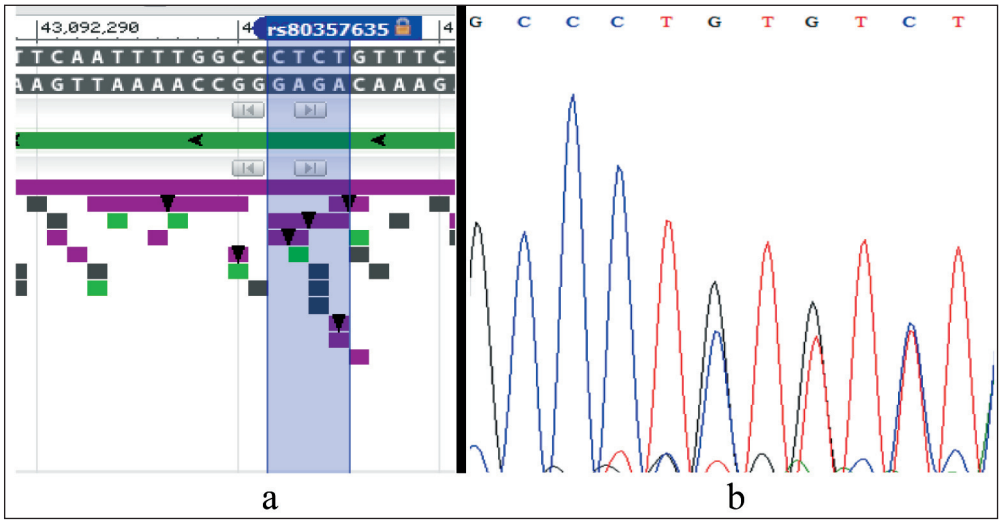


Fig. 2. Detection of the *BRCA1* gene variant: NM_007297: exon9: c.3087_3088del: p.R1029fs, rs80357635 by Sanger sequencing.
Notes: a – is the location of the *BRCA1* gene variant according to dbSNP PubMed; b – is the positive sample, the canonical forward sequence (c.3087_3088del); created by the authors

Рис. 2. Выявление варианта гена BRCA1: NM_007297: exon9: c.3087_3088del: p.R1029fs, rs80357635 методом секвенирования по Сэнгеру. Примечания: а – расположение варианта гена BRCA1 согласно dbSNP PubMed; б – положительный образец, каноническая прямая последовательность (c.3087_3088del); рисунок выполнен авторами

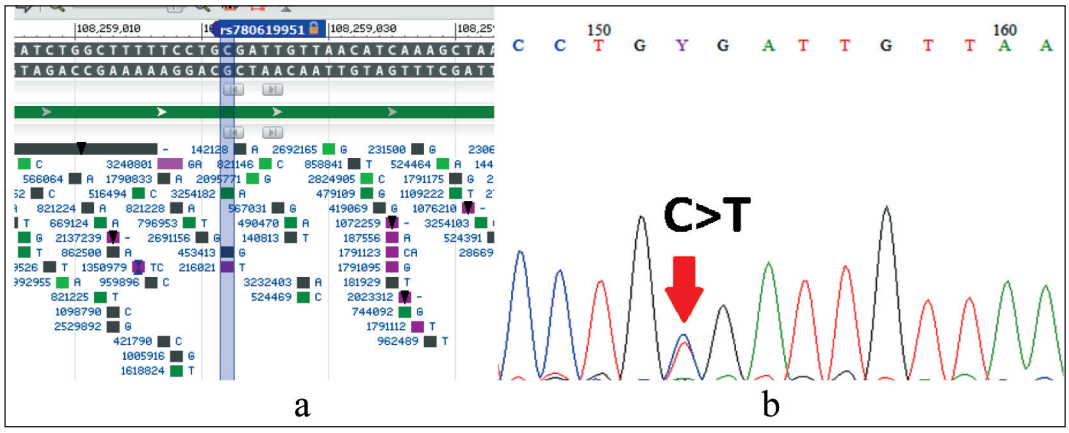


Fig. 3. Detection of the ATM variant (rs780619951, NM_000051:exon16:c.C2413T:p.R805X) by Sanger sequencing.
Notes: a – is the location of the ATM gene variant according to dbSNP PubMed;
b – is the positive sample, the canonical forward sequence (c.C2413T); created by the authors

Рис. 3. Выявление варианта ATM (rs780619951, NM_000051:exon16:c.C2413T:p.R805X) методом секвенирования по Сэнгеру. Примечания: а – расположение варианта гена ATM согласно dbSNP PubMed; б – положительный образец, каноническая прямая последовательность (c.C2413T); рисунок выполнен авторами

tion) was found in a 36-year-old patient with metachronous BC. A variant of the *ATM* gene (rs529296539, NM_000051: exon58: c.G8495A: p.R2832H, CADD SCORE: 25.9) and a variant of the *AXIN2* gene (rs758075343, NM_001363813: exon4: c.971_973del: p.324_325del) were found in a 45-year-old Yakut patient with bilateral synchronous BC. Four young Yakut BC patients were found to have mutations in genes associated with BC (*RECQL5, FANCL, ATM, RECQL*) with a CADD score > 25. Two patients had a pathogenic variant in the *CUL7* gene (NM_001168370: exon25: c.4833dupT: p.R1612fs), leading to Yakut short stature syndrome (secondary finding) (Table 1).

In the group of Tuvan patients diagnosed with BC and a burdened family history, pathogenic variant of the *ATM* and *TDP2* genes were detected (Table 2). Four BC patients of Tuvan, Yakut and Altai origin were found to have mutations in the *TDG* gene (rs765686214, rs764159587) (Table 3).

## Discussion

Our study included BC patients who belonged to ethnic groups of Siberia: Tuvans, Yakuts and Altaians. These ethnic groups are the largest in Siberia and the Russian Far East. The search for ethnospecific variants associated with BC for these groups has not yet completed and the question of the pathogenesis of hereditary BC remains to be answered.

***Yakut ethnic group***

In a group of young Yakut BC patients aged 22 to 45 years, a pathogenic variants of the *BRCA1* gene and the *GUL7* gene, as well as other variants were de-

Table 1/Таблица 1

**Variants identified in young BC patients from the Yakut ethnic group**

**Варианты, найденные у молодых пациенток с диагнозом РМЖ якутской этнической группы**

| Patients/ Пациентки | Age at diagnosis/ Возраст постановки диагноза | Pathogenic variants in BC associated genes/ Диагноз и/или семейная история | Pathogenic variants in BC associated genes/ Патогенные варианты в генах, ассоциированных с РМЖ | Variants in BC associated genes/ Варианты в генах, ассоциированных с РМЖ | Pathogenic variants in non-BC associated genes/ Патогенные варианты генов, не ассоциированных с РМЖ |
|---|---|---|---|---|---|
| PLA/ ПЛА | 41 | Invasive BC, Luminal B, stage IIIC, no family history/ Инвазивный рак молочной железы, Люминальный В, стадия IIIC, нет семейной истории | | | **CUL7**: **rs730880301** NM_001168370: exon25: c.4833dupT: p.R1612fs (Yakut short stature syndrome)/ **CUL7**: **rs730880301** NM_001168370: экзон25: c.4833dupT: p.R1612fs (3M синдром) |
| KGU/ КГУ | 44 | Invasive BC, the *HER2* status of the tumor is not clear, stage IIIB, no family history/ Инвазивный рак молочной железы, *HER2* статус не определен, стадия IIIB, нет семейной истории | | | **SBDS**: **rs113993993** NM_016038: exon2: c.258+2T>C (Shwachman syndrome)/ **SBDS**: **rs113993993** NM_016038: экзон2: c.258+2T>C (Синдром Швахмана) |
| SNG/ СНГ | 37 | Invasive BC, Luminal B, stage IIIC, no family history/ Инвазивный рак молочной железы, Люминальный В, стадия IIIC, нет семейной истории | | **RECQL5: rs762104670** NM_001003715: exon4: c.G665A: p.R222Q (**CADD score: 27.4**, PolyPhen: 0.995), **MAF* 0,00001**/ **RECQL5: rs762104670** NM_001003715: экзон4: c.G665A: p.R222Q (**CADD score: 27.4**, PolyPhen: 0.995), **MAF* 0,00001** | **CUL7**: **rs730880301** NM_001168370: exon25: c.4833dupT: p.R1612fs (Yakut short stature syndrome)/ **CUL7**: **rs730880301** NM_001168370: экзон25: c.4833dupT: p.R1612fs (3M синдром) |
| NNI/ ННИ | 42 | Invasive BC, Luminal B, stage IIIC, no family history/ Инвазивный рак молочной железы, Люминальный В, стадия IIIC, нет семейной истории | | **FANCL**: **rs199564543** NM_001114636: exon8: c.G637A: p.D213N (**CADD score: 28.1**, **PolyPhen: 1.00**), **MAF 0,002**/ **FANCL**: **rs199564543** NM_001114636: экзон8: c.G637A: p.D213N (**CADD score: 28.1**, **PolyPhen: 1.00**), **MAF 0,002** | |
| AMA/ AMA | 45 | Invasive bilateral synchronous BC, Luminal B, stage IIA, no family history/ Инвазивный рак молочной железы, билатеральный рак, Люминальный В, стадия IIA, нет семейной истории | | **ATM**: **rs529296539** NM_000051: exon58: c.G8495A: p.R2832H, (**CADD score: 25.9,** PolyPhen: 0.742), **MAF 0,0005** **AXIN2**: rs758075343 NM_001363813: exon4: c.971_973del: p.324_325del/ **ATM**: **rs529296539** NM_000051: экзон58: c.G8495A: p.R2832H, (**CADD score: 25.9,** PolyPhen: 0.742), **MAF 0,0005** **AXIN2**: rs758075343 NM_001363813: экзон4: c.971_973del: p.324_325del | |

**End of Table 1/Окончание таблицы 1**

| | | | | |
|---|---|---|---|---|
| STV/ СТВ | 41 | Invasive bilateral BC, the *HER2* status of the tumor is not clear, stage I, burdened family history/ Инвазивный рак молочной железы, билатеральный рак, *HER2* статус не определен, стадия I, отягощенная семейная история | | |
| SKV/ СКВ | 38 | Invasive BC, Luminal B, stage I, no family history/ Инвазивный рак молочной железы, Люминальный В, стадия I, нет семейной истории | | **RECQL**: **rs544551114** NM_002907: exon7: c.C736G: p.P246A, (**CADD score: 25.4**, PolyPhen: 0.812), **MAF 0,00001**/ **RECQL**: **rs544551114** NM_002907: экзон7: c.C736G: p.P246A, (**CADD score: 25.4**, PolyPhen: 0.812), **MAF 0,00001** |
| IMG/ ИМГ | 40 | Invasive BC, Luminal A, stage IIA, no family history/ Инвазивный рак молочной железы, Люминальный А, стадия IIA, нет семейной истории | | |
| TMV/ TMB | 36 | Invasive metachronous BC, Luminal B (left) triple-negative (right), stage IIIB, no family history/ Инвазивный метахронный рак молочных желез, слева – Люминальный В, справа – трижды негативный, стадия IIIB, нет семейной истории | **BRCA1**: **rs80357635** NM_007297: exon9: c.3087_3088del: p.R1029fs, frameshift deletion/ **BRCA1**: **rs80357635** NM_007297: экзон9: c.3087_3088del: p.R1029fs, frameshift deletion | |
| SVA/ СВА | 22 | Invasive BC, HER2 positive, stage IIIB, no family history/ Инвазивный рак молочной железы, HER2 позитивный, стадия IIIB, нет семейной истории | | |

Notes: MAF* – minor allele frequency; created by the authors.

Примечания: MAF* – частота минорного аллеля; таблица составлена авторами.

Table 2/Таблица 2

**Variants identified in young BC patients from the Tuvan ethnic group**

**Варианты, найденные у молодых пациенток с диагнозом РМЖ тувинской этнической группы**

| Patients/ Пациентки | Age at diagnosis/ Возраст постановки диагноза | Diagnosis and/or family history/ Диагноз и/или семейная история | Pathogenic variants in BC associated genes/ Патогенные варианты в генах, ассоциированных с РМЖ | Variants in BC associated genes/ Варианты в генах, ассоциированных с РМЖ | Pathogenic variants in non-BC associated genes/ Патогенные варианты генов, не ассоциированных с РМЖ |
|---|---|---|---|---|---|
| SLA/ СЛА | 39 | Medullary BC, IIIA stage/uncle – colon cancer/ Медуллярная карцинома молочной железы, IIIA стадия/дядя – колоректальный рак | | | |
| CHAF/ ЧАФ | 52 | Invasive BC, IVB stage/mother – pancreas cancer/ Инвазивный рак молочной железы, IVB стадия/мать – рак поджелудочной железы | **ATM: rs780619951** NM_000051:exon16:c.C2413T:p.R805X stopgain/ **ATM: rs780619951** NM_000051:экзон16:c.C2413T:p.R805X stopgain | **TDG**: **rs765686214** NM_001363612: exon8: c.661_662insTTGAGAGC: p.I221fs **(CADD score: 31.0)** **MAF 0.000/** **TDG**: **rs765686214** NM_001363612: экзон8: c.661_662insTTGAGAGC: p.I221fs **(CADD score: 31.0)** **MAF 0.000** | |
| MAD/ МАД | 42 | Scirrhous metachronous BC, I stage/father – esophageal cancer, grandmother and aunt – stomach cancer/ Скиррозная карцинома молочной железы, метахронный рак, I стадия/отец – рак пищевода, бабушка и тетя – рак желудка | | **TDG: rs764159587** NM_001363612: exon7: c.536dupA: p.E179fs (**CADD score: 36.0,** SpliceAI: 0.580) **MAF 0.026/** **TDG: rs764159587** NM_001363612: экзон7: c.536dupA: p.E179fs (**CADD score: 36.0,** SpliceAI: 0.580) **MAF 0.026** | **TDP2**: **rs770844602** NM_016614: exon1: c.G4T: p.E2X/ **TDP2: rs770844602** NM_016614: экзон1: c.G4T: p.E2X |
| ОНСН/ОШЧ | 34 | BC/mother – breast cancer/ РМЖ/мать – РМЖ | | **TDG**: **rs765686214** NM_001363612: exon8: c.661_662insTTGAGAGC: p.I221fs **(CADD score: 31.0)** **MAF 0.000/** **TDG**: **rs765686214** NM_001363612: экзон8: c.661_662insTTGAGAGC: p.I221fs **(CADD score: 31.0)** **MAF 0.000** | |

Notes: *MAF – minor allele frequency; created by the authors.

Примечания: *MAF – частота минорного аллеля; таблица составлена авторами.

Table 3/Таблица 3

**Variants identified in young BC patients from the Altai**

**Варианты, найденные у молодых пациенток с диагнозом РМЖ алтайской этнической группы**

| Patients/ Пациентки | Age at diagnosis/ Возраст постановки диагноза | Diagnosis and/or family history/ Диагноз и/или семейная история | Pathogenic variants in BC associated genes/ Патогенные варианты в генах, ассоциированных с РМЖ | Variants in BC associated genes/ Варианты в генах, ассоциированных с РМЖ | Pathogenic variants in non-BC associated genes/ Патогенные варианты генов, не ассоциированных с РМЖ |
|---|---|---|---|---|---|
| КАК/ КАК | 35 | Invasive BC, I stage/mother, grandmother – breast cancer/ Инвазивная карцинома молочной железы, I стадия/ мать, бабушка – РМЖ | | **TDG**: **rs765686214** NM_001363612: exon8: c.661_662insTTGAGAGC: p.I221fs **(CADD score: 31.0)** **MAF 0.000/** **TDG**: **rs765686214** NM_001363612: экзон8: c.661_662insTTGAGAGC: p.I221fs **(CADD score: 31.0)** **MAF 0.000** | |

Notes: *MAF – minor allele frequency; created by the authors.

Примечания: *MAF – частота минорного аллеля; таблица составлена авторами.

tected. The *BRCA1* gene variant: NM_007297: exon9: c.3087_3088del: p.R1029fs, rs80357635, frameshift deletion, «pathogenic» according to the NCBI SNP db, was detected in a 36-year-old patient with metachronous BC (Yakut). This variant has a low minor allele frequency (0.000004). It was described in more than 30 families diagnosed with breast/ovarian cancer [6-10].According to literature, rs80357635 is associated with hereditary breast/ovarian cancer and is a founder variant for the Norwegian and Italian populations [11,12]. The *BRCA1* gene variant: NM_007297: exon9: c.3087_3088del: p.R1029fs, rs80357635 is not a common variant for Slavs; this variant of the *BRCA1* gene was discovered for the first time in the Yakut population. It is necessary to study the frequency of this variant in an extended sample of Yakut women with BC. To consider this variant as ethnospecific (founder mutation) for Yakut patients with BC, it must be recurrent.

A 45-year-old female patient (Yakut) with bilateral synchronous BC was found to have two variants of the *AXIN2* and *ATM* genes. Pathogenic variants of the *AXIN2* (Axin-related protein) gene lead to the formation of Oligodontia-Colorectal Cancer Syndrome, associated with an increased risk of various malignancies, including gastrointestinal polyposis, early-onset colorectal cancer, and breast cancer. Oligodontia-colorectal cancer syndrome is an autosomal dominant disorder with an estimated prevalence of <1:1,000,000 (Orphanet) [13]. According to Laura Roht data (2023), the *AXIN2* gene has recently been included in the panel of genes associated with cancer syndromes [14]. The variant of the *AXIN2* gene (rs1567759412, NM_001363813: exon4: c.971_973del: p.324_325del) revealed in the Yakut patient did not lead to a frameshift, the CADD score < 25, and the variant was determined to be of uncertain significance according to db SNP ClinVar. This patient also had the variant of the *ATM* gene (rs529296539, NM_000051: exon58: c.G8495A: p.R2832H), CADD score > 25, PolyPhen2: 0.742, MAF 0.0005. The variant was determined to be of conflicting significance according to db SNP ClinVar classification. Thus, in the Yakut patient with bilateral synchronous BC two variants of the *AXIN2* and *ATM* genes were detected. Further studies are required to assess their significance.

Bioinformatic analysis of WES data showed that gene variants associated with BC, such as *RECQL5* rs762104670, *FANCL* rs199564543, *ATM* rs529296539, *RECQL* rs544551114 were found in Yakut BC patients. These variants were determined to be of uncertain significance according to NCBI SNP db, with CADD score > 25, MAF equal to 0.000, and deleterious effect on protein according to predictive programs (PolyPhen2, SIFT, MutationTaster, MutationAssessor, PROVEAN, CADD). CADD is a widely used measure of variant deleteriousness that can effectively prioritize causal variants in genetic analyses (missense variants, nonsense mutations, insertions/deletions causing reading frame shift) [15]. Since these genes are well studied and their role in the pathogenesis of BC has been proven, we will not dwell on them in detail.

Two young Yakut women with BC were found to have a pathogenic variant rs730880301 in the *CUL7* gene, which was associated with the 3-M syndrome or Yakut short stature syndrome. Yakut short stature syndrome is a rare autosomal recessive disease characterized by severe prenatal and postnatal growth retardation and facial dysmorphism, but normal intelligence. The prevalence of short stature syndrome with a

*CUL7* mutation in Yakuts is 0.01 % (at least 43 patients out of 440,000 people) [16]. This finding confirms the ethnicity of the patients included in our study.

***Tuvan ethnic group***

Pathogenic variants of the *ATM* and *TDP2* genes (not associated with BC) and variants of the *TDG* gene affecting splicing were found in Tuvan BC patients. The pathogenic *ATM* gene variant (rs780619951 NM_000051:exon16:c.C2413T:p.R805X) was found in a 52-year-old Tuvan woman with a burdened family history (mother had pancreatic cancer). We described this variant earlier in a group of young Khakass women with BC [17].

A 42-year-old Tuvan woman with a metachronous BC and burdened family history (grandmother and aunt had stomach cancer) was found to have a pathogenic variant of the *TDP2* repair gene (rs770844602, NM_016614: exon1: c.G4T: p.E2X) and a variant of the *TDG* gene (rs764159587, NM_001363612: exon7: c.536dupA: p.E179fs). The *TDG* gene belongs to the TDG/mug DNA glycosylase family. The *TDG* gene coding enzyme that plays a central role in cellular defense against genetic mutation caused by the spontaneous deamination of 5-methylcytosine and cytosine [18]. The *TDG* gene variant rs764159587 (NM_001363612: exon7: c.536dupA: p.E179fs, uncertain significance by ClinVar, CADD score 36.0, Splice Donor Variant, SpliceAI score 0.580) indicates that this gene variant leads to a change in the coding sequence of the protein. This *TDG* gene variant affects splicing and should be studied using the technology of minigene. The *TDP2* gene germinal variant (rs770844602 NM_016614:exon1:c.G4T:p.E2X) another variant that was also detected in this patient. The *TDP2* gene encodes 5'-tyrosyl DNA phosphodiesterase which is necessary for efficient repair of double-strand breaks caused by abortive activity of DNA topoisomerase II (TOP2). In accordance with literature, homozygous pathogenic variants of the *TDP2* gene were registered in patients with spinocerebellar ataxia 23 (SCAR23). Cases of spinocerebellar ataxia with cancer were also described in the literature [19, 20] and a case of Fanconi anemia was described in one of the patients [21] (a genetic disease that is transmitted in an autosomal recessive manner and is characterized by a violation of hematopoiesis and development of malignant neoplasms). In our study, a young 42-year-old female BC (metachronous BC) patient (Tuvan) with burdened family history (grandmother and aunt had stomach cancer) was found to have a pathogenic variant of the *TDP2* repair DNA gene (rs770844602, NM_016614: exon1: c.G4T: p.E2X) in a heterozygous genotype. Similar cases have not been described in the literature. However, since the objective of this study was to search for new genes associated with hereditary forms of BC, we cannot exclude the *TDP2* repair gene from the list of candidate genes for BC. Therefore, further research is required. Thus, it is possible that the *TDP2* gene, by analogy with the *BLM* gene, can lead to the development of spinocerebellar ataxia in a homozygous genotype and to malignant neoplasms (for example, BC) in a heterozygous genotype. For example, *BLM* gene encodes a protein that belongs to the RecQ helicase class and is involved in maintaining genome stability and DNA repair. A rare autosomal recessive disease, Bloom syndrome, develops in the case of homozygous carriage of mutations in the *BLM* gene [22]. Several studies have shown that heterozygous carriage of mutations in the *BLM* gene increases the risk of developing hereditary breast and prostate cancer [23].

In accordance with recent advances in sequencing, in particular whole-exome sequencing, the genetic basis of the disease can be identified in 25–40% of patients (in our study, only 12.5% of patients). It may be possible to continue searching for significant variants using other methods such as the MLPA (multiplex ligation-dependent probe amplification) method. MLPA is a method that detects deletion/insertion in up to 600 bp, which are usually filtered out during bioinformatics analysis of sequencing data [24].

## Conclusion

This report is the first to describe the germinal variant in the *BRCA1* (rs80357635) gene in the Yakut ethnic group. Further studies are required to confirm pathogenicity of germinal variants in non-well studied genes *TDP2, TDG* in ethnic BC patients (Tuvan).

ЛИТЕРАТУРА/REFERENCES


1. *Grann V.R., Panageas K.S., Whang W., Antman K.H., Neugut A.I.* Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. J Clin Oncol. 1998; 16(3): 979–85. doi: 10.1200/JCO.1998.16.3.979.

2. *Adam M.P., Feldman J., Mirzaa G.M., Pagon R.A., Wallace S.E., Amemiya A.* GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle, 1993–2024. [cited 2024 Oct 22]. URL: https://www.ncbi.nlm.nih.gov/books/NBK1116/.

3. *Rebbeck T.R., Friebel T.M., Friedman E., et al.* Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations. Hum Mutat. 2018; 39(5): 593–620. doi: 10.1002/humu.23406.

4. *Karami F., Mehdipour P.* A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int. 2013. doi: 10.1155/2013/928562.

5. *Shulskaya M.V., Alieva A.K., Vlasov I.N., Zyrin V.V., Fedotova E.Y., Abramycheva N.Y., Usenko T.S., Yakimovsky A.F., Emelyanov A.K., Pchelina S.N., Illarioshkin S.N., Slominsky P.A., Shadrina M.I.* Whole-Exome Sequencing in Searching for New Variants Associated With the Development of Parkinson's Disease. Front Aging Neurosci. 2018; 10: 136. doi: 10.3389/fnagi.2018.00136.

6. *Alemar B., Gregório C., Herzog J., Matzenbacher Bittar C., Brinckmann Oliveira Netto C., Artigalas O., Schwartz I.V.D., Coffa J., Alves Camey S., Weitzel J., Ashton-Prolla P.* BRCA1 and BRCA2 mutational profile and prevalence in hereditary breast and ovarian cancer (HBOC) probands from Southern Brazil: Are international testing criteria appropriate for this specific population? PLoS One. 2017; 12(11). doi: 10.1371/journal.pone.0187630. Erratum in: PLoS One. 2018; 13(5). doi: 10.1371/journal.pone.0197529.

7. *Santonocito C., Rizza R., Paris I., Marchis L., Paolillo C., Tiberi G., Scambia G., Capoluongo E.* Spectrum of Germline BRCA1 and BRCA2 Variants Identified in 2351 Ovarian and Breast Cancer Patients Referring to a Reference Cancer Hospital of Rome. Cancers. 2020 12(5): 1286. doi: 10.3390/cancers12051286.

8. *Singh J., Thota N., Singh S., Padhi S., Mohan P., Deshwal S., Sur S., Ghosh M., Agarwal A., Sarin R., Ahmed R., Almel S., Chakraborti B., Raina V., DadiReddy P.K., Smruti B.K., Rajappa S., Dodagoudar C., Aggarwal S., Singhal M., Joshi A., Kumar R., Kumar A., Mishra D.K., Arora N.,*

*Karaba A., Sankaran S., Katragadda S., Ghosh A., Veeramachaneni V., Hariharan R., Mannan A.U.* Screening of over 1000 Indian patients with breast and/or ovarian cancer with a multi-gene panel: prevalence of BRCA1/2 and non-BRCA mutations. Breast Cancer Res Treat. 2018; 170(1): 189–96. doi: 10.1007/s10549-018-4726-x.

9. *Santonocito C., Rizza R., Paris I., Marchis L., Paolillo C., Tiberi G., Scambia G., Capoluongo E.* Spectrum of Germline BRCA1 and BRCA2 Variants Identified in 2351 Ovarian and Breast Cancer Patients Referring to a Reference Cancer Hospital of Rome. Cancers (Basel). 2020; 12(5): 1286. doi: 10.3390/cancers12051286.

10. *Fanale D., Incorvaia L., Filorizzo C., Bono M., Fiorino A., Calò V., Brando C., Corsini L.R., Barraco N., Badalamenti G., Russo A., Bazan V.* Detection of Germline Mutations in a Cohort of 139 Patients with Bilateral Breast Cancer by Multi-Gene Panel Testing: Impact of Pathogenic Variants in Other Genes beyond BRCA1/2. Cancers (Basel). 2020; 12(9): 2415. doi: 10.3390/cancers12092415.

11. *Møller P., Heimdal K., Apold J., Fredriksen A., Borg A., Hovig E., Hagen A., Hagen B., Pedersen J.C., Maehle L.; Norwegian Inherited Breast Cancer Group; Norwegian Inherited Ovarian Cancer Group.* Genetic epidemiology of BRCA1 mutations in Norway. Eur J Cancer. 2001; 37(18): 2428–34. doi: 10.1016/s0959-8049(01)00299-4.

12. *Papi L., Palli D., Masi L., Putignano A.L., Congregati C., Zanna I., Marini F., Giusti F., Luzi E., Tonelli F., Genuardi M., Brandi M.L., Falchetti A.* Germline mutations in MEN1 and BRCA1 genes in a woman with familial multiple endocrine neoplasia type 1 and inherited breast-ovarian cancer syndromes: a case report. Cancer Genet Cytogenet. 2009; 195(1): 75–79. doi: 10.1016/j.cancergencyto.2009.06.019.

13. *Lammi L., Arte S., Somer M., Jarvinen H., Lahermo P., Thesleff I., Pirinen S., Nieminen P.* Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. Am J Hum Genet. 2004; 74(5): 1043–50. doi: 10.1086/386293.

14. *Roht L., Hyldebrandt H.K., Stormorken A.T., Nordgarden H., Sijmons R.H., Bos D.K., Riegert-Johnson D., Mantia-Macklin S., Ilves P., Muru K., Wojcik M.H., Kahre T., Õunap K.* AXIN2-related oligodontia-colorectal cancer syndrome with cleft palate as a possible new feature. Mol Genet Genomic Med. 2023; 11(6). doi: 10.1002/mgg3.2157.

15. *Rentzsch P., Witten D., Cooper G.M., Shendure J., Kircher M.* CADD: predicting the deleteriousness of variants throughout the human genome. Nucleic Acids Res. 2019; 47(1): 886–94. doi: 10.1093/nar/gky1016.

16. *Maksimova N., Hara K., Miyashia A., Nikolaeva I., Shiga A., Nogovicina A., Sukhomyasova A., Argunov V., Shvedova A., Ikeuchi T., Nishizawa M., Kuwano R., Onodera O.* Clinical, molecular and histopathological features of short stature syndrome with novel CUL7 mutation in Yakuts: new population isolate in Asia. J Med Genet. 2007; 44(12): 772–8. doi: 10.1136/jmg.2007.051979.

17. *Gervas P., Molokov A., Zarubin A., Topolnitskiy E., Shefer N., Pisareva L., Choynzonov E., Cherdyntseva N.* Germline variants associated with breast cancer in Khakass women of North Asia. Molecular Biology Reports. 2023; 50(3): 2335–41. doi: 10.1007/s11033-022-08215-1.

18. *Koliadenko V., Wilanowski T.* Additional functions of selected proteins involved in DNA repair. Free Rad Biol Med. 2020; 146: 1–15. doi: 10.1016/j.freeradbiomed.2019.10.010.

19. *Zagnoli-Vieira G., Bruni F., Thompson K., He L., Walker S., de Brouwer A.P.M., Taylor R.W., Niyazov D., Caldecott K.W.* Confirming TDP2 mutation in spinocerebellar ataxia autosomal recessive 23 (SCAR23). Neurol Genet. 2018; 4(4). doi: 10.1212/NXG.0000000000000262. Erratum in: Neurol Genet. 2018; 4(5). doi: 10.1212/NXG.0000000000000277. Taylor, Robert [corrected to Taylor, Robert W].

20. *Zheng Y., She Y., Su Z., Huang K., Chen S., Zhou L.* A novel pathogenic variant in TDP2 causes spinocerebellar ataxia autosomal recessive 23 accompanied by pituitary tumor and hyperhidrosis: a case report. Neurol Sci. 2024; 45(6): 2881–85. doi: 10.1007/s10072-024-07397-9.

21. *Zagnoli-Vieira G., Brazina J., van Den Bogaert K., Huybrechts W., Molenaers G., Caldecott K.W., van Esch H.* Inactivating TDP2 missense mutation in siblings with congenital abnormalities reminiscent of fanconi anemia. Hum Genet. 2023; 142(9): 1417–27. doi: 10.1007/s00439-023-02589-3.

22. *Кунсбаева Г.Б., Гилязова И.Р., Климентова Е.А., Измайлов А.А., Сафиуллин Р.И., Хасанов Э.Х., Мустафин А.Т., Папоян А.О., Султанов И.М., Иткулов А.Ф., Павлов В.Н., Хуснутдинова Э.К.* Поиск мутаций в гене синдрома блума (BLM) у больных раком предстательной железы. Медицинский вестник Башкортостана. 2015; 10(3): 216–19. [*Kunsbaeva G.B., Gilyazova I.R., Klimentova E.A., Izmailov A.A., Safiullin R.I., Khasanov E.Kh., Mustafin A.T., Papoyan A.O., Sultanov I.M., Itkulov A.F., Pavlov V.N., Khusnutdinova E.K.* Mutations in the bloom syndrome (BLM) gene in prostate cancer patients. Bashkortostan Medical Journal. 2015; 10(3): 216–19. (in Russian)].

23. *Prokofyeva D., Bogdanova N., Dubrowinskaja N., Bermisheva M., Takhirova Z., Antonenkova N., Turmanov N., Datsyuk I., Gantsev S., Christiansen H., Park-Simon T.W., Hillemanns P., Khusnutdinova E., Dörk T.* Nonsense mutation p.Q548X in BLM, the gene mutated in Bloom's syndrome, is associated with breast cancer in Slavic populations. Breast Cancer Res Treat. 2013; 137(2): 533–9. doi: 10.1007/s10549-012-2357-1.

24. *Matsionis A.E., Petrov A.V., Gorelik M.Z., Zavalishina L.E.* [Numerical impairments in genes in breast cancer: a multiplex ligation-dependent probe amplification study]. Arkh Patol. 2014; 76(4): 15–17. Russian.

Поступила/Received 16.09.2024
Одобрена после рецензирования/Revised 20.10.2024
Принята к публикации/Accepted 28.10.2024

## ABOUT THE AUTHORS

**Polina A. Gervas,** MD, PhD, Researcher, Laboratory of Molecular Oncology and Immunology, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences (Tomsk, Russia). Researcher ID (WOS): C-5846-2012. Author ID (Scopus): 13613767400. ORCID: 0000-0003-0051-8814.

**Aleksey Yu. Molokov,** Junior Researcher, Laboratory of Molecular Oncology and Immunology, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences (Tomsk, Russia). Researcher ID (WOS): AAF-7302-2021. Author ID (Scopus): 57217493727. ORCID: 0000-0002-1475-1185.

**Nataliya N. Babyshkina,** MD, DSc, Senior Researcher, Laboratory of Molecular Oncology and Immunology, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences; Associate Professor, Department of Biochemistry and Molecular Biology with a course in clinical laboratory diagnostics, Siberian State Medical University of the Ministry of Health of Russia (Tomsk, Russia). Researcher ID (WOS): A-7526-2012. Author ID (Scopus): 26641099700. ORCID: 0000-0002-0562-3878.

**Feodosia G. Ivanova,** MD, PhD, Head of Department of Drug Treatment, Yakut Republican Cancer Center (Yakutsk, Russia).

**Tatiana I. Nikolaeva,** MD, PhD, Chief Physician, Yakut Republican Cancer Center (Yakutsk, Russia).

**Dmitrii G. Tikhonov,** MD, DSc, Professor, Chief Researcher, Medical Institute, M.K. Ammosov North-Eastern Federal University (Yakutsk, Russia). ResearcherID C-1032-2014, Author ID: 7006659217, ORCID: 0000-0003-3385-9471

**Evgeny L. Choynzonov,** MD, DSc, Professor, Full Member of the Russian Academy of Sciences, Director, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences (Tomsk, Russia). Researcher ID (WOS): P-1470-2014. Author ID (Scopus): 6603352329. ORCID: 0000-0002-3651-0665.

**Nadezhda V. Cherdyntseva,** DSc, Professor, Corresponding Member of the Russian Academy of Sciences, Deputy Director for Science, Head of the Department of Molecular Oncology and Immunology, Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences (Tomsk, Russia). Researcher ID (WOS): C-7943-2012. Author ID (Scopus): 6603911744. ORCID: 0000-0003-1526-9013.

## AUTHOR CONTRIBUTIONS

**Polina A. Gervas:** study conception, critical revision with the introduction of valuable intellectual content, data collection and analysis, writing of the manuscript, editing of the manuscript.

**Aleksey Yu. Molokov:** data collection and analysis, editing of the manuscript.
**Nataliya N. Babyshkina:** study conception and design, critical revision with the introduction of valuable intellectual content.
**Feodosia G. Ivanova:** study conception and design, critical revision with the introduction of valuable intellectual content.
**Tatiana I. Nikolaeva:** study conception and design, critical revision with the introduction of valuable intellectual content.
**Dmitrii G. Tikhonov:** study conception and design, critical revision with the introduction of valuable intellectual content.
**Evgeny L. Choynzonov:** study conception and design, critical revision with the introduction of valuable intellectual content.
**Nadezhda V. Cherdyntseva:** study conception and design, critical revision with the introduction of valuable intellectual content.
All authors approved the final version of the manuscript prior to publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

***Funding***

*The reported study was funded by Russian Foundation Science according to research project №23-25-00386.*

***Conflict of interests***

*Prof. Choinzonov is the Editor-in-Chief of Siberian Journal of Oncology. Prof. Cherdyntseva N.V. is Deputy Editor-in-Chief of Siberian Journal of Oncology. The authors are not aware of any other potential conflicts of interest related to this manuscript.*

***Compliance with Ethical Standards***

*The study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki approved by Ethics Committee of Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences (5, Kooperativny St., Tomsk, 634009, Russia), protocol No. 10 dated September 24, 2022.*

***Voluntary informed consent***

*Written informed voluntaries consents were obtained from the patients for the publication of data in medical journal.*

## СВЕДЕНИЯ ОБ АВТОРАХ

**Гервас Полина Анатольевна,** кандидат медицинских наук, научный сотрудник лаборатории молекулярной онкологии и иммунологии, Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук (г. Томск, Россия). SPIN-код: 2934-7970. Researcher ID (WOS): C-5846-2012. Author ID (Scopus): 13613767400. ORCID: 0000-0003-0051-8814.

**Молоков Алексей Юрьевич,** младший научный сотрудник лаборатории молекулярной онкологии и иммунологии, Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук (г. Томск, Россия). SPIN-код: 1347-8410. Researcher ID (WOS): AAF-7302-2021. Author ID (Scopus): 57217493727. ORCID: 0000-0002-1475-1185.

**Бабышкина Наталия Николаевна,** доктор медицинских наук, старший научный сотрудник лаборатории молекулярной онкологии и иммунологии, Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук, Россия, доцент кафедры биохимии и молекулярной биологии с курсом клинической лабораторной диагностики, ФГБОУ ВО «Сибирский государственный медицинский университет» Минздрава России (г. Томск, Россия). Researcher ID (WOS): A-7526-2012. Author ID (Scopus): 26641099700. ORCID: 0000-0002-0562-3878.

**Иванова Феодосия Гавриловна,** кандидат медицинских наук, заведующая отделением противоопухолевой лекарственной терапии, ГБУ РС(Я) «Якутский республиканский онкологический диспансер» (г. Якутск, Россия). SPIN-код: 4878-9307.

**Николаева Татьяна Ивановна,** кандидат медицинских наук, главный врач, ГБУ РС(Я) «Якутский республиканский онкологический диспансер» (г. Якутск, Россия). SPIN-код: 2820-9540.

**Тихонов Дмитрий Гаврильевич,** доктор медицинских наук, профессор, главный научный сотрудник, Медицинский институт, Северо-Восточный федеральный университет им. М.К. Аммосова (г. Якутск, Россия). Researcher ID (WOS): C-1032-2014. Author ID (Scopus): 7006659217. ORCID: 0000-0003-3385-9471.

**Чойнзонов Евгений Лхамацыренович,** доктор медицинских наук, профессор, академик РАН, директор, Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук (г. Томск, Россия). SPIN-код: 2240-8730. Researcher ID (WOS): P-1470-2014. Author ID (Scopus): 6603352329. ORCID: 0000-0002-3651-0665.

**Чердынцева Надежда Викторовна,** доктор биологических наук, профессор, член-корреспондент РАН, заместитель директора по научной работе, заведующая лабораторией молекулярной онкологии и иммунологии, Научно-исследовательский институт онкологии, Томский национальный исследовательский медицинский центр Российской академии наук (г. Томск, Россия). SPIN-код: 5344-0990. Researcher ID (WOS): C-7943-2012. Author ID (Scopus): 6603911744. ORCID: 0000-0003-1526-9013.

## ВКЛАД АВТОРОВ

**Гервас Полина Анатольевна:** разработка концепции научной работы, критический пересмотр с внесением ценного интеллектуального содержания, сбор и обработка данных, подготовка и редактирование рукописи статьи.
**Молоков Алексей Юрьевич:** сбор и обработка данных, редактирование рукописи статьи.

**Бабышкина Наталия Николаевна**: общее руководство проектом, разработка концепции научной работы, критический пересмотр с внесением ценного интеллектуального содержания.
**Иванова Феодосия Гаврильевна:** общее руководство проектом, разработка концепции научной работы, критический пересмотр с внесением ценного интеллектуального содержания.
**Николаева Татьяна Ивановна:** общее руководство проектом, разработка концепции научной работы, критический пересмотр с внесением ценного интеллектуального содержания.
**Тихонов Дмитрий Гаврильевич:** общее руководство проектом, разработка концепции научной работы, критический пересмотр с внесением ценного интеллектуального содержания.
**Чойнзонов Евгений Лхамацыренович:** общее руководство проектом, разработка концепции научной работы, критический пересмотр с внесением ценного интеллектуального содержания.
**Чердынцева Надежда Викторовна:** общее руководство проектом, анализ результатов научной работы, разработка концепции исследования, критический пересмотр с внесением ценного интеллектуального содержания.
Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью и добросовестностью любой части работы.

***Финансирование***

*Исследование выполнено при финансовой поддержке РНФ, проект №23-25-00386.*

***Конфликт интересов***

*Автор Чойнзонов Е.Л. (доктор медицинских наук, профессор, академик РАН) является главным редактором «Сибирского онкологического журнала». Автор Чердынцева Н.В. (доктор биологических наук, профессор, член-корреспондент РАН) является заместителем главного редактора «Сибирского онкологического журнала». Авторам неизвестно о каком-либо другом потенциальном конфликте интересов, связанном с этой статьей.*

***Соответствие принципам этики***

*Проведенное исследование соответствует стандартам Хельсинкской декларации, одобрено независимым этическим комитетом Научно-исследовательского института онкологии (Россия, 634009, г. Томск, пер. Кооперативный, 5), протокол № 10 от 24.09.22.*

***Информированное согласие***

*Все пациенты подписали письменное информированное согласие на публикацию данных в медицинском журнале, включая его электронную версию.*