

## NEW GERMLINE MUTATIONS IN *BRCA1*, *ATM*, *MUTYH*, AND *RAD51D* GENES IN TUVANS EARLY-ONSET BREAST CANCER PATIENTS

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**Background:** In Russia, more than 50,000 women are diagnosed with breast cancer (BC) every year. Russia is a multinational country — about 200 ethnic groups live on its territory. Khakass, Buryats, Tuvans and other ethnic groups show higher rate of increase in BC incidence and a younger age of first diagnosed BC compared to Caucasian ethnicities. We focused on Tuvan ethnic group to find specific genetic aberrations associated with BC. There are no BC prevention models as well as standards for the treatment of inherited BC in Tuvans. In this context, the search for genetic markers of early cancer detection and the development of criteria for therapy response are relevant. **Aim:** To identify hereditary mutations in BC-associated genes in Tuvan women. **Materials and Methods:** 24 patients with early-onset BC (range, 25 to 46 years) were enrolled in the study. Genomic DNA isolated from blood samples was used to prepare libraries using a capture-based target enrichment kit covering 27 genes (*ATM*, *APC*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *FAM175A*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIK3CA*, *PMS2*, *PMS2CL*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11*, *TP53* and *XRCC2*). Next-generation sequencing was performed using the Illumina NextSeq500 System. **Results:** In our study, one pathogenic mutation was detected in *BRCA1* (rs80357868) gene (prevalence of 4%, 1/24). We identified the truncating 3875\_3878delGTCT mutation of *BRCA1* gene in Tuvans BC patient aged 34 years. We also detected three mutations that were probably damaging by PolyPhen2 and/or deleterious by SIFT in *ATM* (rs781023264), *MUTYH* (rs199840380) and *RAD51D* (rs145309168) genes. **Conclusion:** To the best of our knowledge, this is the first report that describes the highly pathogenic variant in the *BRCA1* gene (rs80357868) and possibly damaging (PolyPhen2) germline variants in the *ATM* (rs781023264), *MUTYH* (rs199840380) and *RAD51D* (rs145309168) genes in young Tuvans BC patient. **Key Words:** BRCA, germline mutation, breast cancer, Tuvans, Mongoloid race.

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More than 1.5 million new cases of breast cancer (BC) are diagnosed annually worldwide. In Russia, more than 50,000 women are diagnosed with BC every year. Russia is a multinational country — about 200 ethnic groups live on its territory. Racial/ethnic minority individuals have a significant burden of cancer and limited access to genetic cancer risk assessments. A higher rate of increase in BC incidence and a younger age of first diagnosed BC in indigenous ethnic groups can be noted, which makes it relevant to search for BC associated mutations to improve the management of patients [1].

Worldwide recommendations for *BRCA1* and *BRCA2* mutation testing include all women diagnosed with ovarian cancer and BC before age 45 and triple-negative BC before age 60. In Russians (Slavic ancestors), a strong founder effect was observed for the *BRCA1* 5382insC mutation, which accounted for up to 90% of all known BC-associated mutations in this population [2]. For “slavic” BC patients with a family history, the *BRCA1/2* mutation testing is the standard

of care. To date, there are a limited number of reports on inherited gene mutations associated with BC among Tuvans, Altaians, Buryats, Yakuts (Mongoloid indigenous people in Russia). BC prevention models for indigenous population have not been developed yet. For the indigenous population, there are no standards for the treatment of inherited BC and the advances in molecular oncology for the treatment of hereditary BC are not available. In this context, the search for markers of early cancer detection and the development of criteria for therapy response are relevant for indigenous people [3]. The aim of this study was to assess the prevalence of mutations in Tuvan women with early-onset BC.

### MATERIALS AND METHODS

Our study included 24 patients with early-onset BC (range, 25 to 46 years). Forty-one percent of patients were diagnosed with BC prior to age 40. Eight percent of patients (2/24) were diagnosed with synchronous or metachronous BC. Almost all tested women were diagnosed with invasive (ductal) carcinoma of no special type. Relevant information including personal and familial history, geographic family origin, age at diagnosis, and histological type of cancer was obtained. The description of other clinical characteristics of the study cohort is presented in Table 1.

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Abbreviations used: BC – breast cancer; MAF – minor allele frequency.

**Table 1.** The characteristics of Tuvan BC patients enrolled into the study

| Sample | Number | Age at diagnosis | Tumor side | Family history                     | TNM    |
|--------|--------|------------------|------------|------------------------------------|--------|
| 1      | 6      | 35               | Right      | Unknown                            | T2N2M1 |
| 2      | 7      | 38               | Right      | Unknown                            | T2N2M0 |
| 3      | 14     | 33               | Right      | Not burdened                       | T3N2M0 |
| 4      | 77     | 36               | Left       | Unknown                            | T2N2M0 |
| 5      | 147    | 39               | Right      | Aunt – BC, CRC                     | T3N0M0 |
| 6      | 160    | 33               | Right      | Not burdened                       | T4N2M1 |
| 7      | 278    | 42               | Bilateral  | Grandmother, aunt – stomach cancer | T1N0M0 |
| 8      | 267    | 46               | Right      | Unknown                            | T2N2M0 |
| 9      | 292    | 41               | Right      | Unknown                            | T2N1M0 |
| 10     | 410    | 43               | Bilateral  | Unknown                            | T4N2M0 |
| 11     | 637    | 45               | Right      | Unknown                            | T2N1M0 |
| 12     | 642    | 34               | Left       | Mother BC                          | T1N0M0 |
| 13     | 647    | 43               | Right      | Not burdened                       | T4N1M0 |
| 14     | 645    | 39               | Right      | Unknown                            | T1N0M0 |
| 15     | 646    | 40               | Right      | Unknown                            | T2N1M0 |
| 16     | 656    | 45               | Left       | Not burdened                       | T1N0M0 |
| 17     | 676    | 46               | Right      | Not burdened                       | T1N0M0 |
| 18     | 1073   | 45               | Left       | Not burdened                       | T2N1M0 |
| 19     | 1467   | 43               | Right      | Not burdened                       | T1N0M0 |
| 20     | 1642   | 25               | Right      | Not burdened                       | T4N1M0 |
| 21     | 1666   | 41               | Right      | Not burdened                       | T3N1Mx |
| 22     | 1686   | 39               | Right      | Not burdened                       | T2N1M0 |
| 23     | 1721   | 37               | Left       | Father-colorectal cancer           | T3N2M0 |
| 24     | 1741   | 44               | Right      | Not burdened                       | T1N0M0 |

Blood samples were collected in EDTA-containing tubes. DNA was extracted using phenol-chloroform method according to the standard protocol [4]. DNA purity was assessed by A260/A280 ratio measured using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, USA). DNA concentration was measured with a Qubit® dsDNA HS Assay Kit (Thermo Fisher Scientific, USA). DNA integrity (DIN) was verified on a 2200 TapeStation system (Agilent, USA).

Library preparation was performed using a capture-based target enrichment kit (Hereditary Cancer Solution, Sophia GENETICS, Switzerland) covering 27 genes: *ATM*, *APC*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *FAM175A*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIK3CA*, *PMS2*, *PMS2CL*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11*, *TP53*, and *XRCC2*. Paired-end sequencing (2 × 150 bp) was performed on a NextSeq500 System (Illumina, USA).

Allele frequency values were taken from the 1000 Genomes project (1000G; Based on Project Phase III Data), Exome Variant Server (NHLBI Exome Sequencing Project), Exome Aggregation Consortium (ExAC), and the SOPHiA DDM® Platform. Sequencing data were also analyzed according to GATK best practice recommendation for WES using GRCh37 as reference for BWA-mem alignment. Obtained variants were annotated with ANNOVAR software and ranged according to population frequency (gnomic exome, gnomAD genome, and ExAC), ClinVar, CADD, and literature data [5–7]. The clinical significance of detected sequence variants was assessed using PolyPhen2, Mutation Taster, and SIFT.

## RESULTS AND DISCUSSION

In accordance with epidemiologic data, the number of new cancer cases and the age-standardized cancer incidence rate increased in the Republic of Tuva from 2005 to 2018. The average age of men and women diagnosed with cancer decreased. Many of the most

prevalent cancers were associated with the “westernized lifestyle” of developed countries [1]. Tuvans are mainly distributed in Siberia (the Republic of Tuva), Mongolia, and China [8]. Our study aimed at searching for mutations of *BRCA1/2* and other genes in Tuvans living in the Republic of Tuva (Siberia). In our study we used the Hereditary Cancer Solution kit (Sophia GENETICS, Switzerland) covering 27 genes (see Materials and Methods section). The Hereditary Cancer Solution kit was expertly designed to accurately characterize the complex mutational landscape of the major hereditary cancer syndromes such as breast and ovarian cancer, Lynch and intestinal polyposis syndromes.

In terms of external characteristics, Tuvans belong to the Mongoloid race [9]. The Mongoloid or Asian-American race is one of the most numerous races in the world, covering about 50% of the world population. Molecular genetic and other aspects of BC of the Mongoloid or Asian-American race have been thoroughly studied by the Asian *BRCA* Consortium. According to the Asian *BRCA* Consortium, there is a significant difference in the spectrum of mutations between the Mongoloid and Caucasoid races. Nakamura *et al.* [10] and Bhaskaran *et al.* [11] showed the differences of *BRCA* variation between Chinese and non-Chinese populations. It was reported that the standard Caucasian *BRCA1/2* mutations (1100delAT, 1081delG, c.5154G>A, c.5468-1del8, c.3109C>T, c.7436\_7805del370 and c.9097\_9098insA) were not adequate to introduce the *BRCA* status in non-Caucasian populations [10–11].

In our study, we identified the truncating CM000679.2:g.43091772\_43091775delAGAC mutation of *BRCA1* gene in a young Tuvan BC patient aged 34 years (Table 2). It is known that CM000679.2:g.43091772\_43091775delAGAC mutation of *BRCA1* gene creates a premature translational stop signal (p.Ser1253Argfs\*10) in *BRCA1* gene and as result, absent or disrupted protein product. This loss-of-function variant in *BRCA1* is known to be pathogenic (ClinVar). This variant of *BRCA1* gene is present in population databases (rs80357868, ExAC 0.004%) and has been reported in individuals affected with breast and/or ovarian cancer [12]. This deleterious mutation was also detected among Chinese and Korean familial BC patients [13, 14].

We also detected three mutations that were probably damaging by PolyPhen2 and/or deleterious by SIFT (prevalence of 25%, 6/24) (see Table 2). We have found for the first time the c.737A>G mutation of the *ATM* gene in a Tuvan patient diagnosed with BC prior to 45 years. The c.737A>G mutation (rs781023264, p.Asn246Ser) results in a conservative amino acid change in the encoded sequence of the *ATM* gene. Three of five *in silico* tools predict a damaging effect of the variant on protein function. In ClinVar database, this variant is classified as uncertain significance. The available data on the occurrence of rs781023264 in the general population are insufficient to allow any conclusion about a clinical significance of this variant.

**Table 2.** Functional annotation (ClinVar, PolyPhen2, SIFT) of the identified genetic variants in early-onset Tuvan BC patients

| Gene          | db SNP ID   | Chr: position | Nucleotide change(HGVS) | Amino acid change (HGVS) | ClinVar | PolyPhen2         | SIFT        |
|---------------|-------------|---------------|-------------------------|--------------------------|---------|-------------------|-------------|
| <i>BRCA1</i>  | rs80357868  | 17: 41243788  | delAGAC                 | p.Ser1253fs              | HP      | -                 | -           |
| <i>ATM</i>    | rs781023264 | 11: 108115589 | A>G                     | p.Asn246Ser              | US      | Possibly damaging | Deleterious |
| <i>MUTYH</i>  | rs199840380 | 1: 45797891   | G>A                     | p.Arg291Cys              | US      | Possibly damaging | Tolerated   |
| <i>RAD51D</i> | rs145309168 | 17: 33428027  | A>T                     | p.Ile331Asn              | US      | Possibly damaging | Deleterious |

Note: SNP – single nucleotide polymorphism; HGVS – mutation type according to the Human Genome Variant Society nomenclature; US – variants of unknown significance; HP – highly pathogenic; PolyPhen2 – Polymorphism Phenotyping version 2; possibly damaging, i.e., it is supposed to affect protein function or structure; SIFT – Sort Intolerant From Tolerant.

**Table 3.** Identified genetic variants in early-onset Tuvan BC patients and their frequency in different populations in accordance with Gnome AD

| Gene          | db SNP ID   | MAF (ExAC) | Gnome AD               |            |             |           |
|---------------|-------------|------------|------------------------|------------|-------------|-----------|
|               |             |            | European (non Finnish) | East Asian | South Asian | Other     |
| <i>BRCA1</i>  | rs80357868  | 0.00002    | 0.00003097             | -          | -           | -         |
| <i>ATM</i>    | rs781023264 | 0.000008   | 0.000008811            | -          | 0.00003267  | -         |
| <i>MUTYH</i>  | rs199840380 | 0.000017   | 0.00001552             | 0.00005015 | 0.00009799  | 0.0001385 |
| <i>RAD51D</i> | rs145309168 | -          | 0.0002013              | 0.004310   | 0.0002940   | 0.0002767 |

Note: SNP – single nucleotide polymorphism; gnom AD – the Genome Aggregation Database.

Interesting, the mutation of the *MUTYH* gene (rs199840380, NC\_000001.10:g.45797891G>A) with MAF=0.00002 (ExAC) (MAF — minor allele frequency) was seen in four Tuvan patients diagnosed with BC prior to 45 years. This mutation of the *MUTYH* gene at the coding DNA level (p.Arg294Cys (R294C)) leads to an Arginine to Cysteine amino acid substitution. *In silico* analysis, which includes protein predictors and evolutionary conservation, confirms a deleterious effect of this variant. Based on currently available evidence, it is unclear whether *MUTYH* Arg294Cys is a pathogenic or benign variant. The rs199840380 of *MUTYH* gene was also mentioned by Liu *et al.* [15].

The mutation of the *RAD51D* gene (rs145309168, NC\_000017.10:g.33428027A>T) was seen in a BC patient 33 years old. The c.932T>A mutation of the *RAD51D* gene at the cDNA level leads to the Isoleucine to Asparagine substitution (ATT>AAT) at the protein level (p.Ile311Asn (I311N)). *In silico* analysis, which includes protein predictors and evolutionary conservation, confirms a deleterious effect of this variant. Based on currently available evidence, it is unclear whether *RAD51D* Ile311Asn is a pathogenic or benign variant. The rs145309168 was observed at minor allele frequency equal to 0.004 (83/18,868) in individuals of East Asian ancestry in large population cohorts by Lek *et al.* [16] and was observed at minor allele frequency equal to 0.005 in ExAC. This variant was mentioned in multiple Chinese patients with BC [16–18].

According to the The Genome Aggregation Database (gnomAD), mutations of *BRCA1* (rs80357868), *ATM* (rs781023264), *MUTYH* (rs199840380) and *RAD51D* (rs145309168) genes, that were found in Tuvan BC patients were previously described among European population (Table 3).

A limitation of our study is the lack of information regarding family history of early-onset BC patients. Several factors may make the family history difficult to interpret, including paternal transmission of the mutation, reduced penetrance and others [19].

To the best of our knowledge, this is the first report that describes the highly pathogenic variant in the *BRCA1* gene (rs80357868) and possibly damaging

(PolyPhen2) germline variants in the *ATM* (rs781023264), *MUTYH* (rs199840380) and *RAD51D* (rs145309168) genes in a young Tuvan BC patient. Further studies are necessary to evaluate the contribution of novel sequence variants to BC predisposition in Tuvan indigenous ethnic group of Siberia. Moreover, clinical validation of ethno-specific pathogenic mutations is expected to improve BC prophylaxis, early diagnosis and treatment.

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**CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.

**ETHICAL APPROVAL**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

**AUTHOR CONTRIBUTIONS**

Polina Gervas, Aleksey Molokov, Anna Ivanova, Artem Kiselev, Alena Chernyshova, Yelena Panferova, Lubov Pisareva recruited patients, collected samples and conducted experiments. Polina Gervas wrote the manuscript. Evgeny Choyzonov, Nadezda Cherdyntseva and Lubov Pisareva supervised the project. All authors reviewed and approved the manuscript.

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### НОВІ ГЕРМІНАЛЬНІ МУТАЦІЇ У ГЕНАХ *BRCA1*, *ATM*, *MUTYH* ТА *RAD51D* У ТУВИНСЬКИХ ХВОРИХ НА РАК МОЛОЧНОЇ ЗАЛОЗИ МОЛОДОГО ВІКУ

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**Стан питання:** У Росії щорічно більше ніж у 50 000 жінок виявляють рак молочної залози (РМЗ). Росія — багатонаціональна країна, на її території проживає близько 200 етнічних груп. Серед хакасів, бурятів, тувинців та деяких інших етнічних груп темпи зростання захворюваності на РМЗ більш високі, а вік, у якому вперше діагностують РМЗ, молодший у порівнянні з європеоїдними етносами. Ми зосередилися на тувинському етносі з метою виявити специфічні генетичні аберації, пов'язані з РМЗ. Для цієї етнічної групи поки ще не розроблені моделі профілактики РМЗ та стандарти лікування спадкового РМЗ. У цьому контексті актуальним є пошук генетичних маркерів для раннього виявлення раку і розробка критеріїв відповіді на терапію. **Мета:** визначити спадкові мутації в генах, що асоційовані з РМЗ у тувинських жінок. **Матеріали та методи.** У дослідження було включено 24 пацієнтки з РМЗ молодого віку (від 25 до 46 років). Геномна ДНК, виділена зі зразків крові, була використана для підготовки бібліотек з використанням набору для захоплення та збагачення цільових послідовностей, що включає 27 генів (*ATM*, *APC*, *BRD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *FAM175A*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIK3CA*, *PMS2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11*, *TP53* та *XRCC2*). Секвенування нового покоління було проведено з використанням системи Illumina NextSeq500. **Результати:** У нашому дослідженні виявлено одну патогенну мутацію в гені *BRCA1* (rs80357868) (частота 4%, 1/24). Ми визначили транкуючу мутацію 3875\_3878delGTCT гена *BRCA1* у тувинської хворої на РМЗ у віці 34 років. Ми також виявили три мутації, які, ймовірно, є пошкоджуючими за PolyPhen2 та/або шкідливими за SIFT у генах *ATM* (rs781023264), *MUTYH* (rs199840380) та *RAD51D* (rs145309168). **Висновок:** Уперше, наскільки нам відомо, описано високопатогенний варіант гена *BRCA1* (rs80357868) та, ймовірно, пошкоджуючі (PolyPhen2) гермінальні варіанти в генах *ATM* (rs781023264), *MUTYH* (rs199840380) і *RAD51D* (rs145309168) у тувинських хворих на РМЗ молодого віку.

**Ключові слова:** BRCA, гермінальна мутація, рак молочної залози, тувинці, монголоїдна раса.