New pathogenic germline mutation in ATM gene in Khakass breast cancer patients

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INTRODUCTION

• 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. 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.
• Russia is a multinational country – about 200 ethnic groups live on its territory (Russians, Khakass, Altaians, Buryats, Yakuts, Tyvans and others). Racial/ethnic minority individuals have a significant burden of cancer and limited access to genetic cancer risk assessments.
• To date, there are a limited number of reports on inherited gene mutations associated with BC among Khakass, Buryats, Yakuts, Tyvans (Mongoloid indigenous people in Russia).
• The aim of this study was to assess the prevalence of mutations in Khakass women with BC.

MATERIALS AND METHODS

Our study included 29 Khakass patients with BC (range, 28 to 69 years). Seventy five percent of patients were diagnosed with BC prior to age 50.

Blood samples were collected in EDTA-containing tubes. DNA was extracted using phenol-chloroform method according to the standard protocol. 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, PMS2CL1, Pten, RAD50, RAD51C, RAD51D, STK11, TP53, and XRCC2.

Paired-end sequencing (2×150 bp) was performed on a NextSeq500 System (Illumina, USA).

RESULTS

Mutations in BRCA1 and BRCA2 genes are responsible for hereditary BC were not found among Khakass BC patients. In our study, one pathogenic mutation was detected in ATM gene (rs780619951, NC_000011.10:g.108259022C>T) in two unrelated individuals with family history of cancer (prevalence of 7.4%, 2/27). Both of these BC patients aged 56 and 48 years old had a family history of stomach or colorectal cancer in second-degree relatives.

• As known, this sequence change creates a premature translational stop signal at codon 805 (p.Arg805*).
• It is also expected to result in an absent or disrupted protein product.
• This variant has been reported in individuals affected with ataxia-telangiectasia, as well as an individual with a personal or family history of breast or ovarian cancer.

CONCLUSION

In our study, we first describe pathogenic mutation in the ATM gene (rs780619951) found in Khakass BC patients with family history of cancer.

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