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The ethnic-specific spectrum of germline nucleotide variants in DNA damage response and repair genes in hereditary breast and ovarian cancer patients of Tatar descent

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Abstract

© 2018 Frontiers Media S.A. All Rights Reserved. The Russian population consists of more than 100 ethnic groups, presenting a unique opportunity for the identification of hereditary pathogenic mutations. To gain insight into the landscape of heredity pathogenic variants, we employed targeted next-generation sequencing to analyze the germline mutation load in the DNA damage response and repair genes of hereditary breast and ovary cancer syndrome (HBOCS) patients of Tatar ethnicity, which represents ~4% of the total Russian population. Several pathogenic mutations were identified in DNA double-strand break repair genes, and the spectrum of these markers in Tatar patients varied from that previously reported for patients of Slavic ancestry. The CDK12 gene encodes cyclin-dependent kinase 12, the key transcriptional regulator of the genes involved in DNA damage response and repair. CDK12 analysis in a cohort of HBOCS patients of Tatar decent identified a c.1047-2A>G nucleotide variant in the CDK12 gene in 8 of the 106 cases (7.6%). The c.1047-2A>G nucleotide variant was identified in 1 of the 93 (1.1%) HBOCS patients with mixed or unknown ethnicity and in 1 of the 238 (0.42%) healthy control patients of mixed ethnicity (Tatars and non-Tatars) ($p = 0.0066$, $OR = 11.18$, CI 95% = 1.53-492.95, Tatar and non-Tatar patients vs. healthy controls). In a group of mixed ethnicity patients from Tatarstan, with sporadic breast and/or ovarian cancer, this nucleotide variant was detected in 2 out of 93 (2.2%) cases. In a cohort of participants of Slavic descent from Moscow, comprising of 95 HBOCS patients, 80 patients with sporadic breast and/or ovarian cancer, and 372 healthy controls, this nucleotide variant was absent. Our study demonstrates a strong predisposition for the CDK12 c.1047-2A>G nucleotide variant in HBOCS in patients of Tatar ethnicity and identifies CDK12 as a novel gene involved in HBOCS susceptibility.

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Keywords

BRCA1, BRCA2, Breast cancer, CDK12, Homologous recombination repair, Next-generation sequencing, Ovarian cancer

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