Analysis of germline variants in the immune response-related genes in BRCA1 mutation carriers: possible modifying effect on age-dependent BRCA1 penetrance

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POSTER 21P

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Background & Purpose

Most of female carriers of germline BRCA1 mutation develop breast and/or ovarian cancer during the lifetime. However, the penetrance of BRCA1 pathogenic variants does not reach 100%, and the age of BRCA1-associated breast cancer (BC) onset varies widely. BRCA1-driven tumors are chromosomally unstable and may have excessive antigenicity.

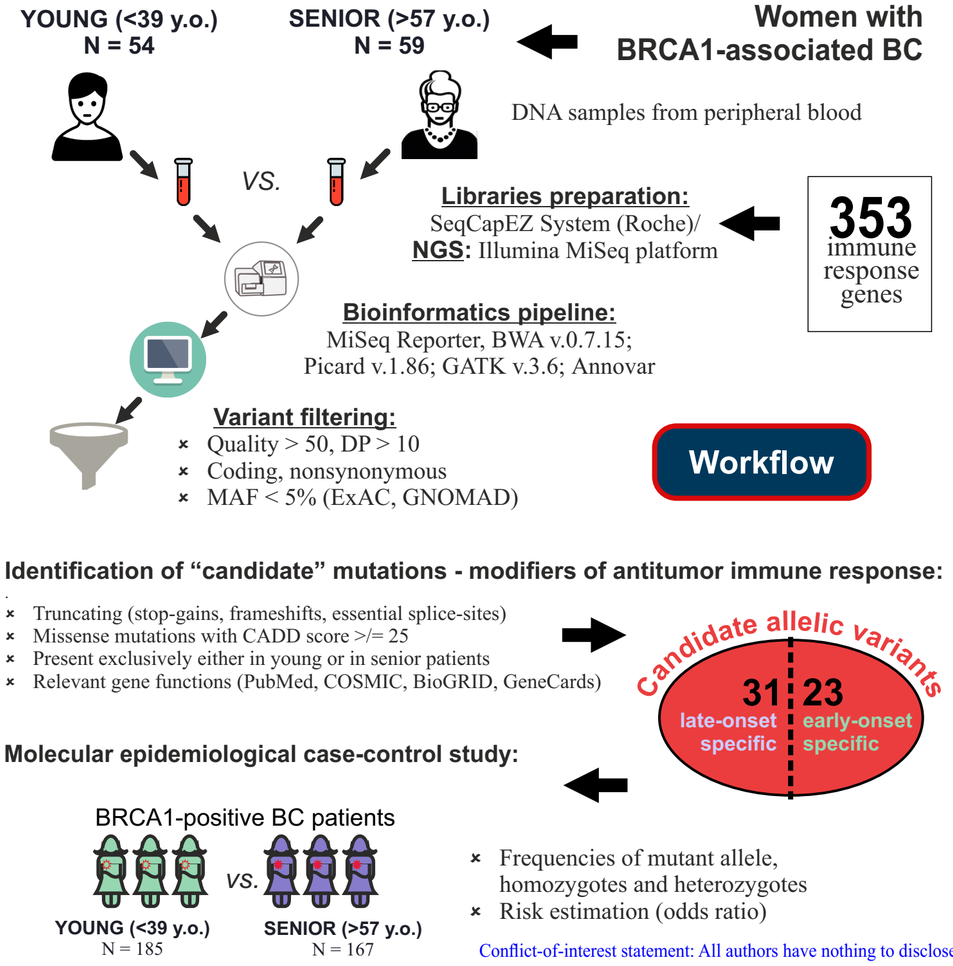
We hypothesized that hereditary variations in immune response pathways may contribute in the variability of BRCA1 penetrance.

Patients & Methods

The entire coding sequence of 353 immune response genes was analyzed by next generation sequencing (NGS) in 54 young (<39 y.o.) and 59 senior (>57 y.o.) BRCA1-mutated BC patients. Newly identified candidate variants were genotyped in the extended study, which included 185 young and 167 senior BC Slavic patients affected by BRCA1-driven BC.

Results

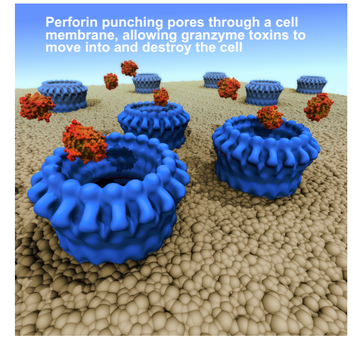
NGS analysis identified 54 allelic variants with gnomAD frequency <5% and a CADD-score of at least>/= 25, which were found exclusively either in young or in senior patients. Prevalence of 26 top candidates was analyzed in the extension study.



Conflict-of-interest statement: All authors have nothing to disclose

Known pathogenic variant in the perforin gene (PRF1 p.Ala91Val) was significantly overrepresented in young BC patients compared with senior women (20 carriers from 239 (8.4%) vs. 8/226 (3.5%), p = 0.032). PRF1 p.Ala91Val heterozygosity was associated with statistically significant elevation of the risk of acquiring BC before the age of 39 years as compared to the BRCA1 mutation carriers with the wild-type PRF genotype [OR = 2.49, 95% CI: 1.073 - 5.771, p = 0.034].

Perforin is one of the principal cytotoxic proteins responsible for cell lysis mediated by T-lymphocytes and NK cells; p.Ala91Val substitution leads to a 10-fold decrease in the lytic activity of the enzyme, thus heterozygous mutation PRF1 p.Ala91Val may cause subclinical symptoms of immunodeficiency and affect antitumor immunity.



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We calculated that BRCA1-carriers harboring PRF1 p.Ala91Val allele had overtly increased risk of acquiring breast cancer before the age of 39 compared with wild-type PRF BRCA1-carriers [OR = 2.49, 95% CI: 1.073 - 5.771, p = 0.034].

Conclusions

This study revealed that the inherited haploinsufficiency of immunodeficiency-related gene PRF1 caused by pathogenic missense p.Ala91Val may increase the risk of early breast cancer manifestation in BRCA1-carriers.