

Mutations in the ATRIP gene predispose to breast cancer

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Abstract

Several breast cancer susceptibility genes have been discovered, but more are likely to exist. To identify additional breast cancer susceptibility genes, we used the founder population of Poland and performed whole-exome sequencing on 510 women with familial breast cancer and 308 control subjects. We identified a rare mutation in ATRIP (GenBank: NM_130384.3: c.1152_1155del [p.Gly385Ter]) in two women with breast cancer. At the validation phase, we found this variant in 42/16,085 unselected Polish breast cancer-affected individuals and in 11/9,285 control subjects (OR = 2.14, 95% CI = 1.13-4.28, p = 0.02). By analyzing the sequence data of the UK Biobank study participants (450,000 individuals), we identified ATRIP loss-of-function variants among 13/15,643 breast cancer-affected individuals versus 40/157,943 control subjects (OR = 3.28, 95% CI = 1.76-6.14, p < 0.001). Immunohistochemistry and functional studies showed the ATRIP c.1152_1155del variant allele is weakly expressed compared to the wild-type allele, and truncated ATRIP fails to perform its normal function to prevent replicative stress. We showed that tumors of women with breast cancer who have a germline ATRIP mutation have loss of heterozygosity at the site of ATRIP mutation and genomic homologous recombination deficiency. ATRIP is a critical partner of ATR that binds to RPA coating single-stranded DNA at sites of stalled DNA replication forks. Proper activation of ATR-ATRIP elicits a DNA damage checkpoint crucial in regulating cellular responses to DNA replication stress. Based on our observations, we conclude ATRIP is a breast cancer susceptibility gene candidate linking DNA replication stress to breast cancer.

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