New breast cancer susceptibility gene candidate identified

March 30 2023, by Justin Jackson

Credit: Unsplash/CC0 Public Domain

A paper published in the *American Journal of Human Genetics* proposes ATRIP gene variants as a breast cancer susceptibility gene candidate based on a study of women without any of the known breast cancer-

associated gene variants.

The team of Canadian and Polish researchers led by the University of Toronto compiled data on 510 women from Poland with a strong family history of breast cancer but none of the confirmed moderate to high susceptibility breast cancer genes.

Whole-exome sequencing was performed, and genes with confirmed loss of function variants were selected for association analyses. They limited this next step in the analysis to genes that were known to play a role in cancer pathogenesis and those with a recurrent loss of function variant. This narrowed the list down to nine genes of interest, with ATRIP being the most frequent.

Of the 510 women with breast cancer and no confirmed susceptibility genes, 3 had ATRIP loss of function variants. In a control group of 308 subjects, none showed modified ATRIP. This was a seemingly insignificant find on its own until compared to a previous genomic study that showed the frequency of ATRIP loss of function variants among 22,928 cancer-free non-Finnish European females where the variants only affected 1 in every 2,293 women.

The team then turned to a larger data set to interrogate the initial finding. In a larger set of 16,085 Polish women with unselected breast cancer and 9,285 unaffected women in the validation phase, the ATRIP variant was detected in 42 of 16,085 affected women (1 in every 383 women with breast cancer) compared to 11 of 9,285 control subjects (1 in every 844 individuals).

ATRIP is a step in the much larger picture of DNA repair. Most hereditary genes linked to breast cancer (15 known to be moderate to high risk) are part of this DNA repair system. A loss of function or mutated variant in any of them increases the risk of developing breast

cancer. Most women have some risk factors but do not get breast cancer. Around 13% of women will develop at some point, with less than 10% of those attributable to hereditary causes.

While the potential role of ATRIP may be small in the overall number of cases, every case of cancer that can be narrowed down to a causal mechanism helps in clinical prognosis and prevention. The discovery of a previously unknown risk factor in this study is now the starting point for the next as more research is needed until a cure is found.

More information: Cezary Cybulski et al, Variants in ATRIP are associated with breast cancer susceptibility in the Polish population and UK Biobank, *The American Journal of Human Genetics* (2023). DOI: 10.1016/j.ajhg.2023.03.002