genomeweb

Breast Cancer Recurrence Risk Predicted by Immune-Related Germline Variants

Nov 01, 2019 | staff reporter

NEW YORK – A Canadian team has demonstrated that variants in the germline, mostly in genes related to the immune system, can help to find breast cancer patients at increased risk of disease recurrence.

Researchers at the National Research Council Canada, the University of Calgary, and McGill University used their so-called eTumorMetastasis algorithm to search for germline signatures of recurrence based on protein-coding sequences for nearly 800 individuals with estrogen receptor (ER)-positive breast cancer. Their results, published online on Friday in the journal *NPJ Precision Oncology*, indicated that it is possible to determine recurrence risk from germline variants, particularly those falling in or around genes from adaptive immune and cell proliferation pathways.

"Prognostic prediction using a patient's germline genomic landscape opens up the possibility of assessing cancer patients' risk of recurrence, which allows for a better forecasting of cancer recurrence in a quick, convenient, and noninvasive manner," senior author Edwin Wang, a researcher at the University of Calgary, and his colleagues wrote.

For their analysis, the researchers compiled exome sequence data for 755 ER-positive breast cancers from the US National Cancer Institute's Genomic Data Commons, which included tumors profiled for the Cancer Genome Atlas project.

Using its eTumorMetastasis tool, which combines variant, signaling, and network information, the team initially tracked down 18 network operational gene (NOG) signatures, each containing variants involving dozens of genes.

When they combined these signatures, the investigators came up with a unified germline gene set that appeared to coincide with recurrence in 60 more ER-positive breast tumors. They went on to validate the signature in a group of 200 ER-positive breast cancer patients, and in a second cohort comprised of 295 ER-positive breast cancer cases.

In those validation cohorts, the authors reported, "germline variants are significantly correlated with tumor recurrence and support our hypothesis that the original germline genomic landscape of a cancer patient has a significant impact on clinical outcome."

The investigators noted that the germline variant-based prediction strategy compared favorably with prognostic insights that could be gleaned from Genomic Health's Oncotype DX test, which considers expression levels for 21 genes in biopsied or surgically-removed tumor samples. Even so, they cautioned that expression-based approaches appeared to more accurately predict recurrence for breast cancer cases classified as high risk.

Although more work is needed to untangle the underlying biology, the genes overrepresented in the germline recurrence signatures had ties to altered cell division, immune cells, or other features in the tumor or microenvironment.

"Germline variants associated with tumor recurrence likely impair the adaptive immune response function of affected individuals, increasing the susceptibility to relapse," the authors proposed. "These results highlight the important role of germline variants in tumor evolution and recurrence."

Filed Under Sequencing Cancer North America Breast Cancer cancer subtypes genetic risk variants algorithm computational biology exome sequencing