Early life gene epimutation may contribute to breast cancer development

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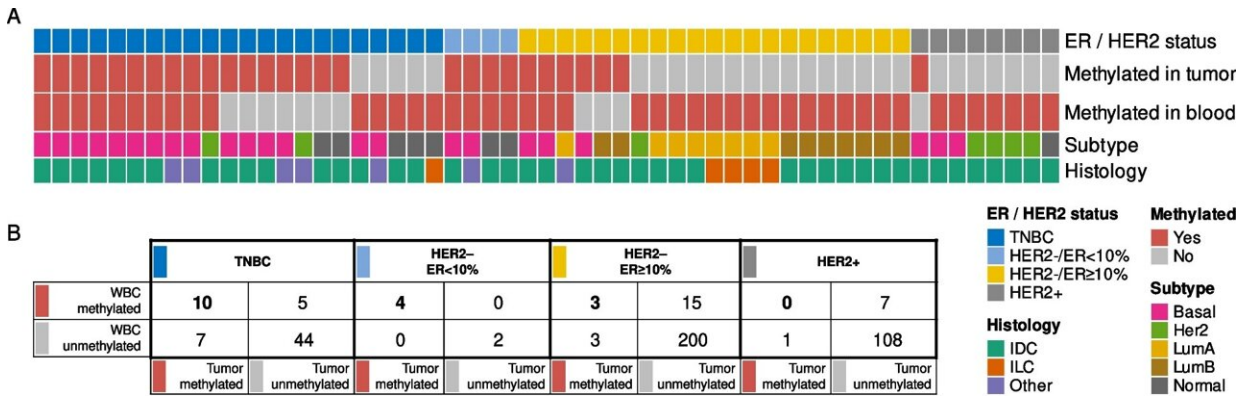

BRCA1 methylation in matched blood and tumor samples in breast cancer patients. A Molecular and histological characteristics (rows) of all samples (N = 55; columns) belonging to matched sample pairs carrying BRCA1 methylation in the blood (WBC) and/or tumor. TNBC, triple-negative breast cancer; HER2, Human epithelial-like receptor-2; ER, estrogen receptor; basal, basal-like gene expression profile; Her2, HER2-enriched gene expression profile; LumA, luminal A gene expression profile; LumB, luminal B gene expression profile; Normal, normal-like gene expression profile; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma. B Concordance of BRCA1-methylation status in WBC and tumor tissue among all patients analyzed, stratified for tumors belonging to the different breast cancer subgroups. Credit: *Genome Medicine* (2023). DOI: 10.1186/s13073-023-01262-8

Research reveals that around 20 percent of all cases of the most severe

form of breast cancer may arise from the small group of normal tissue cells carrying an epimutation of a specific gene.

Cancer is a major health challenge worldwide, affecting many lives. Despite progress in understanding its causes, most cancer forms, including breast cancer, continue to increase in many countries.

Scientists have been looking closely at both genes and the environment, trying to figure out what sets the stage for cancer. One interesting area of study is something called "epimutations." Instead of changes to the actual genes, these are changes in how our genes are turned on or off.

In a recent study investigators at the University of Bergen, in collaboration with the US Women's Health Initiative, found a link between certain epimutations in a gene called BRCA1 and a higher risk of triple-negative breast cancer (TNBC), the most severe type of breast cancer.

"This higher risk was found despite the fact that epimutations affected a very small portion of normal cells in the affected individuals," says professor Per Eystein Lønning.

May originate from the pregnancy

While this was a breakthrough, it left the researchers wondering when and where these epimutations happened. In a new study now featured in the journal *Genome Medicine* the Bergen Group, and to be presented at the international SABCS, the world's largest breast cancer conference in San Antonio on December 6, in collaboration with other Norwegian researchers, the Bergen researchers dug deeper.

Analyzing DNA from both breast tissue and white blood from over four hundred breast cancer patients, they made several important discoveries,

providing new light on the subject.

For many cases of TNBC, BRCA1 gene epimutations were found in both the white blood cells and tumor tissue. Moreover, epimutations in the white blood cells and tumor tissue from the same individual revealed the same profile.

"This suggests they might have a common cell origin, possibly occurring very early during pregnancy," says Lønning.

Gender differences not previously recorded

The findings also indicate that as many as around 20 percent of all TNBC may arise from the small group of normal tissue cells carrying BRCA1 epimutations.

Analyzing blood samples from newborns, they found similar BRCA1 epimutations as those detected in cancer patients. Surprisingly, these epimutations happened twice as often in girls than in boys. Finally, no concordance in epimutations between newborns and their parents was observed, arguing against direct inheritance.

"The fact that epimutations might be happening early during pregnancy challenges conventional theories on carcinogenesis and cancer risk. Moreover, the fact that they occur twice as commonly in girls than boys reveals an important gender difference not previously recorded," says Lønning.

This discovery is opening new avenues for research. The Bergen Breast Cancer Group now works on the exact mechanism of early life epimutations. In addition, in collaboration with WHI investigators, they study whether epimutations in other genes might be linked to other types of cancer.

"Understanding this could potentially be a game-changer in how we approach and prevent cancer in the future," Lønning concludes.

More information: Oleksii Nikolaienko et al, Prenatal BRCA1 epimutations contribute significantly to triple-negative breast cancer development, *Genome Medicine* (2023). DOI: 10.1186/s13073-023-01262-8

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