Research: Subset of breast cancers have two PIK3CA mutations on the same allele

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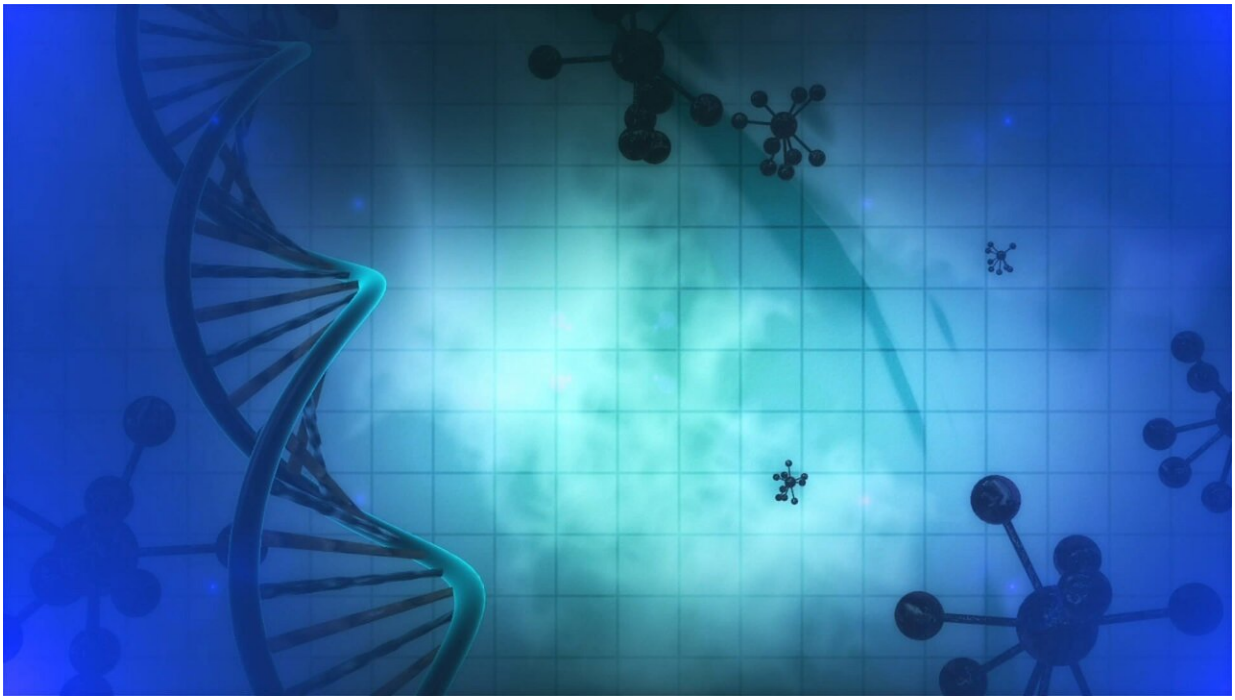

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A team of researchers affiliated with a large number of institutions in the U.S. has found that a subgroup of breast cancers have two PIK3CA mutations, and that such mutations occur on the same allele. In their paper published in the journal *Science*, the group describes their study of the PIK3CA gene and its involvement in the development of cancerous tumors in humans. Alex Toker with Harvard University Medical School

has published a Perspective piece in the same journal issue outlining the work done by the team and its possible implications.

PIK3CA is an oncogene, and is one of the most frequently mutated genes in human cancers. Under normal conditions, it is the gene that codes properly for the protein p110a. Growth factors activate receptor tyrosine kinase which lead to the recruitment of the PI3K pathway. This leads to conversion of PIP_2 to PIP_3 (both components of cell membranes), which in turn recruit downstream effectors, one of which is the AKT pathway—it stimulates healthy cell growth. In cancer cases, mutations in PIK3CA lead to hyperactivation of the process, which means more AKT is produced, resulting in overstimulation of cell growth and subsequent tumor development. In this new effort, the researchers have found that sometimes, there is more than one mutation in PIK3CA and it happens in the same allele—and the result is enhanced tumor growth. More specifically, the team found double mutations in PIK3CA occurring in approximately 8 to 12 percent of breast cancer patients (who had both primary and metastatic tumors).

The researchers report that they were able to narrow down the single-hotspot mutations that were more frequent in PIK3CA. They also found the most common minor sites where secondary mutations occurred. And they also report that they were able to show that double mutations in PIK3CA were factors in inducing hyperactivation of PI3K due to a disruption of p85-p110a interaction, and also in an increase in bonding effectiveness between p110a and membranes. The end result was an increase in production of the PI3K lipid, which in turn resulted in overstimulating downstream effectors and enhanced tumor growth.

Toker suggests the findings are likely to lead to the development of PI3K inhibitors that can be used with other chemotherapy drugs, hopefully improving the outcome for patients with double mutations.

More information: Neil Vasan et al. Double PIK3CA mutations in cis increase oncogenicity and sensitivity to PI3Kα inhibitors, *Science* (2019). DOI: 10.1126/science.aaw9032