It takes more than one mutant copy of the PIK3CA gene to make breast cancer more aggressive

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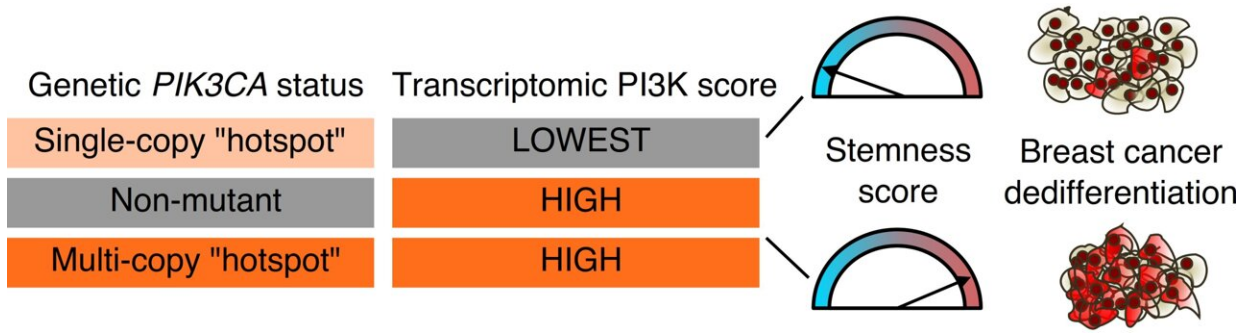

Counterintuitive relationship between PIK3CA genotype and transcriptomic stemness and PI3K signaling scores in human breast cancer. Credit: Ralitsa Madsen, CC-BY 4.0 (creativecommons.org/licenses/by/4.0/)

Breast cancers that have an overactive PI3K enzyme, involved in cell growth and division, tend to be more aggressive and to spread and divide more like stem cells. But a new study by Ralitsa Madsen of University College London and colleagues publishing November 11 in the journal *PLOS Genetics* uncovers a surprising relationship between PI3K activity and mutations in the PIK3CA gene that codes for the enzyme. Breast cancer tumors with one mutant copy of the PIK3CA gene tend to have lower PI3K activity. In comparison, patients with two or more copies often had higher PI3Kα activity, resulting in more aggressive tumors and

a poorer prognosis for patients with certain types of breast cancer.

Experiments in the lab previously showed that two but not one mutant *PIK3CA* gene can promote a persistent stem cell state—a quality called "stemness". But until now, there was no evidence from human patients to support this idea. In the new study, researchers investigate the relationship among PI3K mutations, PI3K activity and stemness in breast cancer. They used publicly available data from nearly 3,000 breast cancer tumors and applied computational methods to infer PI3K activity and stemness. They discovered that aggressive tumors had more PI3K activity and a higher degree of stemness. However, they were surprised to find that cancer cells with only one mutant copy of *PIK3CA* had lower levels of stemness and are potentially less aggressive.

The new study supports the idea that overactive PI3K enzymes are linked to more aggressive breast cancers. Additionally, the researchers warn that the number of copies of mutant PIK3CA mutations in a tumor may affect how it responds to cancer therapies. They conclude that this information, along with data on PI3K activity, should be considered when choosing patients to participate in clinical trials of new drugs.

Madsen adds, "Breast cancer stratification by *PIK3CA* mutant dose reveals a counterintuitive relationship with functional indices of PI3K pathway activity and tumor dedifferentiation."

More information: Madsen RR, Erickson EC, Rueda OM, Robin X, Caldas C, Toker A, et al. (2021) Positive correlation between transcriptomic stemness and PI3K/AKT/mTOR signaling scores in breast cancer, and a counterintuitive relationship with PIK3CA genotype. *PLoS Genet* 17(11): e1009876. doi.org/10.1371/journal.pgen.1009876