We may be looking at wrong mutation for breast cancer treatment

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A leading gene candidate that has been the target of breast cancer drug development may not be as promising as initially thought, according to research published in open access journal *Genome Medicine*.

Mutation in the gene PIK3CA is the second most prevalent gene mutation in breast cancer and is found in 20% of all breast cancers. This has led people to think these changes may be driving breast cancer. Yet these mutations are also known to be present in neoplastic lesions -pre-cancerous growths many of which are thought to be benign, that have not invaded the surrounding tissue.

Researchers from Stanford University wanted to better understand these neoplastic growths and how they related to the carcinoma. They sequenced the genes from tissue taken from the breasts of six women who had undergone a mastectomy, leading to a total of 66 samples, which included 18 carcinomas and 34 neoplastic lesions.

A specific mutation in the PIK3CA gene occurs in the same patient multiple times. This was found to be the case for four out of the six women. In two out of these four cases, this mutation occurs in the neoplastic lesions, which are not considered tumors, but does not occur in the invasive carcinoma.

One of the lead researchers, Arend Sidow, said: "There are currently several drugs in development that target PIK3CA, attesting to the fact that many companies and clinicians believe PIK3CA to be a promising

target. Our finding that PIK3CA may recur multiple times at various stages of tumor or neoplastic development suggests that it is more of a moving target than one would like."

The researchers constructed phylogenetic trees to track the mutations back to their original cell to determine how the lesions were related to each other. From this, the researchers discovered that in each of the four PIK3CA-positive patients the mutation arose independently multiple times. This is something that has never been seen before. Following the PIK3CA mutation through these phylogenetic trees, and its lack of presence in the final carcinoma in two cases, would suggest that it is not driving the cancer, and instead suggests that it is a driver of benign proliferation.

This new information will have implications for the development of future drugs that target PIK3CA. Future studies should attempt to replicate this one with more patients and attempt to show whether PIK3CA mutations are ancestrally present in the tumor cells of positive patients, in which case it may be good target, or whether it is present in only a subset of tumor cells, in which case it is not a good target.

More information: Cell-lineage heterogeneity and driver mutation recurrence in pre-invasive breast neoplasia, Ziming Weng, Noah Spies, Shirley X Zhu, Daniel E Newburger, Dorna Kashef-Haghighi, Serafim Batzoglou, Arend Sidow and Robert B West, *Genome Medicine*, DOI: 10.1186/s13073-015-0146-2

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