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Gene responsible for many spontaneous breast cancers identified

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Cancerous tumors contain hundreds of mutations, and finding these mutations that result in uncontrollable cell growth is like finding the proverbial needle in a haystack. As difficult as this task is, it's exactly what a team of scientists from Cornell University, the University of North Carolina, and Memorial Sloan-Kettering Cancer Center in New York have done for one type of breast cancer. In a report appearing in the journal *Genetics*, researchers show that mutations in a gene called NF1 are prevalent in more than one-fourth of all noninheritable or spontaneous breast cancers.

In mice, NF1 mutations are associated with hyper-activation of a known cancer-driving protein called Ras. While researchers have found earlier evidence that NF1 plays a role in other types of cancer, this latest finding implicates it in breast cancer. This suggests that the drugs that inhibit Ras activity might prove useful against breast cancers with NF1 mutations.

"As we enter the era of personalized medicine, genomic technologies will be able to determine the molecular causes of a woman's breast cancer," said John Schimenti, Ph.D., a researcher involved in the work from the Center for Vertebrate Genomics at Cornell University College of Veterinary Medicine in Ithaca, New York. "Our results indicate that attention should be paid to NF1 status in breast cancer patients, and that drug treatment be adjusted accordingly both to reduce the cancer and to avoid less effective treatments."

To make this discovery, scientists analyzed the genome of mammary tumors that arise in a mouse strain prone to genetic instability—whose activity closely resembles the activity in human breast cancer cells—looking for common mutations that drive tumors. The gene NF1 was missing in 59 out of 60 tumors, with most missing both copies. NF1 is a suppressor of the oncogene Ras, and Ras activity was extremely elevated in these tumors as a consequence of the missing NF1 gene. Researchers then examined The Cancer Genome Atlas (TCGA) data, finding that NF1 was missing in more than 25 percent of all human breast cancers, and this was associated with a decrease in NF1 gene product levels, which in turn is known to increase Ras activity.

"This research is compelling because it helps us understand why some breast cancers are more likely to respond to only certain types of treatment," said Mark Johnston, Editor-in-Chief of the journal *Genetics*. "The findings reported in this article may guide clinicians to better treatments specific to the needs of each patient."

More information: Marsha D. Wallace, Adam D. Pfefferle, Lishuang Shen, Adrian J. McNairn, Ethan G. Cerami, Barbara L. Fallon, Vera D. Rinaldi, Teresa L. Southard, Charles M. Perou, and John C. Schimenti Comparative Oncogenomics Implicates the Neurofibromin 1 Gene (NF1) as a Breast Cancer Driver, *Genetics*, October 2012 192:385-396

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