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New insights reported about the Angelina Jolie gene

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Scientists from the Cancer Therapy & Research Center (CTRC) in San Antonio today (March 4) published work that provides deeper insight into how the Angelina Jolie gene, BRCA1, functions in normal breast tissue and how its loss results in breast cancer.

The CTRC—a National Cancer Institute-designated Cancer Center—is part of UT Medicine San Antonio, the clinical practice of the School of Medicine at The University of Texas Health Science Center at San Antonio.

BRCA1 is known to suppress cancer by repairing breaks in DNA, the molecule that contains the genetic blueprint of each cell. This DNA damage occurs with aging and environmental insults.

In the new study, published in *Nature Communications,* CTRC researchers found that BRCA1 also serves as a limiter or governor on a gene called COBRA1 that regulates breast cell growth.

"We now have solid and compelling evidence that BRCA1 in breast tissue is doing something independent of DNA repair," said study lead author Rong Li, Ph.D., professor of molecular medicine at the Health Science Center. "We still think DNA repair is important for BRCA1 to suppress tumor development, but we just don't think it's the whole story."

Clues to a puzzle

Since DNA repair is needed in every cell of the body, scientists including Dr. Li have puzzled over why loss of BRCA1 function predisposes women to only breast and ovarian cancers. Also, diminished BRCA1 activity doesn't affect men significantly, as it does women.

"From very early on, we and others in the field speculated that maybe there is a DNA repair-independent function associated with BRCA1 that can better explain this tissue and gender specificity," Dr. Li said.

The new finding provides at least part of that answer, he said, and could one day translate into better diagnostic and treatment tools for this form

of breast cancer. "The ultimate goal would be to slow down or even prevent breast cancer development in BRCA1 mutation carriers," he said.

"The work by Dr. Li and his lab has shown us a totally different side of BRCA1," said Virginia Kaklamani, M.D., professor of medicine at the Health Science Center and leader of the CTRC breast oncology program. "We have come to know BRCA1 as a gene responsible for repairing DNA errors. Dr. Li has found that BRCA1 plays an important role in breast tissue development, a finding that may help in developing more effective ways of preventing breast cancer in women carrying BRCA1 mutations."

Tough to treat

BRCA1 is mutated in up to 10 percent of invasive breast cancers—about 25,000 new cases in the U.S. annually. These cancers are frequently very difficult to cure. A mutation in BRCA1 put Ms. Jolie at higher risk for the disease, and she opted to undergo a double mastectomy to prevent it.

Women who carry the mutation have an 80 percent increased risk of developing breast cancer.

Human tissue studies

Dr. Li and his colleagues conducted the study in mice and want to confirm the finding in human tissue. They are collaborating with CTRC breast oncologists to obtain tissue from BRCA1 mutation carriers and assess whether the same BRCA1-COBRA1 relationship exists.

"If we can validate this relationship in human tissue, then the next step will be to see if we can intervene using pharmacological tools to re-establish the balance, if it is lost, in a BRCA1 mutation carrier," Dr. Li

said.

More information: Sreejith J. Nair et al. Genetic suppression reveals DNA repair-independent antagonism between BRCA1 and COBRA1 in mammary gland development, *Nature Communications* (2016). DOI: 10.1038/ncomms10913

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