Four new genes confirmed to increase familial breast cancer risk

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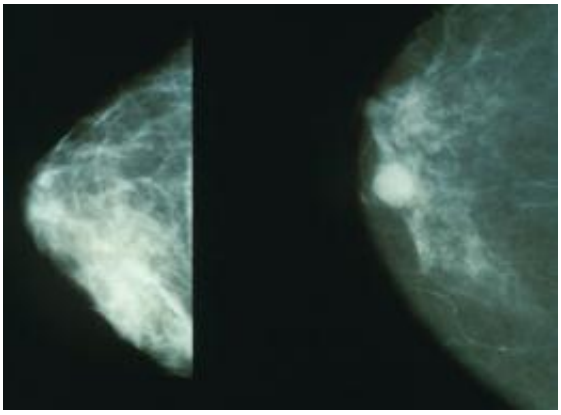

Mammograms showing a normal breast (left) and a cancerous breast (right). Credit: Wikipedia.

Four new genes have been added to the growing list of those known to cause increased breast cancer risk when mutated through the efforts of researchers at Huntsman Cancer Institute (HCI) at the University of Utah, who lead an international consortium working to find more gene mutations that cause inherited breast cancer susceptibilities.

"BRCA1 and BRCA2 aren't the whole story when it comes to inherited breast cancer risk. We've known for a long time that more genes had to be responsible and several have since been discovered, by us and by others," according to Sean Tavtigian, Ph.D., an HCI investigator, professor in the Department of Oncological Sciences at the University of

Utah (U of U), and one of three joint-principal investigators on the study. "Originally, the gene we are currently studying, called RINT1, was not considered a human cancer susceptibility gene. But then we discovered there was a two- to three-fold increase in risk for breast cancer in families that carry a mutation in that gene." The RINT1 findings were published this month in the journal *Cancer Discovery*.

Surprisingly, RINT1 was also found to increase risk for a broad spectrum of gastrointestinal and gynecological cancers in these families. "Many genes responsible for a strong increase in cancer risk at one or two sites in the body are also connected with lesser increases in risk at other sites," said David Goldgar, Ph.D., professor in the Department of Dermatology at the U of U, an HCI investigator, and another of the study's joint-principal investigators. "However, with RINT1 mutations, the increased risk for other cancers is about equal to that for breast cancer."

In another study led by Tavtigian, mutations in three other genes—MRE11A, RAD50, and NBN—were also confirmed to increase breast cancer risk, as reported in the journal *Breast Cancer Research* June 3. "The proteins encoded by these three genes form a tight complex that is involved in DNA repair, and the three genes had been considered likely candidates.

Interestingly, RINT1's name is an abbreviation for 'RAD50 Interactor 1,' and it's just one step downstream from the MRE11A, RAD50, NBN complex in a biochemical sense," said Tavtigian. "But we don't know yet if that biochemical connection explains RINT1's cancer susceptibility role."

Now almost 50% of the familial risk for breast cancer can be explained by the ensemble of rare mutations in known breast cancer susceptibility genes and more common genetic variation in about 75 areas of the

genome each of which is associated with only a small increased risk of breast cancer according to Goldgar, compared to about 30% only five years ago. The consortium's ongoing efforts continue to enlarge the panel of genes known to account for increased occurrence of breast cancer within families with a history of the disease.

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