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Researchers find new gene linked to breast cancer

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Researchers in a multicenter international study have identified a new gene that, if mutated, may increase a woman's risk of breast cancer by more than a third.

Further, the researchers found that the gene, HMMR, interacts with the well-known breast cancer gene BRCA1. Alternations in either gene cause genetic instability and interfere with cell division, which could be a path to breast cancer developing. This leads researchers to not just a single gene, but a pathway that may be a potential target for treating or detecting breast cancer.

Results of the study appear in the advance online edition of *Nature Genetics*.

HMMR is mutated in about 10 percent of the population. Mutations in the two main genes involved in breast cancer susceptibility, BRCA1 and BRCA2, occur in about one of every 300 individuals, or less than 1 percent of the population.

"If we can identify variations of genes that are more common in the population that increase breast cancer risk, then targeting that gene for early detection or treatment will have a greater impact," says Kristen Stevens, M.P.H., a doctoral student in epidemiology at the University of Michigan School of Public Health and one of the lead authors on the paper.

The study was an international collaboration with researchers from Spain, Israel and several centers in the United States, including the U-M Comprehensive Cancer Center.

Researchers started by developing a computerized network-modeling tool that allows many different types of existing scientific data sources to be analyzed easily to identify genes that impact cancer development. The researchers started with four genes already known to play a role in breast cancer – BRCA1, BRCA2, ATM and CHEK2. They were then able to see how each of these genes interacts with other genes in the body. Through this model, HMMR emerged as a key player in breast cancer. The authors then showed that alterations of either BRCA1 or HMMR can lead to genetic instability and interfere with cell division.

“These findings made us wonder whether HMMR might also be a breast cancer susceptibility gene,” says study author Stephen Gruber, M.D., Ph.D., M.P.H., the H. Marvin Pollard Professor of Internal Medicine at the U-M Medical School. Gruber is an associate professor of internal medicine and of human genetics in the U-M Medical School, and of epidemiology in the U-M School of Public Health. He directs the Cancer Genetics program in the U-M Comprehensive Cancer Center, which focuses on inherited cancer risks.

To understand whether variation in HMMR increases breast cancer risk, the researchers looked at the genes of 923 Jewish Israeli women with breast cancer and similar women without breast cancer in a study led by Gadi Rennert, M.D., director of the CHS National Cancer Control Center in Haifa, Israel. The Ashkenazi Jewish population in Israel carries a higher risk of breast cancer than other ethnicities.

This component of the study found that women with a variation in the HMMR gene had a higher risk of breast cancer, even after accounting for mutations in the BRCA1 or BRCA2 genes. In particular, the risk of

breast cancer in women under age 40 who carry the HMMR variation was 2.7 times the risk in women without this variation.

The researchers further verified the finding in a second group of Ashkenazi Jewish women in New York who had a family history of breast cancer but no identified BRCA1 or BRCA2 mutations and a third study of Jewish women with and without breast cancer in New York. In total, 2,475 women with breast cancer and 1,918 healthy women were studied in Israel and New York.

Overall, the risk of breast cancer was 23 percent higher in women who had one copy of genetic variant, and 46 percent higher in women who had inherited two copies. In addition, those women were diagnosed an average of 12 months younger than women from the control group, suggesting that HMMR is linked to early-onset breast cancer.

“Identifying genes involved in cancer in the general population is important, because not all of the causes of breast cancer have been found. Through discoveries such as this, someday we might be able to more precisely estimate a person’s risk of cancer based on their genes,” says study author Laura Rozek, Ph.D., a postdoctoral research fellow at the U-M Medical School.

Source: University of Michigan