Genetic 'hotspot' for breast cancer risk

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Vanderbilt-Ingram Cancer Center investigators have identified a new genetic hotspot for breast cancer.

Reporting this week in Nature Genetics, Wei Zheng, M.D., Ph.D, and colleagues have identified a region on chromosome 6 that is strongly associated with breast cancer susceptibility in Asian women. This genetic "locus" may help guide efforts to find the specific genes linked with sporadic - or non-inherited - forms of the disease, the authors suggest.

Breast cancer is one of the most common cancer types among women worldwide.

Genetics plays an important role in the disease, and a handful of breast cancer susceptibility genes - such as BRCA1 and BRCA2 - have been identified. Mutations in these genes increase risk of inherited forms of breast cancers.

"But the genetic factors identified so far explain only a small percent of all the cases in the general population," said Zheng, an Ingram Professor of Cancer Research, professor of Medicine and the director of the Vanderbilt Epidemiology Center.

The genetic factors responsible for the vast majority of cases are unclear, "so there has been a lot of interest to identify additional genetic factors for breast cancer," said Zheng, the senior author on the study.

To date, most breast cancer susceptibility genes have been studied primarily in Caucasian or European populations, but women of other ethnic backgrounds may have important genetic differences from these groups, Zheng noted. So the researchers turned to a population of Asian women in Shanghai, China, which they had been studying for more than a decade to identify nutritional, environmental and genetic factors associated with disease risk.

Using an approach called "genome-wide association," Zheng and colleagues began looking for genetic variations in Asian women with breast cancer compared to healthy controls. The investigators analyzed more than 600,000 genetic markers - called SNPs (single nucleotide polymorphisms) - for differences between the groups.

From the first group of more than 3,000 women, they selected 29 of the most promising SNPs associated with breast cancer. Through two more rounds of validation in two independent groups of women, the researchers narrowed down these 29 candidate SNPs to a single SNP that exhibited strong and consistent association with breast cancer. The researchers also found a similar association in an independent group of American women, indicating that the results might be relevant for other ethnic populations.

The influence of the SNP on breast cancer risk appears very large, Zheng noted.

"This SNP explains about 18 percent of the (breast cancer) cases in the general population," Zheng said. Compared to other previously identified SNPs, "this one would probably rank as No. 1 or No. 2 in terms of effect size."

If a woman has just one copy of this SNP, her risk of breast cancer increases about 40 percent. With two copies of this SNP, the risk increases about 60 percent.

But just how this SNP confers risk is unclear; it lies on chromosome 6 in a part of the genome with no known genes, "upstream" from the gene that encodes the estrogen receptor 1 (ER?). While ER? is known to influence breast cancer aggressiveness, the impact of this candidate SNP on ER? is unclear.

"At this point, we actually don't know the function of this SNP we identified," he said.

But the SNP does appear strongly associated with

ER-negative cases of breast cancer, which carry a worse prognosis than ER-positive cases.

"In most of the previous studies, the SNPs they identified were associated strongly with ER-positive cases, so this is the first study to find SNP associated with ER-negative cases."

Zheng and colleagues are now conducting studies in the laboratory to characterize the function of this SNP. And he notes that they will continue to probe the multitude of genetic variations they initially identified in the first phase of the study for additional susceptibility genes. Zheng hopes to use this SNP and others to build a risk prediction model.

"Eventually, we hope that we can use this model to identify high-risk women for chemoprevention or regular cancer screening to reduce their breast cancer mortality," he said.

Zheng also emphasizes the importance of teamwork in a research project of this scope, including investigators at the Shanghai Cancer Center and the Shanghai Institute of Preventive Medicine. Working together with these and other investigators, he is pulling together a consortium of more than 40,000 Asian and American breast cancer patients and controls for further studies.

Source: Vanderbilt University Medical Center