Discovery suggests location of genes for breast density, a strong risk factor for breast cancer

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Studying the DNA of 889 people, gene hunters at the Mayo Clinic and H. Lee Moffitt Cancer Centers have identified a region on chromosome 5p that is significantly associated with dense breast tissue, a known risk factor for breast cancer. The findings, published in the September 1 issue of *Cancer Research*, a publication of the American Association for Cancer Research, suggest that genes which influence breast density could serve as a predictive marker for disease and provide a biological target for agents that may reduce breast cancer risk by reducing breast density.

Women with dense breasts – meaning the breast has a smaller proportion of fat relative to stromal and epithelial tissues ? are three to five times more likely to develop breast cancer than women with less dense breasts, according to the researchers. Scientists have estimated the total influence of genes on breast density to be about 60 percent.

The study, the first reported genetic linkage analysis for genes influencing breast density, “provides further evidence that this trait does appear to be genetically influenced,” said the study’s lead investigator, Celine Vachon, Ph.D., an epidemiologist at the Mayo Clinic in Rochester, Minnesota.

Although the investigators have strong evidence that a gene residing in this chromosomal region influences breast density, the exact gene that is responsible is not yet known. “One or more of the 45 candidate genes in this region could explain a large proportion of mammographic breast density, and potentially, breast cancer,” she said.

Within the region on chromosome 5p, the gene which encodes the prolactin receptor in particular, stands out as a possible contributor to dense breasts. Prolactin is a hormone that helps enlarge mammary glands during pregnancy and, after childbirth, is involved in milk production. Previous research has found a correlation between mammographic density and prolactin levels in postmenopausal women, the researchers note.

Vachon’s team took what they term an “agnostic” approach to uncovering genes, or gene regulators like microRNA, that are involved in the development of dense breasts. “We assume we don’t know anything about the biology of the trait and we let the genomes of our participants and their breast densities guide us,” Vachon said.

Their method contrasts the traditional “candidate gene” approach, where scientists look at variations in specific genes thought to be involved with the disease or trait of interest. Such linkage studies have been used to uncover many high-impact risk genes, such as the breast cancer susceptibility genes BRCA1 and BRCA2.

The Mayo researchers performed a genome-wide linkage scan to identify possible chromosome regions in 89 families, part of a multi-generational Minnesota family study that began in 1944 at the University of Minnesota. Blood samples and mammograms were collected and analyzed for 756 female participants; 133 men were also included to help clarify genetic information in their offspring, mothers and sisters. “We used the relationship between family members and breast density to inform where a gene might be,” Vachon says.

Researchers first studied 403 DNA markers spaced across the genome to determine the amount of genetic information shared at and between each of these genomic signposts and its correlation to breast density as measured on mammography. They found three regions of interest, and narrowed the most promising region further by studying 21

additional, more densely spaced DNA markers. This secondary analysis highlighted one region consisting of approximately 45 known genes on chromosome 5p that was significantly associated with increased breast density.

The researchers then adjusted their analysis to eliminate the contribution of body mass index (BMI), which is a known breast cancer risk factor and also inversely associated with breast density, and found the “signal” was just as strong. “That means the location that we have identified on chromosome 5p does not appear to affect breast density through its influence on BMI,” she said.

Only age, diagnosis of abnormal cells on a breast biopsy and inheritance of rare breast susceptibility genes, such as BRCA1 and BRCA2, are stronger risk predictors of breast cancer than is breast density, Vachon said.

“At this point, we have not identified a gene or genes for breast density but a promising location to investigate further,” Vachon said. “Identification of genes for breast density will improve our understanding of how breast density influences breast cancer development in women.”

“In this study we focused on the genetics of a risk factor for cancer. This approach has not been tried before,” said Thomas Sellers, Ph.D., a coauthor on this study and currently director of the Moffitt Research Institute in Tampa, Florida.

Source: American Association for Cancer Research