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Study points to new breast cancer-susceptibility gene

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A gene whose existence was detected only a couple of years ago may increase women's risk of breast cancer when inherited in a mutated form, and may contribute to prostate cancer as well, researchers at Dana-Farber Cancer Institute and colleagues in Finland report in a new study.

The gene, known as PALB2, may play a role in only about 1 percent of breast cancer cases in the select population that was studied (Finnish women), but its discovery sheds light on the complex web of gene interactions that underlies the disease, say the authors of the study, which is being published by the journal *Nature* on its Web site and later in a print edition.

"Breast cancer can arise from a wide variety of genetic abnormalities, and mutations acquired during the evolution of breast tumor cells are relatively common in the disease," said the study's co-lead author, Bing Xia, PhD, of Dana-Farber. "However, only about 10 percent of all cases are the result of inherited mutations, and, of those, only about 20-30 percent result from mutations in the two main breast cancer-susceptibility genes, BRCA1 and BRCA2. So there is room for other such genes to be discovered."

The new study stems from research by Xia and Dana-Farber's David Livingston, MD, a senior author of the paper, into BRCA2's "binding partners" – proteins that interact with the BRCA2 protein. They found that the PALB2 protein is an especially close partner of BRCA2, with substantial portions of the proteins binding to each other.

"We found that PALB2 helps anchor BRCA2 in key areas of the cell nucleus, where BRCA2 repairs damaged DNA," Xia said. Mutations in BRCA2 can prevent such repairs from being made, which can lead to runaway cell growth. If BRCA2 is normal, but PALB2 is defective, BRCA2 may be out of position for fixing damaged DNA, with similar pathological effects on cell growth.

To determine whether PALB2 mutations are implicated in both hereditary and sporadic breast cancer, researchers at Oulu University Hospital in Finland screened tissue from 113 Finnish families with a history of the disease. Three of the families were found to have the same mutation of the gene.

The Finnish team next screened tissue from 1,918 breast cancer patients, some of whom had inherited cancer-susceptibility genes, some of whom had not. Eighteen patients – or about 1 percent of the entire group – were found to carry the same PALB2 mutation; and most of them turned out to have a family pattern of the disease.

"The mutation causes the middle portion of the PALB2 protein to be truncated," Xia remarked. "That seems to hinder its ability to bind to BRCA2, which, in turn, hinders DNA repair. The screening result suggests that carrying the mutation increases one's risk of breast cancer approximately four fold."

The Finnish researchers also screened tissue from 141 male breast cancer patients, 476 colorectal cancer patients, and 639 prostate cancer patients. In one family where prostate cancer had occurred in several generations, every family member with prostate cancer whom it was possible to test was found to carry the PALB2 mutation, suggesting that the gene plays a role in this form of cancer as well. The mutation did not turn up in male breast and colorectal cancer patients, however.

"Our research suggests that mutations in PALB2 can be an influential factor in breast cancer development, like those affecting BRCA2," Xia observed. "But since we suspect that such mutations occur less frequently in PALB2 than BRCA2, they are not responsible for as many breast cancer cases as BRCA2 mutations."

Xia added that the discovery of a PALB2 mutational link to breast cancer "may well increase one's ability to identify women at elevated risk for the disease and to devise appropriate prevention and, possibly, treatment strategies, as well."

Source: Dana-Farber Cancer Institute