

Gene elevating breast cancer risk also causes prostate cancer

February 8 2007

Cancer is a complex and common disease caused by a combination of both genetic and environmental factors. An inherited predisposition seems to be involved in at least 5–10 per cent of all cases of breast cancer. The two major familial breast cancer susceptibility genes BRCA1 and BRCA2 only explain 20-30 per cent of families with site-specific female breast cancer, which suggests the contribution of additional susceptibility genes.

According to Dr Robert Winqvist, who coordinates the research effort, the identification of these genes may help to clarify the genetic background contributing to breast cancer and suggest novel pharmaceutical targets. It could also lead to genetic screening that identifies individuals at increased breast cancer risk and result in improved prevention efforts and treatment.

About a year ago, Dr Bing Xia and Professor David Livingston at the Dana-Farber Cancer Institute in Boston identified a novel BRCA2 binding factor, PALB2 that regulates certain key functions of normal BRCA2 activity. The next step was to set out to evaluate the newly detected PALB2 gene as a potential heritable breast cancer susceptibility candidate by screening for disease-related alterations. The results of this international research effort were recently published in *Nature*.

The research first involved comprehensive screening for genetic aberrations in 113 Finnish breast cancer families. The same constitutional mutation in PALB2 was observed in three families. It was

later showed that the relevant mutant protein is deficient in its ability to support the kinds of DNA damage responses in which PALB2 normally participates. The mutation was further also investigated in 1,918 specimens from an unselected series of Finnish breast cancer individuals. This study revealed 18 mutation-positive individuals, about one per cent of the studied patients, most of whom turned out to have a familial pattern of disease development. The study also involved 141 unselected male breast cancer patients, 188 familial and 288 unselected colorectal cancers, as well as 164 familial and 475 unselected prostate cancer patients. In prostate cancer, one multigenerational cancer family was found where cancer occurred in several generations and all patients showed the single mutation in PALB2 that was studied. According to Winqvist, this suggests that this Finnish founder mutation may be important in heritable prostate cancer as well. Male breast cancer and colorectal cancer cases did not display the mutation.

The constitutional mutation elevates the risk of breast cancer four-fold

"Present results show that the discovered PALB2 mutation elevates the risk of breast cancer four-fold. However, we still need more research to better assess the effect on cancer development. As the comprehensive mutation analysis was originally conducted on only 113 cancer families, it may be that there still are other PALB2 genetic defects accounting for heritable breast and prostate cancer susceptibility. Recent results also imply that PALB2 might be a cancer susceptibility gene in other populations as well. It's been shown that two of the mutations identified in Fanconi anemia patients in non-Finnish populations seem to be associated with familial breast cancer," says Winqvist.

Winqvist points out that, in spite of recent advances, known factors can only explain a fraction of heritable susceptibility to breast cancer. He is

nonetheless disposed to believe that the evaluation of yet other biologically significant factors will in time improve the situation. "Hopefully, increased knowledge of underlying mechanisms will provide better conditions for cancer prevention, diagnostics and treatment," Winqvist says.

Source: Academy of Finland

Citation: Gene elevating breast cancer risk also causes prostate cancer (2007, February 8) retrieved 15 May 2024 from <https://medicalxpress.com/news/2007-02-gene-elevating-breast-cancer-prostate.html>

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