MedicalXpress

Two genetic deletions in human genome linked to aggressive prostate cancer development

April 9 2012

An international research team led by Weill Cornell Medical College investigators have discovered two inherited-genetic deletions in the human genome linked to development of aggressive prostate cancer. The findings, published online today in the *Proceedings of the National Academy of Sciences* (*PNAS*), indicate a man's risk of developing prostate cancer either triples or quadruples, depending on the genetic variant they inherit.

In the study, one genetic deletion is shown to affect the functioning of a known gene, while the other, found in a non-coding area of the genome once considered to be "junk DNA," seems to be regulating a cascade of genes. According to the lead co-authors, the study is potentially groundbreaking because it demonstrates that so-called copy number variations (CNVs) in either protein coding or non-coding areas of the human genome play a significant role in the development of cancer in general, and in aggressive prostate cancer, specifically.

"We used to think that only genes that made proteins were responsible for disease, but this study shows us that there is inherited information in the non-coding areas of the genome that appear to play a strong role in development of cancer," says study co-author, Dr. Mark A. Rubin, the Homer T. Hirst Professor of Oncology in Pathology at Weill Cornell Medical College. Other researchers have linked CNVs to Alzheimer's and Parkinson's disease, mental retardation, autism, schizophrenia and

neuroblastoma, a type of brain cancer. "This study suggests there are other cancers that might be associated with CNVs," says Dr. Rubin. "It's an exciting new field of research."

"The study shows that copy number variations matter in cancer," says co-lead investigator, Dr. Francesca Demichelis, who is now an Assistant Professor at the Center of Integrative Biology at the University of Trento in Italy and an Adjunct Assistant Professor in the Institute for Computational Biomedicine at Weill Cornell Medical College.

The two genetic variants identified by the research team are not the only cause of aggressive prostate cancer, Dr. Demichelis says. "These variants likely collaborate with other factors early in a man's life leading to development of prostate cancer."

Prostate cancer affects one in six men during their lifetime, and family history is the strongest risk factor for prostate cancer. Because of the inheritable nature of the disease, for the study Weill Cornell researchers hunted to find DNA that is either significantly deleted or duplicated in the genome of patients with prostate cancer to compare it to men without the disease.

In this collaboration between Weill Cornell Medical College, the Brigham and Women's Hospital and Innsbruck University Hospital, researchers examined blood samples from a population of men from the Tyrol Early Prostate Cancer Detection Program in Austria. Since 1993, this program has been aggressively screening men, age 45-75, who live in the Tyrol region with prostate specific antigen (PSA) in order to detect prostate cancer as early as possible. The population includes men who developed prostate cancer as well as men with elevated PSA who have no prostate cancer based on a biopsy. In addition, researchers looked at the germline variation in these patients to see if there is a risk factor as to why some men with elevated PSA have prostate cancer and

some men do not.

Molecular studies were performed in the U.S. on more than 1900 blood samples from Tyrolean men (867 unrelated cancer patients and 1,036 controls). Researchers discovered two CNVs that were significantly different between Tyrolean individuals with aggressive prostate cancer and those without cancer, and then reproduced that finding in another group of 800 U.S. patients. The researchers then tested the effect of the two variants in laboratory cells and discovered they increase the ability of cancer cells to grow and to invade.

Both of these variants are small deletions in DNA that lead to over-expression of genes, Dr. Demichelis says. She and her colleagues found that one gene that is over-expressed due to the variant deletion is MGAT4C, which leads to the ability of cells to grow and migrate. "A man with the variant is four times more likely to develop prostate cancer if he inherited this variant than if he did not," Dr. Demichelis says. "Interestingly, MGAT4C was found to be significantly over-expressed in metastatic versus localized prostate cancer," she adds.

The role of the other genetic variant, located in the "junk" region of the human genome, is not yet known, but the researchers believe it activates a cascade of other genes. They calculated a man is three times more likely to develop prostate cancer if he has inherited this variant.

The investigators calculated these two newly identified variants occur at a frequency of between 1.5-3 percent of the overall population, but are found at a significantly higher percentage in men diagnosed with aggressive prostate cancer. "For the gene coding variant, MGAT4C, we were able to analyze metastatic human samples where we observed that the high-risk gene is abundantly present," says Dr. Demichelis.

Now researchers are looking for other variants they hope to be able to

build into a comprehensive DNA test to be used as a diagnostic tool to help clinicians identify men whose prostate cancer will likely progress to advanced stages. "We could also potentially use such a DNA test for chemoprevention if risk of developing aggressive prostate cancer is deemed to be high," says Dr. Demichelis. "This is the start of a new strategy. It would not replace PSA, but would identify other risk factors."

"In this new area of research, we are starting to appreciate that the differences in inherited genomic variants account not only for why we look different or respond in various ways to medication, but also for why we develop disease," Dr. Rubin says. "This is the first study to suggest these variants may account for susceptibility to cancer. This new line of research will also allow us to study the biology around prostate cancer initiation."

Provided by New York- Presbyterian Hospital