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Researchers Discover a Common Variation in a Gene Segment that Increases the Risk for Prostate Cancer

Researchers report that a variation in a portion of DNA strongly predicts prostate cancer risk and that this common variation may be responsible for up to 20 percent of prostate cancer cases in white men in the United States. The research was conducted by investigators from the National Cancer Institute (NCI), part of the National Institutes of Health, and their partners in the Cancer Genetic Markers of Susceptibility (CGEMS) initiative. CGEMS researchers are scanning the entire human genome to identify common, inherited gene mutations that increase the risks for breast and prostate cancers. The results appear in the May 1, 2007 issue of *Nature Genetics* and were published online April 1, 2007.

"Discovery of this common variation is very exciting. Building on this finding we may be able to identify men at highest risk for prostate cancer, diagnose the disease earlier, and hopefully prevent it all together. One of the next steps is to understand the mechanism by which this genetic variation exerts its effect on cancer risk," said NCI Director John E. Niederhuber, M.D.

This gene variation was discovered on chromosome 8. Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 8, one inherited from each parent, form one of the pairs. Chromosome 8 spans about 146 million base pairs (the chemicals that comprise DNA), represents about 5 percent of the total DNA in cells, and contains an estimated 700 to 1,100 genes.

The region the CGEMS study identified on chromosome 8 is marked by a number of single nucleotide polymorphisms (SNPs), including rs6983267. SNPs are the most common type of gene variant in which a single unit of DNA may vary from one person to

the next. The rs6983267 SNP is located in a segment of DNA that has few known or predicted genes for prostate cancer.

The researchers also confirm that a previous finding of a different variant, marked by SNP rs1447295, is also associated with prostate cancer. The rs1447295 SNP is located nearby on the same arm of chromosome 8. The old and the new susceptibility loci, or gene locations, appear to act independently; a change in one region did not affect the degree of risk conferred by the other. “We now have two significant regions in the same general area that convey risk for prostate cancer. This will undoubtedly focus multidisciplinary studies on this stretch of DNA, called 8q24,” said Meredith Yeager, Ph.D., lead author on the study.

The rs1447295 location could be responsible for about seven percent of prostate cancer cases in white men of north European descent. Thus, taken together with rs6983267, these two genetic changes could account for as much as one quarter of prostate cancer cases in white men. The increased risk conferred by these loci was observed for all age groups studied.

“CGEMS allows us to look systematically across the entire human genome and search for common genetic variations that confer risk for prostate cancer, a very common and very complex disease” said Stephen Chanock, M.D., director of NCI’s Core Genotyping Facility in the Advanced Technology Center.

“Identification of new regions like 8q24 furthers efforts to uncover the genetic basis of prostate cancer, which may eventually lead to more insights into cancer causation in general," added Gilles Thomas, M.D., Ph.D., lead scientist of CGEMS.

An initial genome-wide association study was conducted in 2,329 men from across the United States who are participating in the NCI’s Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) that began in 1993. The PLCO analysis compared 1,172 men with prostate cancer to 1,157 who did not have cancer.

CGEMS results were further confirmed by a number of other studies, including the American Cancer Society Cancer Prevention Study II, the Health Professionals Follow-up Study, the CeRePP French Prostate Case-Control Study, and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Combined, these studies enrolled 6,266 men.

Prostate cancer is the third-leading cause of cancer-related death in men yet very little is known about its origins. In 2007, there will be an estimated 219,000 new prostate cancer cases and an estimated 27,000 deaths in the U.S.

Similar data on breast cancer, the second-leading cause of cancer-related deaths in women in the U.S., are now being generated and are expected to be released soon. The CGEMS database will soon contain close to 2.5 billion genotypes, allowing researchers to identify genetic risk factors for breast and prostate cancers using 540,000 SNPs across the genome. By comprehensively surveying for common genetic variations and following-up promising findings in confirmatory studies, researchers hope to identify and verify associations that increase or decrease the risk of these cancers.

Analyses and data from the CGEMS study will be available through NCI's caBIG™ (Cancer Biomedical Informatics Grid™), at http://caIntegrator.nci.nih.gov/cgems/. The summary results from the scan in PLCO are already freely available to other researchers at this Web site.

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Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second locus at 8q24. *Nature Genetics.* Online April 1, 2007.

For more information on NCI's Cancer Genetic Markers of Susceptibility (CGEMS) initiative and NCI's Cohort Consortium, including collaborating studies and institutions, please visit http://cgems.cancer.gov, and http://epi.grants.cancer.gov/Consortia/cohort.html.

For more information about cancer or the National Cancer Institute, please visit the NCI Web site at http://www.cancer.gov or call NCI's Cancer Information Service at 1-800-4 CANCER (1-800-422-6237).