Study identifies multiple genetic risk factors for prostate cancer

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A study led by researchers at the Keck School of Medicine of the University of Southern California (USC) and Harvard Medical School has identified seven genetic risk factors—DNA sequences carried by some people but not others—that predict risk for prostate cancer. According to the study's findings, these risk factors are clustered in a single region of the human genome on chromosome 8 and powerfully predict a man's probability of developing prostate cancer. The paper will be published in the online edition of *Nature Genetics* on April 1.

"The study has identified combinations of genetic variants that predict more than a fivefold range of risk for prostate cancer," says senior author David Reich, assistant professor of genetics at Harvard Medical School and associate member of the Broad Institute of Harvard and MIT. "Both high- and low-risk combinations of variants are common in human populations."

"The identification of these genetic variants is an important step in helping us understand the higher risk for prostate cancer in African Americans compared with other U.S. populations and, more importantly, why some men develop prostate cancer and others do not," says lead author Christopher Haiman, assistant professor of preventive medicine at the Keck School of Medicine of USC.

While the HMS/USC team identified seven genetic variants on chromosome 8, two other studies published in the same issue of Nature Genetics highlight the importance of this region in prostate cancer and

each provides independent support for the findings presented by the HMS/USC team. One of the studies is from deCODE Genetics in Iceland while the other is led by Dr. Gilles Thomas and Dr. Stephen Chanock at the National Cancer Institute. Together, the three studies provide robust evidence of the role genetic variants play in prostate cancer.

According to the HMS/USC study, the seven genetic variants each independently predict risk for prostate cancer, with the predictive strength varying depending on the variant. Because almost all the risk factors were of highest frequency in African Americans, they may contribute to the known higher rate of prostate cancer among African Americans compared with other U.S. populations. The predictive power of the variants may also be useful in the prevention of prostate cancer. "Clinical testing of these genetic variants may help us identify men who should be prioritized for early prostate cancer screening and prevention efforts," says Reich.

The study also produced novel biological findings. It revealed that each genetic contributor to prostate cancer risk is located outside of the coding regions of genes, in regions previously designated as junk DNA. "The discovery of multiple, independent genetic changes that are in close proximity to one another, but outside of any known gene, suggests that these results may also teach us about novel molecular mechanisms whereby DNA changes can alter risk of disease," says Brian Henderson, the paper's senior co-author and dean of the Keck School of Medicine of USC.

Two papers in 2006 highlighted this same chromosomal region as important in prostate cancer. The company deCODE genetics in Iceland first identified two specific genetic variants that contributed to risk for prostate cancer. The HMS/USC group then published a paper that identified a small region (about 4 million nucleotides, or 1/1,000th of the

genome) as likely to contain important genetic risk factors. As part of this study, the HMS/USC group carried out a whole-genome screen for prostate cancer genes in about 2,500 African Americans. The paper suggested that more variants were likely in the region.

To find the additional risk factors in the current study, the team systematically tested genetic changes in this region of the genome in roughly 7,500 African American, Japanese American, Native Hawaiian, Latino, and European American men with and without prostate cancer. The majority of the men studied were drawn from the Multiethnic Cohort Study (MEC), an epidemiological study of more than 215,000 people from Los Angeles and Hawaii created in 1993 by USC's Henderson and Laurence Kolonel of the University of Hawaii. The genetic study of the MEC grows out of a multiyear, ongoing collaboration between USC, the University of Hawaii, and collaborators at HMS and the Broad Institute of Harvard and MIT.

Source: University of Southern California