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Study finds first major genetic mutation associated with hereditary prostate cancer risk

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After a 20-year quest to find a genetic driver for prostate cancer that strikes men at younger ages and runs in families, researchers have identified a rare, inherited mutation linked to a significantly higher risk of the disease.

A report on the discovery, published in the January 12, 2012 issue of the *New England Journal of Medicine*, was led by investigators at the Johns Hopkins University School of Medicine and the University of Michigan Health System. The research team found that men who inherit this mutation have a 10 to 20 times higher risk of developing prostate cancer.

While accounting for only a small fraction of all prostate cancer cases, the discovery may provide important clues about how this common cancer develops and help to identify a subset of men who might benefit from additional or earlier screening. This year, an estimated 240,000 men in the United States will be diagnosed with prostate cancer.

"This is the first major genetic variant associated with inherited prostate cancer," says Kathleen A. Cooney, M.D., professor of internal medicine and urology at the U-M Medical School, one of the study's two senior authors.

"It's what we've been looking for over the past 20 years," adds William B. Isaacs, Ph.D., professor of urology and oncology at the Johns Hopkins

University School of Medicine, the study's other senior author. "It's long been clear that prostate cancer can run in families, but pinpointing the underlying genetic basis has been challenging and previous studies have provided inconsistent results."

For this study, the researchers collaborated with John Carpten, Ph.D., at the Translational Genomics Research Institute (TGen) in Phoenix, Arizona, who used the latest technology to sequence the DNA of more than 200 genes in a human chromosome region known as 17q21-22.

Cooney, working with Ethan Lange, Ph.D., of the University of North Carolina on the U-M Prostate Cancer Genetics Project, was the first to identify 17q21-22 as a region of interest.

Researchers started with samples from the youngest patients with prostate cancer in 94 families who had participated in studies at U-M and Johns Hopkins. Each of those families had multiple cases of the disease among close relatives, such as between fathers and sons or among brothers.

Members of four different families were found to have the same mutation in the HOXB13 gene, which plays an important role in the development of the prostate during the fetal stage and its function later in life. The mutation was carried by all 18 men with prostate cancer in these four families.

The researchers collaborated with Jianfeng Xu, Ph.D., and Lilly Zheng, Ph.D., at Wake Forest University to look for the same HOXB13 gene mutation among 5,100 men who had been treated for prostate cancer at either Johns Hopkins or U-M. The mutation was found in 1.4 percent—or 72 of the men. It turned out that those men were much more likely to have at least one first-degree relative, a father or brother, who also had been diagnosed. The researchers also looked for the mutation in

a control group of 1,400 men without prostate cancer, and only one of those men carried the mutation. In addition, the researchers studied men who were specifically enrolled in studies of early-onset or familial prostate cancer.

"We found that the mutation was significantly more common in men with a family history and early diagnosis compared with men diagnosed later, after age 55, without a family history. The difference was 3.1 percent versus 0.62 percent, Cooney says.

"We had never seen anything like this before. It all came together to suggest that this single change may account for at least a portion of the hereditary form of the disease," says study co-author Patrick Walsh, M.D., professor of urology at Johns Hopkins, who is one of the pioneers in prostate cancer treatment. In the 1980s, Walsh was one of the first to publish a study showing that the risk of prostate cancer was higher among men with close relatives who also had the disease.

The researchers say with further study, it may be possible one day to have genetic test for inherited prostate cancer in much the same way that tests are available to look for BRCA1 and BRCA2 mutations that greatly increase a woman's chance of developing breast and/or ovarian cancer.

"We need to continue studying this variant and look at larger groups of men. Our next step will be to develop a mouse model with this mutation to see if it causes prostate cancer," says Isaacs. He adds, "Future DNA sequencing may also identify additional rare variants that contribute to prostate cancer risk in families."

This particular mutation was found in families of European descent, while two different mutations on the HOXB13 gene were identified in families of African descent. Since only seven of the 94 families studied were of African descent, more research will be required before the

significance of those mutations is known. African-American men are more likely to be diagnosed with prostate cancer at younger ages and have a more aggressive form of the disease.

Cooney says patients with questions about prostate cancer screening, particularly if the disease runs in their families, are encouraged to speak with their doctor.

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