Scientists help identify genetic markers for prostate cancer in global DNA download

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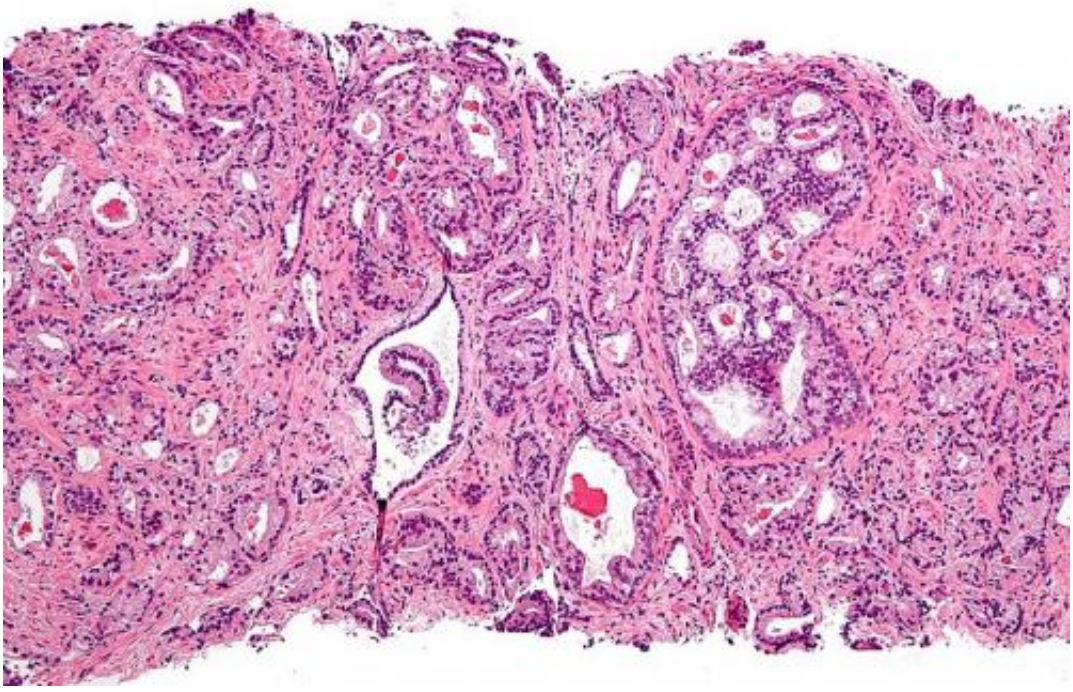

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

An international team of researchers including USC scientists has found scores of new genetic markers in DNA code that increase prostate cancer risk—powerful knowledge likely to prove useful to detect and prevent the disease.

Focusing on DNA of more than 140,000 men worldwide, researchers

were able to identify 63 new genetic markers associated with prostate cancer risk. That greatly increases the number of genetic risk regions, bringing the total to more than 170 and moving scientists closer to using genetic information for clinical treatment.

The results will help bridge the gap between cancer research diagnosis and treatment, equipping physicians with tools to screen at-risk patients. The study, based at USC with collaborators worldwide, including the London-based Institute of Cancer Research, was published today in *Nature Genetics*.

"This is not a cure, but the information can help to identify men at high risk of developing prostate cancer who may benefit from enhanced screening and future targeted prevention," said Christopher A. Haiman, professor of preventive medicine at the Keck School of Medicine of USC and a principal investigator for the project.

Prostate cancer is the second-most common cancer in American men, with one in nine men being diagnosed in their lifetime, and the third-leading cause of cancer death for men.

To identify genetic markers associated with prostate cancer risk, the researchers used "OncoArray," a new DNA analysis, to compare more than half a million single-letter changes in the DNA code of nearly 80,000 men with prostate cancer and more than 61,000 men without the disease. The researchers identified 63 new variants in DNA, which when inherited increased a man's risk of prostate cancer. Each individually had only a small effect on risk, but the combined effect of inheriting multiple variants could be dramatic.

The findings show that 1 percent of men at highest risk were 5.7 times more likely than the general population to develop prostate cancer—an increase in absolute risk from about one in 11 to one in two. The

researchers were able to identify that high-risk population because it inherited many of the harmful genetic variants.

And the top 10 percent in the population risk distribution were 2.7 times more likely to develop the disease than the general population—corresponding to a risk of almost one in four.

With the addition of dozens more genetic markers to previously known markers, almost 30 percent of a man's inherited risk of prostate cancer has been accounted for—which may now be enough to start using the information in practical testing strategies, according to the study.

"We now have the ability to identify men at greater risk of prostate cancer," Haiman said. "We now need to figure out how to use this genetic information to prevent the disease."

These genetic markers may also one day help guide treatment for prostate cancer. Many of the new genetic variants were found in the region of genes involved in communication among cells of the immune system and other cells in the body. This implies that genetic errors in immune pathways may be affecting prostate cancer risk, which could have important implications for potential future treatment of prostate cancer with immunotherapies.

The study comes with caveats. For example, it focuses on white males only. Haiman said parallel studies are underway to study other ethnic groups. For reasons unknown, African-American men face a 74 percent greater risk of prostate cancer than in non-Hispanic white men, according to the American Society of Clinical Oncology.

The global scope of the project enabled researchers to collect massive amounts of DNA and compare genetic variants, which was key to achieving critical mass to make new discoveries. About 200 researchers

worldwide participated, including experts from the United States, United Kingdom, Sweden, Canada, Germany, China, Finland, Belgium, Spain, Poland, Malaysia and Croatia, among others.

Five scientists from the Keck School of Medicine participated in the study, including Haiman, Sue Ann Ingles, Mariana C. Stern, David V. Conti and the late Brian E. Henderson, who proposed the study more than three years ago. Henderson was a former dean of the Keck School, first director of the Zilkha Neurogenetic Institute and director of the USC Norris Comprehensive Cancer.

Aside from non-melanoma skin cancer, prostate cancer is the most common cancer among men in the United States. It is also one of the leading causes of cancer death among men of all races. The U.S. Centers for Disease Control estimates 172,258 men in the United States were diagnosed with prostate cancer and 28,343 men died from prostate cancer in 2014, the most recent year such data is available.

More information: Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci, *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0142-8 , www.nature.com/articles/s41588-018-0142-8

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