Medical Xpress

Genetic markers could help to speed up detection and treatment of prostate cancer

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Prostate cancer is the most commonly diagnosed cancer in men. But it can be difficult to diagnose, and it's hard to know which cancers will become dangerous and which need less-aggressive treatment. Researchers and clinicians alike are eager to identify molecular markers or other characteristics that will enable them to accurately diagnose the disease, and then parse the deadly from the dormant and target treatment accordingly.

Now researchers at the Stanford School of Medicine and the HudsonAlpha Institute for Biotechnology in Huntsville, Ala., have identified a panel of over 80 DNA sites which show modifications by methyl groups that differ between cancerous and normal prostate tissue. The scientists hope that their findings will make both the diagnosis and the prognosis of the disease more sophisticated and spare many men from the side effects of unnecessary treatment.

"We view these methylation patterns as fingerprints," said associate professor of genetics Gavin Sherlock, PhD. "We knew that a handful of genes are known to exhibit a change in their methylation status when comparing normal prostate to prostate tumor. So we wanted to look at a larger set of genes — over 26,000 sites covering over 14,000 genes — to see if we could identify other variations that could be useful in disease diagnosis and prognosis. We found that the differences between the cancer cells and normal prostate cells were striking."

Sherlock, who is also a member of the Stanford Cancer Institute, is the

senior author of the research, which was published online earlier this month in *Genome Research*. The first author of the study is postdoctoral researcher Yuya Kobayashi, PhD, who was a graduate student in genetics when he carried out this work. Sherlock and Kobayashi collaborated with associate professor of urology James Brooks, MD, and professor of urology Donna Peehl, PhD, as well as former chair of genetics Rick Myers, PhD, now the director of the HudsonAlpha Institute, and Devin Absher, PhD, also of HudsonAlpha.

Currently most clinicians rely on the prostate-specific antigen, or PSA, test to screen the blood of men for possible prostate cancer. But it's not perfect. "PSA tests can be problematic," said Sherlock. "Many men have tumors but low PSA levels — or high PSA levels and no tumors. This can lead to unnecessary testing, like imaging or biopsies."

In contrast to the PSA test, which measures the amount of a specific protein in the blood, methylation assays assess the addition of methyl groups directly to the DNA of prostate cells. This methylation is an example of epigenetics, a phenomenon in which chemical modifications to DNA affect how it is packaged and expressed within a cell. Epigenetic changes allow cells to silence or tweak a gene's expression in response to environmental or other external cues.

Specifically, methyl groups added to the promoter regions of genes tend to inhibit that gene's expression. But they can only be tacked on to a specific combination of two nucleotides: when a guanine follows a cytosine, written in biological shorthand as CpG. In the current study, Sherlock and Kobayashi used technology from San Diego-based Illumina Inc. to survey thousands more potential methylation sites than had been previously analyzed.

The researchers studied methylation patterns in cells from 95 prostate tumors and from 86 non-cancerous, nearby prostate tissue samples. They

found nearly 6,000 CpG sites that were more-heavily methylated in prostate cancers as compared with normal tissues, and over 2,000 CpG sites that were less-heavily methylated.

“Out of the thousands of sites, we were able to identify about 80 very solid markers associated with tumors,” said Sherlock. “It’s possible that cancer-specific patterns may one day be useful in both diagnosing the disease and predicting its progression.” Specifically, the researchers identified an additional 69 CpG sites where changes in patterns of methylation appear to correlate with the chances that that a prostate tumor will recur after treatment.

Sherlock and his colleagues are now trying to confirm the correlation between methyl patterns and time to disease recurrence in another set of prostate tumor and normal tissues. They’d also like to identify whether the changes in methylation patterns cause, or are caused by, the cancerous changes. “If we continue to see a reliable association, this type of methylation study becomes very promising as a possible diagnostic and prognostic tool,” said Sherlock, who noted that tests are being developed to assay the content of prostate cells in urine. “This could be a non-invasive way to look for tumor markers.”

Research associate Zulfiqar Gulzar, PhD; research assistant Sarah Young, and associate professor of pathology Jesse McKenney, MD participated in the study. The NIH and the HudsonAlpha Institute supported the work.

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