

## Novel molecular processes controlling key genes in prostate cancer uncovered

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

Researchers at Sweden's Karolinska Institutet and the University of Oulu in Finland have elucidated gene regulatory mechanisms that can explain how known genetic variants influence prostate cancer risk. The findings, published in the journal *Nature Genetics*, reveal widespread deregulation of androgen receptor function, a key player in prostate cancer.



The vast majority of the three billion base-pairs in the human genome are identical across individuals. Nevertheless, genome sequence variation that does occur in the population has a profound effect on an individual's predisposition for developing various diseases. In the case of prostate cancer, 100 regions of genetic variation have been identified through comparative genetic studies. Each have a small but significant influence on prostate cancer risk. Previous studies have demonstrated an association of these genomic regions with disease, but the molecular processes accounting for the disease association have not yet been uncovered for most of these 100 regions.

Using computational and statistical analysis, Thomas Whitington and colleagues at Karolinska Institutet devised a method for analysing the molecular processes at these <u>genomic regions</u>. The researchers identified mechanisms that can explain many of the known associations between genetic variation and prostate cancer risk. These discoveries were validated using molecular techniques by a research team led by Gong-Hong Wei at University of Oulu.

"In particular, we discovered that binding of physical complexes involving the androgen receptor, a key transcription factor in prostate cancer, is often disrupted by DNA sequence variation associated with the disease", says Thomas Whitington at the Department of Medical Epidemiology and Biostatistics at Karolinska Institutet, one of the researchers behind the study.

Transcription factors are key molecular components of the cell that bind to DNA and affect the activity of nearby genes. The androgen receptor is a transcription factor that promotes proliferation and survival of <u>prostate</u> <u>cancer cells</u>. In the current study, the investigators found that binding of androgen receptor at these locations of genetic variation was frequently tumor-specific, and not present in normal prostate tissue.



"This work refines our understanding of how this molecular machinery is involved in disease processes", says Thomas Whitington. "An improved understanding of <u>androgen receptor</u> binding may in particular prove useful, as it's activity becomes pivotal during the treatment of late stage aggressive prostate cancer."

**More information:** 'Gene regulatory mechanisms underpinning prostate cancer susceptibility', Thomas Whitington, Ping Gao, Wei Song, Helen Ross-Adams, Alastair Lamb, Yuehong Yang, Ilaria Svezia, Daniel Klevebring, Ian Mills, Robert Karlsson, Silvia Halim, Mark Dunning, Lars Egevad, Anne Warren, David Neal, Henrik Grönberg, Johan Lindberg, Gong-Hong Wei, Fredrik Wiklund, *Nature Genetics*, online 7 March 2016, <u>DOI: 10.1038/ng.3523</u>

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