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PROSTATE CANCER

HOXB13 and a SNP collaborate to increase risk

Researchers have uncovered a potential mechanism tying HOXB13 to risk of prostate cancer—via interaction with a single nucleotide polymorphism (SNP) that enhances expression of transcription factor *RFX6*. "Our findings demonstrate a causal biological role for the prostate-cancer-risk-associated SNP rs339331," explains Gong-Hong Wei, corresponding author of the study recently published in *Nature Genetics*. "The risk-associated allele of rs339331 enhances HOXB13 chromatin binding, resulting in increased expression of *RFX6*, which might lead to increased risk for the development of prostate cancer."

Germline mutations in *HOXB13* were reported to be associated with risk of prostate cancer in a landmark paper published in 2012, which described the results of linkage analyses performed in patients with a family history of prostate cancer. Since then, the *HOXB13* missense variant G84E has been reported in ~5% of families affected by hereditary prostate cancer.

To investigate the possible mechanisms underlying the association between HOXB13 and risk of prostate cancer, researchers performed a genome-wide search for HOXB13 DNA binding sites in prostate cancer cells. They found an association between these binding regions and a number of SNPs previously identified in genome-wide association studies of prostate cancer. One such SNP was rs339331at locus 6q22, which has been strongly associated with prostate cancer risk in men with distinct ancestry (including cohorts of men of European, Japanese and African descent). "Encouraged by these intriguing observations, we sought to investigate the biological roles of rs339331 and its fundamental interplay with HOXB13 to confer risk of prostate cancer," says Wei.

Their multi-step approach (using binding assays, chromatin immunoprecipitation sequencing and *in silico* analysis) revealed that HOXB13 has much higher affinity for the risk-associated allele of rs339331 than the reference allele, that rs339331 localizes to an enhancer region in intron 4 of the *RFX6* gene and that the risk-associated allele of rs339331 could induce *RFX6* expression.

Moreover, the investigators observed upregulated *RFX6* expression in prostate cancer cell lines, and demonstrated that both *RFX6* and *HOXB13* can promote prostate cancer cell growth and invasion. *RFX6* expression in clinical specimens was associated with tumour aggressiveness.

Wei and colleagues have exciting goals for the future. "We want to use cutting edge genome editing methods to see if we can develop a therapeutic strategy against prostate cancer based on the findings of this study," he explains. "We are also analysing gene regulatory networks driven by HOXB13 and RFX6, and aiming to find druggable target genes to cure patients with prostate cancer."

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Original research Huang, Q. *et al.* A prostate cancer susceptibility allele at 6q22 increases *RFX6* expression by modulating HOXB13 chromatin binding. *Nat. Genet.* doi:10.1038/ng.2862

Further reading Ewing, C. M. *et al.* Germline mutations in HOXB13 and prostate-cancer risk. *N. Engl. J. Med.* **366**, 141–149 (2012)