# Newly identified set of genomic loci selectively associated with prostate cancer in East Asian men

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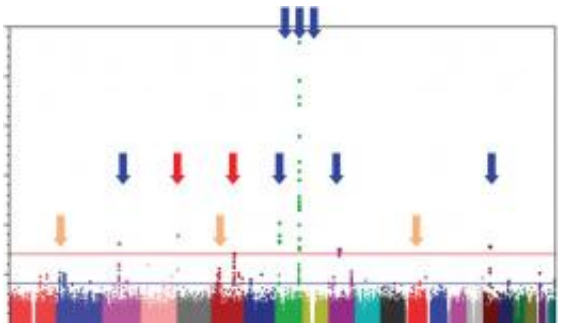

Results from the prostate cancer GWAS of Japanese individuals. Each SNP is plotted horizontally based on chromosomal location and vertically based on the statistical significance of their association with prostate cancer. This study revealed novel associations for five SNPs (red and orange arrows) and confirmed several previously identified associations (blue arrows). © 2010 Hidewaki Nakagawa

Prostate cancer represents a serious threat to men all over the world, especially those over the age of 65, and is the second leading cause of cancer death among males in both the United States and United Kingdom.

Until recently, the risk level for men living in East Asia was lower than virtually any other region of the world. This is now changing, however, as a result of both lifestyle and demographic factors. “This increased risk

is probably due to the shift to a westernized lifestyle, including food, and the rapid increase in the aging population," explains Hidewaki Nakagawa of the RIKEN Center for Genomic Medicine in Yokohama. Indeed, estimates from the United Nations suggest that the percentage of the population of East Asia that are over the age of 65 will more than double between 2009 and 2050, and Japan in particular is projected to have by far the greatest proportion of elderly citizens.

In addition to these environmental factors, researchers have identified dozens of genetic changes that appear to represent potential risk factors for prostate cancer. All of these were identified based on screens performed on individuals of European ancestry, but a new genomic screen performed by Nakagawa and collaborators from throughout Japan has now identified several novel genetic variants that may prove valuable in diagnosing and treating the growing pool of at-risk Asian men.

## Taking it to the bank

Nakagawa's team has routinely partnered with scientists from BioBank Japan, an initiative launched in 2003 at the University of Tokyo in order to help scientists identify the bases for diverse medical conditions. "This project was started with the goal of collecting samples from a total of 300,000 individuals who have had at least one of 47 diseases, from a collaborative network of 66 hospitals located throughout Japan," he explains. For this particular study, the researchers obtained DNA from 1,583 prostate cancer patients and 3,386 cancer-free control subjects.

Nakagawa and his colleagues used these samples to perform what is known as a genome-wide association study (GWAS). Any given human genome is littered with large numbers of individual nucleotide variations, also known as single-nucleotide polymorphisms (SNPs), which reside both within and in-between genes. From a GWAS, researchers aim to identify SNPs that are significantly more likely to appear in affected

individuals than in controls; a SNP with very strong disease association might either represent an actual sequence variation in a relevant gene or provide a useful physical marker for identifying neighboring candidate genes within the same chromosomal region.

The team's initial analysis of more than half a million different SNPs revealed 37 significantly associated variants at eight different genomic loci, two of which had not been previously linked with prostate cancer. A subsequent replication study, performed with an independent set of 3,001 affected and 5,415 control subjects, enabled the investigators to identify three additional loci, for a total of five novel SNPs. Interestingly, although many of the cancer-associated SNPs that had been previously identified in European populations also exhibited significant linkage among Japanese subjects, more than one-third (12 out of 31) did not. On the other hand, several recent large-scale genomic studies conducted using similar analytical methods but focused primarily on subjects of Northern European ancestry failed to find a significant association for any of the five SNPs identified by Nakagawa and colleagues.

## Getting to know the candidates

Beyond the strong evidence supporting their apparent association with disease risk, the majority of these novel SNPs proved to be highly enigmatic. Two of them, rs12653946 and rs9600079, reside within stretches of DNA ranging in length from 20–40,000 bases that contain no known genes. Another two were situated within non-protein-coding regions of a pair of genes; rs13385191 is found in C2orf43, which produces a protein of unknown function, while rs1983891 is located within the gene encoding the so-called 'forkhead box P4' (FOXP4) transcription factor. Although it belongs to a family of proteins that have been associated with cell cycle regulation and tumorigenesis, the function of FOXP4 has not yet been characterized.

The final SNP appears to be the most intriguing candidate, as it occurs within a stretch of DNA containing the gene for G protein-coupled receptor C6A (GPRC6A), a protein normally expressed by testosterone-producing Leydig cells. “The GPRC6A gene is likely to be associated with sex hormone production, as shown [by experiments] in knockout mice,” says Nakagawa, “and male hormone levels are one of the most important factors in prostate carcinogenesis.” However, further analysis will be needed to confirm that this is indeed the gene being flagged by rs339331.

Although much work remains to be done in characterizing how the genomic regions identified here contribute to prostate cancer risk, they nevertheless represent important additions to an already large pool of SNPs with potential diagnostic or prognostic value. “This is a much bigger number than exists for other cancers,” says Nakagawa.

Nakagawa also points out that these five SNPs appear to represent loci that could possibly be used for the selective characterization of prostate cancer predisposition within specific ethnic groups, and that these may represent the first set of Asian-specific cancer risk biomarkers. “We are now dedicated to trying to establish a risk estimation system for prostate cancer among Japanese and other Asians by combining many SNPs and other risk factors of prostate cancer,” he says.

**More information:** -- United Nations. World Population Ageing 2009. Economic and Social Affairs, Population Division, ESA/P/WP/212 December 2009, New York. www.un.org/esa/population/publ … 009_WorkingPaper.pdf
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