Asian Journal of Andrology (2011) 13, 120–121

www.nature.com/aja

RESEARCH HIGHLIGHT

Novel genetic loci associated with prostate cancer in the Japanese population

Yin Sun and Jiao-Ti Huang

Asian Journal of Andrology (2011) **13,** 120–121; doi:10.1038/aja.2010.118; published online 11 October 2010

Takata *et al.*[1] recently reported in *Nature Genetics* that they have identified five novel genetic loci that are associated with prostate cancer in the Japanese population. Using most updated Illumina Quad BeadChip to genotype 3001 prostate cancer patients and 5415 control subjects, they identified 263 single-nucleotide polymorphisms (SNPs) showing significant association with prostate cancer in Japan. Further analysis indicated that 80 SNPs reside in the previously known regions, and five of them are novel susceptibility loci associated with the prostate cancer. These five SNPs apparently are not associated with Gleason score (Gleason score <7 compared with $\geqslant 7$) or cancer stage (non-advanced cancer compared with advanced cancer) in the affected patients. Neither is there any correlation with age. An attempt to identify the genes associated with these loci uncovered three candidate genes that might be associated with Japanese prostate cancer patients: *GPRC6A* (G protein-coupled receptor, family C, group 6, member A), *C2orf43* (open reading frame 43 of chromosome 2) and *FOXP4* (forkhead box P4). Interestingly, *GPRC6A* is known to be highly expressed in the Leydig cells of the testis, and mice deficient in *Gprc6a* show male feminization and a metabolic manifestation of higher circulating estradiol and reduced levels of testosterone, two hormones that are critical for initiation and progression of prostate cancer.

Prostate cancer is the leading cause of male death in the Western world. It has also become more and more prevalent in Asian countries. It is widely accepted that genes are the fundamental determinants in almost all human cancers, so the genetic analysis of prostate cancer can provide a mechanistic understanding of the process of carcinogenesis, thus identifying potential targets for therapeutic intervention. We are also in a very exciting new era when such studies are aided by the availability of the complete sequence of the human genome, as well as increasing collections of SNPs that can be used to associate allelic information of the genes in the whole genome with a disease state in a statistically significant manner, hence the genome-wide association studies (GWAS). Previously, such studies had to be done in high-risk individuals to screen the genome for locations of potential cancer-related genes. Now the high-resolution SNP chips make it possible to conduct a population study of prostate cancer patients to detect possible underlying genetic basis for prostate cancer, and generally more patient genomes are scanned, more new susceptibility genes will be identified, even those with a lower penetrance in and a milder impact on the general population.

The accomplishments by these researchers need to be viewed in the context of prior publications describing GWAS in prostate cancer in European populations.[2–11] Nearly 30 different SNPs have been identified as associated with prostate cancer; some of these are indeed replicated in the current study. The saturation of GWAS on prostate cancer likely suggests a dwindling possibility of finding new prostate cancer susceptibility genes, yet remarkably this study identified five new loci associated with prostate cancer, which suggests that there are complex and diverse etiological processes leading to prostate cancer among different ethnic backgrounds. Quite possibly diet, cultural and behavioral differences might also influence prostate cancer formation. A corollary of their study will be that some of the known SNPs associated with European prostate cancer patients likely do not have the same degree of association in the Japanese population, an outcome confirmed by the current study. It also suggests that the power of GWAS can be enhanced by examining different ethnic populations to uncover gene variants that are responsible for causing human diseases. Furthermore, these GWAS with different genetic backgrounds highlight the most fundamental genetic causes that are common among all ethnic backgrounds while revealing potentially race-specific genetic predispositions to prostate cancer. This information will be helpful in designing or testing pharmaceutical interventions applicable to all peoples or specific to certain ethnic groups.

The rapid discovery of new susceptibility loci associated with various human diseases, in this case, prostate cancer, provides a valuable source of new markers with diagnostic and prognostic value. However, translation of these findings into effective therapies requires new experimental models and human clinical trials. At the moment, the exact nature of these susceptibility loci is unknown, as are their potential molecular mechanisms in the development of prostate cancer. Experiments in all disciplines, including molecular studies, animal models and human tissue examinations, will be necessary to translate the knowledge of GWAS into useful tools to help prostate cancer patients, as well as to prevent new cancers. We are in the beginning of an exciting new era. This paper, while discovering new genetic loci potentially associated with prostate cancer, also provides researchers opportunities to uncover novel molecular mechanisms of prostate carcinogenesis.

Department of Pathology and Laboratory Medicine, Jonsson Comprehensive Cancer Center and Broad Center for Regenerative Medicine and Stem Cell Biology, University of California at Los Angeles, Los Angeles, CA 90095, USA
Correspondence: Professor J T Huang (JiaotiHuang@mednet.ucla.edu)

1 Takata R, Akamatsu S, Kubo M, Takahashi A, Hosono N *et al*. Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population. *Nat Genet* 2010; **42**: 751–4.

2 Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D *et al*. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet* 2007; **39**: 631–7.
3 Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P *et al*. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet* 2007; **39**: 645–9.
4 Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G *et al*. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nat Genet* 2007; **39**: 977–83.
5 Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A *et al*. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. *Nat Genet* 2008; **40**: 281–3.
6 Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M *et al*. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* 2008; **40**: 316–21.
7 Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S *et al*. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* 2008; **40**: 310–15.
8 Gudmundsson J, Sulem P, Gudbjartsson DF, Blondal T, Gylfason A *et al*. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. *Nat Genet* 2009; **41**: 1122–6.
9 Eeles RA, Kote-Jarai Z, Al Olama AA, Giles GG, Guy M *et al*. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. *Nat Genet* 2009; **41**: 1116–21.
10 Yeager M, Chatterjee N, Ciampa J, Jacobs KB, Gonzalez-Bosquet J *et al*. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. *Nat Genet* 2009; **41**: 1055–7.
11 Al Olama AA, Kote-Jarai Z, Giles GG, Guy M, Morrison J *et al*. Multiple loci on 8q24 associated with prostate cancer susceptibility. *Nat Genet* 2009; **41**: 1058–60.