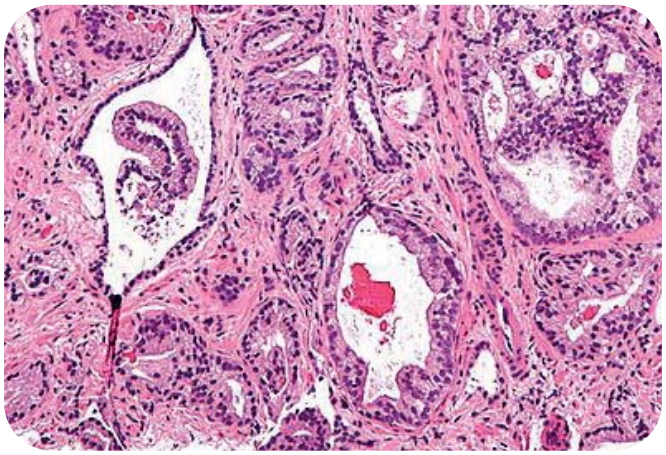
Association study of rs6983267 at 8q24 with prostate cancer in the Greek population

Professor Nikolaos Drakoulis, MD, PhD; Amalia Papanikolopoulou; Olfert Landt; Martin Reczko, PhD

This study aims to determine the frequency of the marker rs6983267 in the Greek population as an independent risk indicator for carriers to develop prostate cancer.

Introduction

Prostate cancer is the most frequently diagnosed cancer in men—the second most common cause of cancer-related male death in the EU [1]. The only firmly established risk factors are age, family history and ethnicity [2]. Men of African descent aged > 65 years, with a first degree relative with the disease are at greater risk than those of European descent with no family history. African Americans are 1.5–2 times more likely to develop prostate cancer, and 2.4–3 times more likely to die from it, than European Americans [3]. Both genetic and environmental factors probably contribute to such differences.



In an attempt to identify genetic variants underlying risk, genome-wide linkage and association studies have been performed and multiple chromosomal regions have been designated to harbour major susceptibility genes for prostate cancer [4]. In men with European ancestry the locus, marked by rs6983267, has shown the highest odds ratio and population attributable risk (PAR) for prostate cancer, compared with other single nucleotide polymorphisms (SNPs) at the same region, with an overall population frequency in northern Europeans of 50% for the at-risk allele [5, 6].

The aim of this study is to determine the frequency of rs6983267 in the Greek population as an independent risk indicator for carriers to develop the disease.

Methods

A total of 208 patients from the same hospital (108 with biopsy-confirmed adenocarcinoma of the prostate and 99 randomly selected controls with no cancer history) participated. Genotyping was performed with melting curve analysis (LightCycler 480) of polymerase chain reaction products from acceptor (5'end-labelled with LCRed 640) and donor probes (3'end-labelled with fluorescein) specific for the polymorphism.

Results

Use of unconditional logistic regression with adjustment for age indicated that the best fitting inheritance model for the rs6983267 is the dominant model. Evaluation of rs6983267 revealed significantly different frequencies in genotypes (OR = 2.83, 95% CI = 1.38–6.00, p = 0.002) and in alleles (OR = 2.06, 95% CI = 1.33–3.02, p = 0.001) between prostate cancer cases and control subjects. Defining exposure as the cases associated with the SNP, PAR % was estimated to be 37.42%, indicating the percentage of disease cases that could have been reduced in the whole population if the exposure was prevented.

In order to combine several risks, e.g. men carrying the rs6983267 with positive family history, we estimated joint PAR % as 43.61%. None of the clinical characteristics in case subjects (aggressiveness of prostate cancer, prostate-specific antigen (PSA) level) were significantly associated with the rs6983267.

Conclusion

Our study confirms the association of rs6983267 at chr8q24 with prostate cancer in the Greek population and indicates the independent risk for carriers to develop the disease. This risk probably has a cumulative effect with positive family history and with other chromosomal regions reported in the literature. For northern Europeans the estimated PAR % of rs6983267 reaches 21%, whereas for the Greek population it is 37%, and has an overall population frequency in northern Europe of 50% for the at-risk G allele, whereas for Greece it is 62%, indicating the greater significance of this SNP to our population [5]. Like that of Zheng et al. [6], our study has not revealed any association of rs6983267 with disease aggressiveness, familial or sporadic forms of prostate cancer or early or late onset. No association between this SNP and serum PSA levels were found, suggesting that rs6983267 is associated with prostate cancer risk directly rather than indirectly, e.g. as a result of increasing the rate of biopsy-driven diagnoses. The use of this marker shows only the risk of developing the disease and has no correlation with clinical characteristics.

Authors

Professor Nikolaos Drakoulis, MD, PhD
Professor of Clinical Pharmacology
drakoulis@pharm.uoa.gr
Amalia Papanikolopoulou

Department of Pharmaceutical Technology
School of Pharmacy
University of Athens
Research Diagnostics
429 Vouliagmenis Avenue
GR-16346 Ilioupolis, Greece

Olfert Landt
TIB MOLBIOL GmbH
22-23 Eresburgstrasse
DE-12103 Berlin, Germany

Martin Reczko, PhD
Biomedical Sciences Research Center Alexander Fleming
34 Fleming Street
GR-16672 Athens, Greece

References

1. Fitzpatrick JM. Optimizing the management of prostate diseases: prostate cancer. BJU Int. 2008;101 Suppl 2:1.
2. Crawford ED. Epidemiology of prostate cancer. Urology. 2003;62(6 Suppl 1):3-12.
3. NCI SEER Program. Ries LAG, et al. Cancer of the prostate (invasive) SEER incidence and US death rates, age-adjusted and age-specific rates, by race. 2002-2006. Annual SEER Cancer Statistics Review (CSR), 1975-2006.
4. Xu J, Dimitrov L, Chang BL, Adams TS, et al. A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. Am J Hum Genet. 2005;77(2):219-29.
5. Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet. 2007;39(5):645-9.
6. Zheng SL, Sun J, Wiklund F, et al. Cumulative association of five genetic variants with prostate cancer. N Engl J Med. 2008;358(9): 910-9.