RESEARCH COMMUNICATION

Associations of Polymorphisms in HPC2/ELAC2 and SRD5A2 Genes with Benign Prostate Hyperplasia in Turkish Men

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Abstract

Benign prostate hyperplasia (BPH) is the most common benign tumor in elderly men for which the HPC2/ELAC2 and SRD5A2 genes are known genetic factors. The HPC2/ELAC2 gene features Ser217Leu and Ala541Thr polymorphisms and the SRD5A2 gene Ala49Thr and Val89Leu polymorphisms. The aim of this study was to examine relationships between these polymorphisms and BPH in Turkish men using amplification by the polymerase chain reaction (PCR) method. Polymorphisms were determined by using restriction fragment length polymorphism (RFLP) with suitable restriction: TaqIα, Fnu4HI, Mwo I and Rsa I. We found statistically significant relationship between the SRD5A2 gene Ala49Thr (OR=2.3; CI 95%, 1.04-5.1; p=0.01<0.05) , but not the other polymorphisms, and BPH. For the first time, our data demonstrate that correlation between SRD5A2 gene Ala49Thr and polymorphism are statistically significant in Turkish men with BPH.

Keywords: HPC2/ELAC2 gene - SRD5A2 gene - polymorphism - BPH - Turkey

Asian Pacific J Cancer Prev, **12**, 731-733

Introduction

Benign prostate hyperplasia, increase in the size of the prostate in ageing men, is a multifactorial disease, including environmental, hormonal and genetic factors. The HPC2/ELAC2 gene is one of the familial prostate cancer susceptibility genes which has a molecular weight of 85kDa and composed of 826 amino acids. HPC2/ELAC2 gene consist of 24 exon that is 25.1 kb and mapped to chromosome 17p11.2. HPC2/ELAC2 gene contains two missense mutations. Ser217Leu is the first variant and the second is Ala541Thr (Rebbeck et al. 2000).

Steroid 5α-reductase type II enzyme irreversibly converts testosterone to dihydrotestosterone in prostatic cells (Thigpen et al. 1993; Reichardt et al. 1995). It is composed of 254 amino acids, and it has a 28.398 kDa molecular weight (Makridakis et al. 1997). The responsible gene is called as SRD5A2 which includes 5 exons and 4 introns (Labrie et al. 1992) located at chromosome 2p22-23 and has approximately 56.4 kb length. So far two single nucleotide polymorphisms in the SRD5A2 gene have been studied in relation to prostate cancer. One of them is Ala49Thr polymorphism and the other is Val89Leu polymorphism (Jaffe et al. 2000).

In the present study, we analyzed relationship between Ser217Leu and Ala541Thr polymorphisms in the HPC2/ELAC2 gene as well as Ala49Thr and Val89Leu polymorphisms in the SRD5A2 gene and Turkish men with BPH. We firstly screened for mentioned polymorphisms in Turkish men with BPH.

Materials and Methods

Study Population

This study was performed on 39 BPH (mean age= 63.7±9.21) 34 healthy controls (mean age= 49.8±18.3) who have no family history with BPH. Patients included Turkish men who are from Cukurova region of southern Turkey. Clinical data were collected from patient records from Cukurova University, Faculty of Medicine Hospitals where the patients had been treated. The research protocols were accepted and given approval by the Ethical Committee of the Faculty of Medicine of Cukurova University.

Laboratory Methods

DNA samples were extracted from whole blood samples using salting-out procedure. PCR amplification, RFLP digestion and PAGE visualization as previously represented by Rebbeck et al. and Cicek et al. for Ser217Leu polymorphism and Ala541Thr polymorphism in ELAC2 gene as well as Ala49Thr and Val89Leu polymorphisms in SRD5A2 gene (Rebbeck et al. 2000; Cicek et al. 2004).

Statistical Analysis

All statistical analyses of the data were performed using the SPSS (11.5 version) program. Pearson Chi-Square test was employed to compare ratios and in all cases $p<0.05$ was used as the cut-off as statistically significant.

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Results

We first compared the allele frequencies regarding Ser217Leu and Ala541Thr polymorphisms in HPC2/ELAC2 gene in Turkish men with BPH and control subjects. Ser217Leu and Ala541Thr polymorphisms were in Hardy-Weinberg equilibrium in Turkish men with controls. The allele frequencies of Ser217 and Leu217 in BPH patients were 70% and 30% and the allele frequencies for each of the two alleles in the control group were 82.8% and 17.2% (Table 1). We observed no significant difference between the patients and controls for Ser217Leu polymorphism (OR=1.5; CI 95%, 0.8-2.6; p=0.09<0.05). As compared to the allele frequencies in patients regarding Ala541 (95.7%) and Thr541 (4.3%) and the allele frequencies in controls as regards Ala541 (98.3%) and Thr541 (1.7%) . We found no differences between the patients and controls regarding Ala541Thr polymorphism (OR=1.8 CI 95%, 0.3-10.14; p=0.40 p>0.05).

For the first time, we compared the genotype frequencies regarding Ala49Thr and Val89Leu polymorphisms in SRD5A2 gene in Turkish men with BPH. Both the Ala49Thr and the Val89Leu polymorphisms in SRD5A2 gene were in Hardy-Weinberg equilibrium in Turkish men in controls. As shown in Table 2, the allele frequencies of Ala49 and Thr49 in BPH were 74.3% and 25.7% respectively and the allele frequencies regarding each of the two polymorphisms in the control group were 91.4% and 8.6% respectively. We demonstrate a significant difference between the patients and controls for Ala49Thr polymorphism. When considering the effect of Thr49 allele, there was a significant elevation in risk (OR=2.3; CI 95%, 1.04-5.1; p=0.01<0.05) in men with BPH. Other polymorphism was not found to be associated with BPH risk. The relationship between BPH patients and controls were investigated, we found that the frequencies of Val89 and Leu89 in BPH patients were 27.1% and 72.9% respectively and for both polymorphisms, the allele frequencies in the control group were 37.9% and 62.1% respectively (Table 2). No differences were found between the BPH patients and controls for Val89Leu polymorphism (OR=1.2 CI 95%, 0.8-1.8; p=0.19 p>0.05).

Table 1. Association of the HPC2/ELAC2 Genotype with BPH

HPC2/ELAC2 Ser217Leu and Ala541Thr Polymorphisms				
Genotype	BPH	Control	p value	OR (95% CI)
Ser217	49 (70.0%)	48 (82.8%)	0.09	1.5 (0.8-2.60)
Leu217	21 (30.0%)	10 (17.2%)		
Total	70 (100%)	58 (100%)		
Ala541	67 (95.7%)	57 (98.3%)	0.40	1.8 (0.3-10.1)
Thr541	3 (4.3%)	1 (1.7%)		
Total	70 (100%)	58 (100%)		

Table 2. Association of the SRD5A2 Genotype with BPH

SRD5A2 Ala49Thr and Val89Leu Polymorphisms				
Genotype	BPH	Control	p value	OR (95% CI)
Ala49	52 (74.3%)	53 (91.4%)	0.01	2.3 (1.04-5.1)
Thr49	18 (25.7%)	5 (8.6%)		
Total	70 (100%)	58 (100%)		
Val89	19 (27.1%)	22 (37.9%)	0.19	1.2 (0.8-1.8)
Leu89	51 (72.9%)	36 (62.1%)		
Total	70 (100%)	58 (100%)		

Discussion

In the present study, we evaluated the relationship between HPC2/ELAC2 and SRD5A2 gene polymorphisms and BPH. We found significant differences between the patients and controls for Ala49Thr in the SRD5A2 gene (for Ala49Thr polymorphism OR=2.3; CI 95%, 1.04-5.1; p=0.01<0.05). We did not see any difference between the patients and controls for Ser217Leu and Ala541Thr in the HPC2/ELAC2 gene and for Val89Leu in the SRD5A2 gene.

Different observations existed regarding HPC2/ELAC2 and SRD5A2 gene's effect on BPH in literature. They concentrated on different populations. These studies appeared the correlation between BPH patients with different ethnic backgrounds. Such as were Caucasian as well as Hispanic men and Val89Leu polymorphism in SRD5A2 gene (Roberts et al. 2005; Salam et al. 2005). In contrast, some studies reported that there was no association between Val89Leu polymorphism and BPH patients which were French-Caucasian, Caucasian, Japanese, African-American, Asian, American and Indian men (Azzuozi et al. 2002; Li et al. 2003; Salam et al. 2005; Klotsman et al. 2004; Rajender et al. 2009). Ala49Thr polymorphism in SRD5A2 gene was studied by a number of investigators for different population. Some of these results were not significant statistically that were studied French-Caucasian, Japanese, Caucasian, Indian, Hispanic, African-American and Asian populations (Azzuozi et al. 2002; Li et al. 2003; Roberts et al. 2005; Salam et al. 2005; Rajender et al. 2009). However, no group found that there was a significant value, association of the Ala49Thr polymorphism and BPH. In contrast we showed that relationship between aforementioned polymorphism and BPH was statistically significant. However, the number of our population was less than studied population.

There is only one study about different population upon HPC2/ELAC2 gene. Takahashi et al. found that association of the Ser217Leu and BPH was not statistically different. In addition, they revealed that relationship between Ala541Thr polymorphism and BPH was not significant (Takahashi et al. 2003).

In conclusion, ethnic factor affects genetic polymorphisms. Thus, we observed Turkish population with BPH about HPC2/ELAC2 gene and SRD5A2 gene. Our study contributes evidence that Ala49Thr polymorphism of SRD5A2 gene cause BPH in Turkish men. These contributions are in agreement with some studies or not agreement with other studies. We think that differences of ethnic background cause this difference. In addition, our population has the small number size due to the initial study. In this manner, the number of population should be increased and the study should be continued.

Acknowledgements

This research was supported by the Cukurova University Research Fund (FEF2008D14).

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