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The association of 5-alpha reductase type 2 (*SRD5A2*) gene polymorphisms with prostate cancer in a Korean population

Se Young Choi, Hae Jong Kim[1], Hyun Sub Cheong[2], Soon Chul Myung

Department of Urology, Chung-Ang University College of Medicine, Seoul, [1]Future Fusion Research Division, Korea Institute of Science and Technology, Department of Genetic Epidemiology, Seoul, [2]SNP Genetics Inc., Seoul, Korea

Purpose: Steroid 5-alpha reductase type 2 (SRD5A2) modifies testosterone to dihydrotestosterone (DHT) in the prostate. Single-nucleotide polymorphisms (SNPs) of the *SRD5A2* gene might affect DHT. We sought to understand the relationship of SRD5A2 SNPs to prostate cancer in the Korean population.

Materials and Methods: Twenty-six common SNPs in the *SRD5A2* gene were assessed in 272 prostate cancer cases and 173 controls. Single-locus analyses were conducted by using conditional logistic regression. Additionally, we performed a haplotype analysis for the SRD5A2 SNPs tested.

Results: Among the 20 SNPs and 4 haplotypes, there were no statistically significant results in the prostate cancer patients and the controls. In the logistic analysis of *SRD5A2* polymorphisms with prostate-specific antigen (PSA) criteria, two SNPs (rs508562, rs11675297) and haplotype 1 displayed significant results (odds ratio [OR], 1.76; p=0.05; OR, 1.88–2.02; p=0.01–0.04; OR, 0.59; p=0.02, respectively). rs508562, rs11675297, rs2208532, and haplotype 1 (OR, 1.49; p=0.05; OR, 2.02; p=0.05; OR, 2.01; p=0.04; OR, 0.56–0.64, p=0.03–0.04, respectively) had significant associations with Gleason score. rs508562, rs11675297, and haplotype 1 (OR, 1.41–2.34; p=0.004–0.05; OR, 1.74–1.82; p=0.03–0.05; OR, 0.42–0.67; p=0.0005–0.03, respectively) were significantly associated with clinical stage.

Conclusions: We conclude that there was no significant association between SRD5A2 SNPs and the risk of prostate cancer in the Korean population. However, we found that some SNPs and 1 haplotype influenced PSA level, Gleason score, and clinical stage.

Keywords: Genetic polymorphism; Human SRD5A2 protein; Prostatic neoplasms

INTRODUCTION

Although prostate cancer has been less common in South Korea than in the West, the incidence has steeply increased recently [1]. Several epidemiologic investigations have tested diet, occupation, and sexually transmitted diseases as exogenous causes of prostate cancer, but the only established risk factors are age, ethnicity, and family history of prostate cancer [2]. We hypothesized that prostate cancer in the Korean ethnic group may be related to genetic polymorphisms of androgen biosynthesis.

The androgen biosynthesis pathway might be

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Corresponding Author: Soon Chul Myung
Department of Urology, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 156-755, Korea
TEL: +82-2-6299-1785, FAX: +82-2-6294-1406, E-mail: uromyung1@gmail.com

associated with prostate carcinogenesis, and single-nucleotide polymorphisms (SNPs) related to this pathway might describe race disparities in prostate cancer [3]. Dihydrotestosterone (DHT) is part of the androgen biosynthesis pathway and is the most potent nuclear androgen in the prostate. DHT adheres to the intracellular androgen receptor and stimulates gene transcription and the cell cycle. More cell division may enhance somatic mutations, leading to more carcinogenesis [3]. The gene encoding steroid 5-alpha reductase type II (*SRD5A2*), which is located on chromosome 2p23, is a key gene that encodes the enzyme that changes testosterone to DHT in the prostate.

Some SNPs in SRD5A2 have been studied for decades. *SRD5A2* polymorphisms may change enzyme activities owing to altered mRNA stability [4]. Prostate cancer cells have greater levels of SRD5A2 expression than do benign prostatic hyperplasia (BPH) cells [5]. Substitution mutations of V89L (a missense substitution of leucine for valine at codon 89 due to a G to C transversion, *rs523349*) and A49T (a missense substitution of threonine for alanine at codon 49 due to a G to A transversion, *rs9282858*) may affect DHT and prostate cancer [6,7]. A TA dinucleotide repeat (located in the 3'-untranslated region in exon 5) in SRD5A2 may be related to an increased risk of prostate cancer [8]. However, molecular epidemiologic research and recent meta-analyses have shown discrepancies. We wanted to confirm the relationship of SRD5A2 SNPs to prostate cancer in the Korean population.

MATERIALS AND METHODS

1. Study population

Both prostate cancer and BPH group members were patients treated for urological problems. Peripheral blood leukocyte samples were obtained for genotyping from 445 men (prostate cancer, 272; BPH, 173) and were stored at –80°C. Subjects with BPH were included after they underwent a prostate-specific antigen (PSA) blood test, digital rectal examination, and transrectal prostate biopsy to confirm that they were free of prostate cancer. The patients' negative cancer status was also confirmed pathologically. The median age of the BPH cohort was 67.3 years, and the median age of the prostate cancer cohort was 68.2 years. Written informed consent was obtained from all study participants. The study was approved by the Institutional Review Board of Chung-Ang University Hospital and Seoul National University Bundang Hospital (IRB No. C2008035 and B-0905/075-011).

BPH samples were used as the control group for several reasons. First, most males have evidence of BPH by the age of 70 or 80 years; thus, the presence of some degree of BPH is 'normal' at the median age of diagnosis in our prostate cancer cohort (68.2 years). Truly normal samples would be obtained in a much younger control cohort, which could introduce bias. Second, blood sample collection requires a hospital visit and a prostate cancer screening procedure, which would only be undertaken in subjects with symptoms of prostate enlargement.

Blood samples were collected in tubes containing sodium ethylenediaminetetraacetic acid before treatment of prostate cancer. The QIAamp blood extraction kit (Qiagen, Seoul, Korea) was used for DNA extraction. Pathologic results were reviewed in the patients' respective hospitals. Gleason scores were classified as low (2–6), intermediate (4+3, 3+4), or high (8–10) grade. The clinical and pathological regional stages were categorized as localized (T1 or T2N0M0), locally advanced (T3 or T4N0M0), or metastatic (TxN+ or M+) on the basis of pathological or radiological reports. The clinical characteristics of the studied cases are shown in Table 1 and were similar to the results of a previous Korean study [9].

2. SNP selection and genotyping

In this study, we selected 26 SNPs from 2 international databases (International HapMap and National Center for Biotechnology Information [NCBI] dbSNP). SNP selection from the International HapMap database (Han Chinese [CHB], Japanese [JPN]) proceeded as follows: (1) extraction of all genotypes from CHB and JPN populations in the *SRD5A2* gene region by using HapMart of the International HapMap database (version: release #27; http://www.hapmap.org), (2) calculation of minor allele frequency (MAF) and linkage disequilibrium (LD) by use of Haploview software (Cambridge, MA, USA; http://www.broad.mit.edu/mpg/haploview), and (3) selection of SNPs with MAF>0.05 and tagging SNPs if several SNPs showed high LD (>0.98). Furthermore, we added SRD5A2 SNPs found in the NCBI dbSNP database. The selection criteria included location (SNPs in exons were preferred) and amino acid changes (nonsynonymous SNPs were preferred).

Genotyping was performed at the multiplex level by using the Illumina Golden Gate genotyping system [10]. Briefly, approximately 250-ng genomic DNA was extracted from the blood of each individual and used to genotype each sample that underwent DNA activation, binding to

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Table 1. Study characteristics of prostate cancer cases and controls

Characteristic	Cases (n=272)	Controls (n=173)	p-value
Age (y)	68.2±6.8	67.3±8.8	0.85
Body mass index (kg/m^2)	24.1±3.3	24.0±3.0	0.41
Prostate volume (cm^3)	37.2±18.6	48.4±26.2	0.02
PSA (ng/mL)	48.2±192.8	5.2±6.7	<0.01
Gleason score			
Low grade	29 (10.7)	-	-
Intermediate grade	202 (74.3)	-	-
High grade	39 (14.3)	-	-
Unknown	2 (0.7)	-	-
Stage			
Localized	252 (92.6)	-	-
Locally advanced	10 (3.7)	-	-
Metastatic	8 (2.9)	-	-
Unknown	2 (0.7)	-	-

Values are presented as mean±standard deviation or number (%).
PSA, prostate-specific antigen.

paramagnetic particles, hybridization to oligonucleotides, washing, extension, ligation, amplification by polymerase chain reaction, and hybridization to the Beadplate in an appropriate hybridization buffer. Image intensities were scanned with a BeadXpress Reader and were genotyped by using Genome Studio software (Illumina Inc., San Diego, CA, USA). The genotype quality score for retaining data was set at 0.25. A total of 20 SNPs were successfully genotyped.

3. Statistics

SNP genotype frequencies were examined for Hardy-Weinberg equilibrium (HWE) by using the chi-square statistic, and all were found to be consistent ($p>0.05$) with HWE among Korean controls. Data were analyzed by using unconditional logistic regression to calculate an odds ratio (OR) as an estimate of relative risk of prostate cancer associated with SNP genotypes [11].

The statistical power of single associations was calculated with a false-positive rate of 5% and a disease lifetime prevalence of 0.46% [12], given minor allele frequencies and sample sizes and assuming a relative risk of 1.5, by use of Power for Genetic Association Analyses software [13]. To determine the association between the genotype and haplotype distributions of cancer and control patients, logistic analysis was carried out, with control for age (a continuous variable) as a covariate to eliminate or reduce any confounding effects that might influence the results. Significant associations are shown in bold ($p\leq0.05$).

Lewontin's D' (|D'|) and the LD coefficient r^2 were examined to measure the LD between all pairs of biallelic loci [14]. Using PHASE algorithm ver. 2.0 [15], haplotypes were inferred from successfully genotyped SNPs, and association analysis was performed by using SAS ver. 9.1 (SAS Inc., Cary, NC, USA). To achieve optimal correction for multiple testing of markers, representing SNPs in LD with each other, the effective number of independent marker loci was calculated by using SNPSpD software (http://genepi.qimr.edu.au/general/daleN/SNPSpD/), a program that is based on the spectral decomposition of matrices of pair-wise LD among markers [16].

Genotypes of major homozygotes (A/A), heterozygotes (A/B), and minor homozygotes (B/B) were given codes of 0, 1, and 2; 0, 1, and 1; and 0, 0, and 1 in the codominant, dominant, and recessive models, respectively. Genetic effects of inferred haplotypes were analyzed in the same way as SNPs. For example, 0 copies of Haplotype-1 (-/-, major homozygote), 1 copy of Ht-1 (-/Ht1, heterozygote), and 2 copies of Ht1 (Ht1/Ht1, minor homozygote) were coded as 0, 1, and 2 in the codominant model.

We defined PSA as a categorical ordinal variable and coded it as 0='PSA≥10,' 1='4≤PSA<10,' and 2='PSA<4'. We defined Gleason score as an ordinal variable and coded it as 0='high grade,' 1='intermediate grade,' and 2='low grade.' We defined clinical stage criteria as an ordinal variable and coded it as 0='metastatic,' 1='locally advanced,' and 2='localized.'

RESULTS

A total of 26 SNPs in the human *SRD5A2* gene of 272 prostate cancer patients and 173 control men were

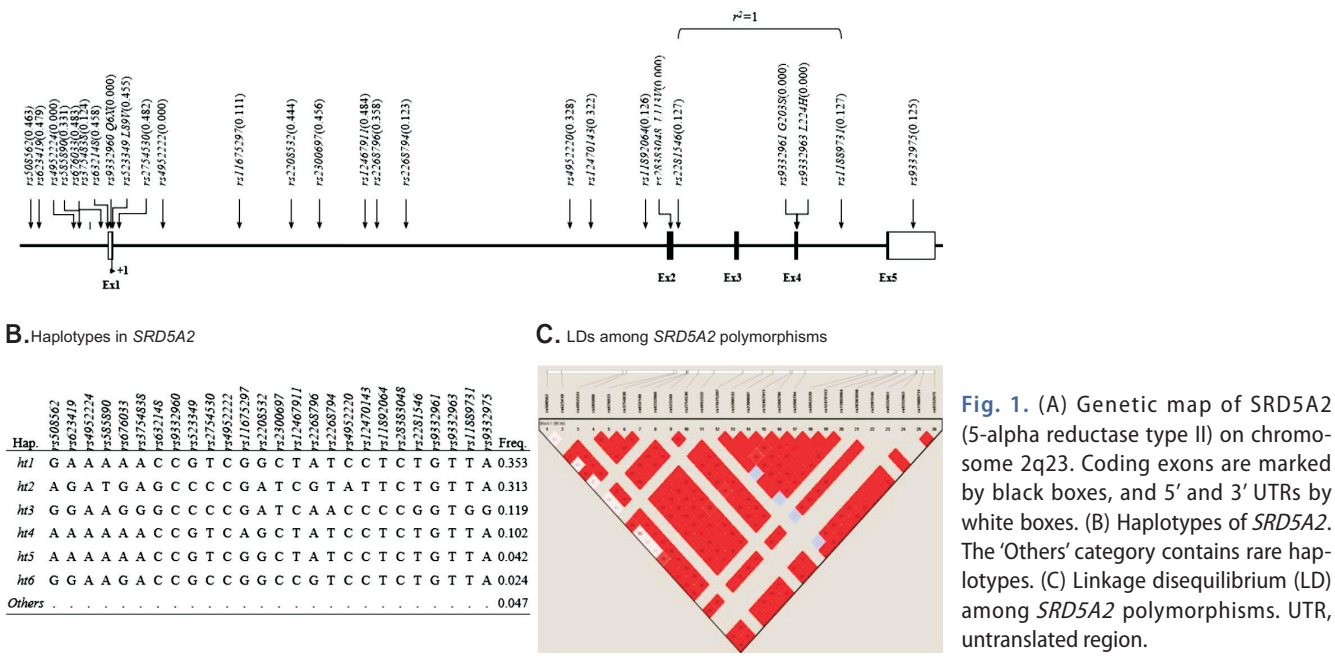

Fig. 1. (A) Genetic map of SRD5A2 (5-alpha reductase type II) on chromosome 2q23. Coding exons are marked by black boxes, and 5′ and 3′ UTRs by white boxes. (B) Haplotypes of *SRD5A2*. The 'Others' category contains rare haplotypes. (C) Linkage disequilibrium (LD) among *SRD5A2* polymorphisms. UTR, untranslated region.

discovered. Thirteen SNPs were located in introns, 6 in the promoter, 5 in the coding regions of exons, 1 in the 3'-untranslated region, and 1 in the 5'-untranslated region (Fig. 1A). There were no significant deviations from HWE in the polymorphisms (p>0.05) (Supplementary Table 1). The minor allele frequencies of the 26 genotyped polymorphisms are shown in Fig. 1B; the frequencies of the 4 major haplotypes were >0.05.

Genotype frequencies of both prostate cancer and control subjects were compared by using a logistic regression model (Table 2). In the 20 SNPs and 4 haplotypes, there were no statistically significant results between the prostate cancer patients and the normal controls. Further analysis of prostate cancer patients revealed that 2 SNPs (*rs508562*, *rs11675297*) displayed significantly positive results, and haplotype 1 showed significantly negative results (Table 3). *rs508562* in the *SRD5A2* gene was more frequent in patients with high PSA than low PSA by use of the recessive model (OR, 1.76; p=0.05). In the codominant and dominant models, *rs11675297* showed a significant correlation with PSA (OR, 2.02; p=0.01; OR, 1.88; p=0.04, respectively). However, haplotype 1 displayed an opposite trend (OR, 0.59; p=0.02).

We investigated the association of *SRD5A2* polymorphisms and Gleason score (Table 4). *rs508562* showed up more frequently in high-grade than in low-grade cancers in the codominant model (OR, 1.49; p=0.05). *rs11675297* of the dominant model and *rs2208532* of the recessive model were significant with positive direction (OR, 2.02; p=0.05; OR, 2.01; p=0.04, respectively). However, haplotype 1 was more frequent in low-grade than in high-grade cancers in the codominant and dominant models (OR, 0.64; p=0.03; OR, 0.56; p=0.04, respectively).

Table 5 depicts information regarding logistic analysis of SRD5A2 SNPs by clinical stage. There were significant results in the codominant and recessive models of *rs508562* (OR, 1.41; p=0.05; OR, 2.34; p=0.004, respectively). Moreover, *rs11675297* was also more frequent in metastatic stage cancer than in localized stage cancer under the codominant and dominant models (OR, 1.74; p=0.03; OR, 1.82; p=0.05, respectively). Again, haplotype 1 showed an opposite trend from the other SNPs in the codominant and dominant models (OR, 0.67; p=0.03; OR, 0.42; p=0.0005, respectively).

DISCUSSION

Our study examined the association of polymorphisms in the *SRD5A2* gene and the risk of prostate cancer. We used a well-defined case-control study that screened for PSA. The controls were negative for prostate cancer after prostate biopsy or BPH surgery, and a total of 26 SNPs and 4 haplotypes from 445 persons were analyzed. We were not able to find any association between *SRD5A2* polymorphisms and the risk of prostate cancer.

As a result of the important role of androgen and androgen receptors in prostate cancer, we paid attention to the gene involved in androgen metabolism, similar

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Table 2. Logistic analysis of association of *SRD5A2* polymorphisms with the risk of prostate cancer among Korean male subjects

SNP name	location	AA change	MAF		Codominant		Dominant		Recessive	
			PCa	NC	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
rs508562	Promoter	-	0.452	0.474	0.86 (0.65–1.13)	0.27	0.95 (0.62–1.47)	0.82	0.68 (0.42–1.08)	0.10
rs623419	Promoter	-	0.480	0.474	0.97 (0.73–1.27)	0.80	0.92 (0.60–1.43)	0.72	0.99 (0.62–1.58)	0.96
rs585890	Promoter	-	0.333	0.332	0.93 (0.70–1.24)	0.63	0.94 (0.63–1.40)	0.76	0.85 (0.47–1.53)	0.58
rs676033	Promoter	-	0.483	0.480	0.97 (0.73–1.27)	0.80	0.99 (0.64–1.53)	0.96	0.92 (0.58–1.46)	0.71
rs3754838	Promoter	-	0.119	0.121	0.97 (0.64–1.48)	0.88	1.06 (0.66–1.71)	0.80	0.39 (0.09–1.71)	0.21
rs632148	5'UTR	-	0.457	0.456	0.94 (0.72–1.24)	0.67	0.94 (0.61–1.44)	0.76	0.91 (0.56–1.46)	0.68
rs523349	CDS	L89V	0.455	0.450	0.96 (0.73–1.27)	0.79	0.95 (0.62–1.45)	0.80	0.96 (0.59–1.56)	0.87
rs2754530	Intron	-	0.482	0.480	0.96 (0.73–1.26)	0.75	0.96 (0.62–1.49)	0.87	0.92 (0.58–1.46)	0.71
rs11675297	Intron	-	0.102	0.116	0.88 (0.57–1.37)	0.57	0.80 (0.49–1.30)	0.37	2.83 (0.32–25.10)	0.35
rs2208532	Intron	-	0.441	0.442	0.93 (0.71–1.22)	0.60	0.88 (0.58–1.35)	0.56	0.94 (0.57–1.52)	0.79
rs2300697	Intron	-	0.452	0.457	0.92 (0.70–1.21)	0.54	0.89 (0.58–1.37)	0.60	0.89 (0.55–1.44)	0.63
rs12467911	Intron	-	0.483	0.483	0.95 (0.72–1.25)	0.70	0.94 (0.60–1.46)	0.77	0.92 (0.58–1.46)	0.72
rs2268796	Intron	-	0.360	0.361	0.95 (0.71–1.26)	0.70	0.94 (0.63–1.41)	0.77	0.90 (0.51–1.58)	0.72
rs2268794	Intron	-	0.118	0.121	0.94 (0.62–1.44)	0.79	1.03 (0.64–1.66)	0.90	0.38 (0.09–1.69)	0.21
rs4952220	Intron	-	0.333	0.324	0.97 (0.73–1.29)	0.83	1.01 (0.68–1.50)	0.96	0.85 (0.47–1.55)	0.60
rs12470143	Intron	-	0.325	0.321	0.95 (0.71–1.26)	0.70	0.99 (0.66–1.46)	0.94	0.81 (0.44–1.48)	0.49
rs11892064	Intron	-	0.121	0.122	0.98 (0.65–1.49)	0.93	1.08 (0.67–1.74)	0.74	0.38 (0.09–1.67)	0.20
rs2281546	Intron	-	0.123	0.124	0.98 (0.64–1.48)	0.90	1.07 (0.67–1.71)	0.78	0.38 (0.09–1.69)	0.21
rs11889731	Intron	-	0.123	0.122	1.00 (0.66–1.52)	0.99	1.10 (0.69–1.77)	0.68	0.38 (0.09–1.68)	0.20
rs9332975	3'UTR	-	0.121	0.121	0.99 (0.65–1.50)	0.95	1.09 (0.68–1.75)	0.73	0.38 (0.09–1.69)	0.21
SRD5A2_ht1	-	-	0.364	0.350	1.11 (0.84–1.46)	0.46	1.21 (0.81–1.80)	0.35	1.04 (0.60–1.81)	0.88
SRD5A2_ht2	-	-	0.314	0.312	0.93 (0.70–1.25)	0.65	1.03 (0.69–1.52)	0.90	0.69 (0.37–1.28)	0.23
SRD5A2_ht3	-	-	0.114	0.116	0.97 (0.63–1.49)	0.89	1.03 (0.64–1.67)	0.91	0.51 (0.11–2.42)	0.40
SRD5A2_ht4	-	-	0.094	0.107	0.86 (0.55–1.35)	0.50	0.77 (0.47–1.27)	0.30	2.79 (0.31–24.77)	0.36

SNP, single-nucleotide polymorphism; MAF, minor allele frequency; PCa, prostate cancer; NC, noncancer; OR, odds ratio; CI, confidence interval; UTR, untranslated region; CDS, coding DNA sequence.

Table 3. Logistic analysis of *SRD5A2* polymorphisms with PSA criteria

SNP name	Minor allele frequency			Codominant		Dominant		Recessive	
	PSA≥10 (n=113)	4≤PSA<10 (n=98)	PSA<4 (n=62)	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
rs508562	0.496	0.393	0.476	1.15 (0.83–1.57)	0.40	0.92 (0.56–1.49)	0.73	1.76 (1.00–3.09)	0.05
rs623419	0.456	0.490	0.508	0.87 (0.64–1.19)	0.38	0.62 (0.38–1.03)	0.06	1.15 (0.68–1.94)	0.60
rs585890	0.327	0.316	0.371	0.90 (0.65–1.24)	0.52	0.80 (0.52–1.26)	0.34	1.05 (0.54–2.05)	0.89
rs676033	0.460	0.495	0.508	0.88 (0.65–1.20)	0.42	0.64 (0.38–1.05)	0.08	1.15 (0.68–1.94)	0.60
rs3754838	0.104	0.144	0.105	0.95 (0.58–1.56)	0.85	1.02 (0.60–1.73)	0.95	0.21 (0.02–1.95)	0.17
rs632148	0.446	0.458	0.475	0.93 (0.69–1.27)	0.67	0.72 (0.44–1.18)	0.19	1.23 (0.71–2.12)	0.46
rs523349	0.441	0.453	0.484	0.90 (0.66–1.23)	0.52	0.76 (0.46–1.23)	0.26	1.05 (0.61–1.81)	0.85
rs2754530	0.460	0.490	0.508	0.89 (0.65–1.21)	0.45	0.65 (0.39–1.07)	0.09	1.15 (0.68–1.94)	0.60
rs11675297	0.150	0.072	0.067	2.02 (1.18–3.45)	0.01	1.88 (1.04–3.40)	0.04	-	-
rs2208532	0.429	0.444	0.460	0.93 (0.69–1.27)	0.66	0.75 (0.47–1.21)	0.24	1.19 (0.69–2.06)	0.54
rs2300697	0.446	0.449	0.468	0.97 (0.71–1.31)	0.83	0.78 (0.48–1.25)	0.30	1.26 (0.73–2.17)	0.40
rs12467911	0.464	0.490	0.508	0.90 (0.66–1.22)	0.49	0.66 (0.40–1.10)	0.11	1.16 (0.69–1.95)	0.59
rs2268796	0.350	0.342	0.411	0.87 (0.63–1.19)	0.38	0.79 (0.51–1.24)	0.31	0.91 (0.48–1.71)	0.77
rs2268794	0.111	0.138	0.097	1.08 (0.66–1.76)	0.77	1.16 (0.68–1.99)	0.58	0.21 (0.02–1.92)	0.17
rs4952220	0.332	0.316	0.363	0.93 (0.67–1.29)	0.66	0.87 (0.56–1.35)	0.53	1.01 (0.51–2.00)	0.97
rs12470143	0.319	0.309	0.363	0.89 (0.64–1.24)	0.50	0.82 (0.53–1.28)	0.39	0.97 (0.49–1.95)	0.94
rs11892064	0.111	0.143	0.105	1.01 (0.62–1.65)	0.96	1.09 (0.64–1.84)	0.76	0.21 (0.02–1.92)	0.17
rs2281546	0.115	0.143	0.105	1.05 (0.65–1.71)	0.84	1.13 (0.67–1.91)	0.64	0.21 (0.02–1.92)	0.17
rs11889731	0.115	0.143	0.105	1.05 (0.65–1.71)	0.84	1.13 (0.67–1.91)	0.64	0.21 (0.02–1.92)	0.17
rs9332975	0.111	0.143	0.105	1.02 (0.63–1.66)	0.94	1.09 (0.65–1.85)	0.74	0.21 (0.02–1.92)	0.17
SRD5A2_ht1	0.323	0.403	0.371	0.82 (0.60–1.12)	0.21	0.59 (0.38–0.94)	0.02	1.25 (0.67–2.35)	0.49
SRD5A2_ht2	0.319	0.296	0.339	0.97 (0.69–1.35)	0.83	0.86 (0.55–1.34)	0.50	1.31 (0.62–2.76)	0.48
SRD5A2_ht3	0.102	0.138	0.097	1.00 (0.61–1.65)	0.99	1.08 (0.63–1.85)	0.79	0.21 (0.02–1.92)	0.17
SRD5A2_ht4	0.128	0.071	0.073	1.62 (0.96–2.76)	0.07	1.42 (0.78–2.58)	0.25	-	-

PSA, prostate-specific antigen; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

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Table 4. Logistic analysis of *SRD5A2* polymorphisms with Gleason score criteria

SNP name	Minor allele frequency			Codominant		Dominant		Recessive	
	High grade (n=39)	Intermediate (n=202)	Low grade (n=29)	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
rs508562	0.441	0.397	0.452	1.49 (1.00–2.20)	0.05	1.52 (0.83–2.79)	0.17	1.91 (0.97–3.74)	0.06
rs623419	0.450	0.534	0.480	1.24 (0.85–1.80)	0.27	1.10 (0.60–2.01)	0.75	1.67 (0.88–3.15)	0.12
rs585890	0.314	0.345	0.331	1.24 (0.84–1.85)	0.28	1.21 (0.70–2.09)	0.49	1.66 (0.74–3.73)	0.22
rs676033	0.453	0.534	0.483	1.28 (0.87–1.87)	0.21	1.19 (0.65–2.19)	0.58	1.67 (0.88–3.15)	0.12
rs3754838	0.108	0.138	0.120	1.30 (0.71–2.37)	0.39	1.25 (0.65–2.39)	0.50	3.28 (0.32–33.43)	0.32
rs632148	0.424	0.500	0.456	1.36 (0.93–2.00)	0.12	1.37 (0.75–2.50)	0.30	1.72 (0.89–3.34)	0.11
rs523349	0.419	0.500	0.454	1.41 (0.96–2.09)	0.08	1.46 (0.80–2.69)	0.22	1.77 (0.91–3.45)	0.09
rs2754530	0.450	0.534	0.481	1.28 (0.88–1.87)	0.20	1.20 (0.65–2.19)	0.57	1.67 (0.88–3.15)	0.12
rs11675297	0.102	0.037	0.103	1.79 (0.99–3.26)	0.06	2.02 (1.00–4.06)	0.05	1.98 (0.29–13.49)	0.49
rs2208532	0.408	0.466	0.441	1.45 (0.99–2.13)	0.06	1.42 (0.79–2.56)	0.24	2.01 (1.03–3.91)	0.04
rs2300697	0.420	0.483	0.451	1.39 (0.95–2.03)	0.09	1.38 (0.76–2.51)	0.28	1.81 (0.93–3.51)	0.08
rs12467911	0.450	0.534	0.483	1.32 (0.90–1.93)	0.16	1.26 (0.68–2.34)	0.45	1.70 (0.90–3.22)	0.10
rs2268796	0.339	0.397	0.359	1.18 (0.80–1.74)	0.41	1.05 (0.60–1.81)	0.87	1.78 (0.83–3.82)	0.14
rs2268794	0.109	0.138	0.119	1.17 (0.64–2.14)	0.60	1.11 (0.58–2.12)	0.76	3.22 (0.32–32.76)	0.32
rs4952220	0.314	0.345	0.331	1.24 (0.83–1.84)	0.29	1.14 (0.66–1.96)	0.65	1.88 (0.84–4.24)	0.13
rs12470143	0.306	0.328	0.323	1.30 (0.87–1.95)	0.20	1.22 (0.71–2.11)	0.47	2.01 (0.87–4.61)	0.10
rs11892064	0.109	0.138	0.122	1.37 (0.76–2.48)	0.30	1.33 (0.70–2.52)	0.38	3.22 (0.32–32.76)	0.32
rs2281546	0.111	0.138	0.124	1.36 (0.76–2.46)	0.30	1.32 (0.70–2.50)	0.39	3.22 (0.32–32.76)	0.32
rs11889731	0.111	0.138	0.124	1.36 (0.76–2.46)	0.30	1.32 (0.70–2.50)	0.39	3.22 (0.32–32.76)	0.32
rs9332975	0.109	0.138	0.122	1.38 (0.76–2.50)	0.29	1.34 (0.71–2.55)	0.37	3.22 (0.32–32.76)	0.32
SRD5A2_ht1	0.218	0.389	0.379	0.64 (0.43–0.95)	0.03	0.56 (0.32–0.98)	0.04	0.54 (0.25–1.18)	0.12
SRD5A2_ht2	0.410	0.292	0.328	1.34 (0.88–2.02)	0.17	1.22 (0.71–2.11)	0.47	2.31 (0.96–5.53)	0.06
SRD5A2_ht3	0.154	0.104	0.138	1.19 (0.65–2.18)	0.57	1.13 (0.58–2.17)	0.73	3.22 (0.32–32.76)	0.32
SRD5A2_ht4	0.103	0.099	0.052	1.26 (0.68–2.34)	0.46	1.24 (0.60–2.56)	0.56	2.02 (0.30–13.69)	0.47

SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table 5. Logistic analysis of *SRD5A2* polymorphisms with clinical stage criteria

SNP name	Minor allele frequency			Codominant		Dominant		Recessive	
	Metastatic (n=60)	Locally advanced (n=53)	Localized (n=159)	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
rs508562	0.481	0.421	0.452	1.41 (1.00–1.98)	0.05	1.13 (0.67–1.90)	0.65	2.34 (1.32–4.14)	0.004
rs623419	0.368	0.497	0.480	1.02 (0.73–1.41)	0.91	0.72 (0.43–1.21)	0.21	1.59 (0.92–2.75)	0.10
rs585890	0.283	0.336	0.333	1.07 (0.76–1.51)	0.70	0.99 (0.62–1.58)	0.95	1.39 (0.69–2.81)	0.36
rs676033	0.377	0.500	0.483	1.02 (0.73–1.41)	0.92	0.71 (0.43–1.20)	0.20	1.59 (0.92–2.75)	0.10
rs3754838	0.087	0.130	0.119	0.84 (0.49–1.43)	0.52	0.83 (0.46–1.47)	0.51	0.88 (0.09–8.34)	0.91
rs632148	0.387	0.465	0.457	1.05 (0.75–1.45)	0.79	0.76 (0.46–1.27)	0.30	1.64 (0.93–2.88)	0.09
rs523349	0.368	0.465	0.455	1.04 (0.75–1.45)	0.83	0.82 (0.49–1.36)	0.43	1.48 (0.84–2.61)	0.17
rs2754530	0.377	0.497	0.482	1.03 (0.74–1.43)	0.86	0.74 (0.44–1.23)	0.25	1.59 (0.92–2.75)	0.10
rs11675297	0.170	0.067	0.102	1.74 (1.05–2.89)	0.03	1.82 (1.01–3.27)	0.05	3.33 (0.63–17.56)	0.16
rs2208532	0.349	0.450	0.441	1.07 (0.77–1.48)	0.70	0.84 (0.51–1.38)	0.49	1.59 (0.90–2.82)	0.11
rs2300697	0.385	0.456	0.452	1.09 (0.79–1.52)	0.60	0.83 (0.50–1.37)	0.47	1.70 (0.97–2.99)	0.07
rs12467911	0.377	0.497	0.483	1.05 (0.75–1.46)	0.79	0.76 (0.45–1.27)	0.30	1.60 (0.93–2.77)	0.09
rs2268796	0.283	0.368	0.360	1.08 (0.77–1.51)	0.67	1.05 (0.65–1.68)	0.86	1.24 (0.63–2.42)	0.54
rs2268794	0.094	0.123	0.118	0.96 (0.57–1.62)	0.88	0.96 (0.55–1.70)	0.89	0.86 (0.09–8.22)	0.90
rs4952220	0.264	0.333	0.333	1.13 (0.80–1.59)	0.50	1.11 (0.69–1.78)	0.66	1.32 (0.65–2.67)	0.45
rs12470143	0.264	0.329	0.325	1.07 (0.76–1.52)	0.70	1.03 (0.64–1.65)	0.91	1.28 (0.62–2.65)	0.51
rs11892064	0.094	0.129	0.121	0.90 (0.53–1.52)	0.68	0.89 (0.51–1.57)	0.69	0.86 (0.09–8.22)	0.90
rs2281546	0.104	0.129	0.123	0.93 (0.55–1.56)	0.77	0.92 (0.53–1.62)	0.78	0.86 (0.09–8.22)	0.90
rs11889731	0.104	0.129	0.123	0.93 (0.55–1.56)	0.77	0.92 (0.53–1.62)	0.78	0.86 (0.09–8.22)	0.90
rs9332975	0.094	0.129	0.121	0.92 (0.54–1.54)	0.74	0.91 (0.52–1.60)	0.75	0.86 (0.09–8.22)	0.90
SRD5A2_ht1	0.267	0.387	0.393	0.67 (0.48–0.95)	0.03	0.42 (0.26–0.69)	0.0005	1.08 (0.56–2.08)	0.83
SRD5A2_ht2	0.367	0.264	0.311	1.16 (0.81–1.66)	0.42	1.06 (0.66–1.70)	0.81	1.74 (0.81–3.73)	0.15
SRD5A2_ht3	0.125	0.075	0.123	0.92 (0.54–1.56)	0.75	0.91 (0.51–1.63)	0.76	0.86 (0.09–8.22)	0.90
SRD5A2_ht4	0.100	0.160	0.069	1.44 (0.86–2.43)	0.17	1.38 (0.75–2.53)	0.31	3.39 (0.64–17.89)	0.15

SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

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to previous researchers, although there previously were no studies on SRD5A2 SNPs and prostate cancer in the Korean population. Although some studies have been performed on other races, no clear consensus exists about the role of this gene. In 1995, Reichardt et al. [4] found that SRD5A2 TA repeat alleles were present only in African Americans and not in whites and Asians. Beuten et al. [17] could not find significant results from 10 SRD5A2 SNPs, but introduced the possibility of a polygenic model of prostate cancer, which meant several interacting genes of the steroid hormone pathway increased the risk of prostate cancer in Hispanic Caucasians and African Americans. According to a meta-analysis by Pearce et al. [18], there was little evidence of effects of the SRD5A2 A49T variant in prostate cancer risk. However, in a more recent meta-analysis, Li et al. [19] reported that, although there was no overall relation between V89L and prostate cancer risk, A49T could be involved in the etiology of prostate cancer in Caucasians. Ntais et al. [20] explained that the interracial differences between Asians and Caucasians were related to the V89L substitution. Because of these differences, we limited our subjects to Asians and selected SNPs that had an MAF>0.05 and LD>0.98. Our results may indicate that common Asian SNPs do not affect the prostate cancer risk and support the low prostate cancer incidence in Asian populations.

We found that some SNPs and 1 haplotype were related to PSA level, Gleason score, and clinical stage, and a dominant model of *rs11675297* had significant results for all 3 factors. Polymorphism in *rs11675297* was supposed to have a negative association with polycystic ovary syndrome by the biosynthesis and metabolism of sex steroids [21]. In a study of 33 men with early onset prostate cancer, Scariano et al. [22] revealed that the expression of a single leucine allele in SRD5A2 resulted in a higher PSA level, Gleason score, and clinical stage. These results are supported by a study by Das et al. [23]. They found that nuclear SRD5A2 expression was associated with vascular endothelial growth factor (VEGF) expression. Duque et al. [24] reported that the metastatic group had more VEGF than did the localized cancer or control groups, the group with PSA>20 ng/mL had more VEGF than did the group with PSA<20 ng/mL, and the group with a Gleason score of 8 to 10 group had more VEGF than did groups with lower Gleason scores. West et al. [25] also identified that increased VEGF immunoreactivity was correlated with high stage, PSA levels, and Gleason score. These studies indicate the possibility that VEGF has a function in prostate cancer progression. However, until now, none of the VEGF SNPs seemed likely to be significantly related to overall risk of advanced prostate cancer [26]. Meanwhile, Setlur et al. [27] proposed another hypothesis. They observed that an SRD5A2 genotype was related with DHT serum levels and speculated that SRD5A2 was not the crucial variant for determining DHT levels in the prostate or that higher DHT did not contribute to prostate cancer development but to tumor progression. However, this hypothesis has a limitation, because clinical data for baseline serum testosterone and DHT levels were not related to prostate cancer grade [28].

This is the first study to associate SRD5A2 SNPs or haplotypes with pretreatment PSA level, Gleason score, and clinical stage in the Korean population. In a Turkish population of 100 prostate cancer patients and 105 healthy controls, there was no evidence of an association between SRD5A2 SNPs and prostate cancer risk, PSA level, Gleason score, and clinical stage [29]. Because of interracial differences, however, these findings suggest that ethnicity should be kept in mind for further SNP research. Furthermore, our results can help to predict prognosis according to individual SNPs, and, considering the effect of SNPs on serum PSA level, SNPs could be useful as screening markers.

However, there were limitations to this study. One important limitation was that this study was limited to genetic research. Although we investigated basic characteristics of the subjects, as shown in Table 1, we did not know their DHT levels, plasma VEGF values, androgen-receptor protein levels, SRD5A2 activity, or whether they were taking a 5-alpha-reductase inhibitor. Because multiple interacting factors, such as clinical status or environment, might affect the risk or progression of prostate cancer, more studies are needed. The second limitation is that our analysis was from a comparison between prostate cancer patients and BPH patients. Although BPH is a common disease in older men, this composition is different from the general population. BPH patients have potential risks for developing prostate cancer, and they might have latent cancer. Thus, nondifferential misclassification bias is possible. In another Korean study, the prostate cancer detection rate was 8.9% in patients with a negative prostate biopsy result before surgery [30]. Third, if Bonferroni correction was used to address the problem of multiple comparisons, most results would lose significance. Last, we obtained data from international databases and this could represent rare variants, population-specific SNPs, and sequencing errors. These limitations can be overcome by more specific future

studies.

CONCLUSIONS

We conclude that there was no significant association between SRD5A2 SNPs and the risk of prostate cancer in the Korean population. However, we found that some SNPs and 1 haplotype influenced PSA level, Gleason score, and clinical stage. This study is useful for understanding the role of ethnicity and provides basic genetic data for prostate cancer research in the Korean population. Further work is necessary to establish associations with the development or progression of prostate cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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SUPPLEMENTARY MATERIALS

Scan this QR code to see the supplementary materials, or visit http://kjurology.org/src/sm/kju-56-19-s001.pdf.

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EDITORIAL COMMENT

A single-nucleotide polymorphism (SNP) is a common DNA sequence variation in a population. Such variations can affect susceptibilities and prognosis in various diseases. In terms of cancer, numerous efforts have been invested to identify the sources of genetic susceptibility. Through the outstanding studies of the International Human Genome Sequencing Project and the International HapMap Project, a large amount of data on genetic variations in the human genome has been accumulated, and this precious information has led to an explosion of investigations about SNPs. Prostate cancer is the most common malignancy in Western men, and the incidence of prostate cancer in Asian men is drastically increasing. More interestingly, prostate cancer shows not only a racial disparity but also a familial susceptibility in incidence, which suggests a strong influence of genetic factors.

The biggest difference between prostate cancer and other malignancies is that androgens play a critical role in cancer progression from an early stage to castration-refractory prostate cancer. For this reason, numerous studies have focused on genetic polymorphisms of androgen and androgen receptor. Several studies have suggested that polymorphisms of repetitive CAG, GGC, and GGN repeats in the androgen receptor gene are associated with the incidence and mortality of prostate cancer, although this remains under debate [1-3]. In addition, genetic variations of cytochrome P450 (CYP17), which mediates activities essential for the production of sex steroids, have been reported to have borderline significant associations with the incidence of prostate cancer [4].

One important factor in the role of androgen in the prostate is 5-alpha-reductase (5-AR), which converts testosterone to dihydrotestosterone (DHT) in prostate cells. SRD5A1 and SRD5A2 encode 5-AR, and Lindstrom et al. [5] reported in a study based on 2,826 cancer cases and 1,705 controls that a polymorphism in SRD5A2 (rs623419) is associated with the risk of prostate cancer. Although this study recruited a relatively large number of cases and controls, the statistical significance was marginal, and the study did not include investigation of genetic influences on clinical or pathological outcomes. Audet-Walsh et al. [6] conducted a retrospective study in two independent cohorts composed of 526 white and 320 Asian men with localized prostate cancer, and four genetic variations (rs2208532, rs12470143, rs523349, and rs4952197 in SRD5A2) were associated with biochemical recurrence in both

races. However, those investigators did not include clinical parameters such as Gleason score, prostate-specific antigen (PSA) level, or stage in their analysis.

In this issue of the Journal, Choi et al. [7] report on the influence of genetic polymorphisms of SRD5A2 on prostate cancer risk and clinical outcomes in a Korean population. They selected 26 SNPs in the human SRD5A2 gene from international databases and investigated the correlations in 272 prostate cancer patients and 173 controls with benign prostatic hyperplasia. The data suggested that some SNPs and one haplotype were related to PSA levels, Gleason score, and clinical stage; however, SRD5A2 SNPs were not associated with susceptibility to prostate cancer. This study is highly informative because 26 SNPs were selected by use of comprehensive bioinformatics methods. Moreover, this case-control study included all available parameters for analysis.

Advances in genotyping technologies have led to the feasibility of studying a large number of genetic polymorphisms, and the number of high-volume studies is rapidly increasing. However, we must keep in mind that the effects of genetic variation in incidence and prognosis of cancer are not outstanding and less than two folds. I believe that such genetic information should be combined with clinico-pathological variables to increase predictability, which could lead to a personalized risk classification for predicting the susceptibility and prognosis of prostate cancer.

Seok Joong Yun, MD, PhD
Associate Editor
Department of Urology, Chungbuk National University College of Medicine, 410 Sunbong-ro, Heungdeok-gu, Cheongju 361-763, Korea
E-mail: sjyun@chungbuk.ac.kr

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Supplementary Table 1. Frequencies of SNPs in prostate cancer patients and BPH controls (n=445)

SNPID	Coordinate	Location	AA Change	Genotype			Total number of genotypes	MAF	Heterozygosity	HWE
				Major homozygote	Heterozygosity	Minor homozygote				
rs508562	31837368	Promoter	-	GG (132)	AG (213)	AA (97)	442	0.460	0.497	0.527
rs623419	31834078	Promoter	-	AA (125)	AG (215)	GG (105)	445	0.478	0.499	0.503
rs4952224	31820256	Promoter	-	AA (445)	AG (0)	GG (0)	445	0.000	0.000	1.000
rs585890	31819430	Promoter	-	AA (205)	AT (184)	TT (56)	445	0.333	0.444	0.148
rs676033	31808970	Promoter	-	AA (123)	AG (215)	GG (107)	445	0.482	0.499	0.494
rs3754838	31808300	Promoter	-	AA (344)	AG (90)	GG (8)	442	0.120	0.211	0.458
rs632148	31806031	5'UTR	-	CC (135)	CG (206)	GG (97)	438	0.457	0.496	0.274
rs9332960	31805954	CDS	Q6X	CC (445)	CT (0)	TT (0)	445	0.000	0.000	1.000
rs523349	31805706	CDS	L89V	GG (135)	CG (207)	CC (94)	436	0.453	0.496	0.381
rs2754530	31803403	Intron	-	TT (124)	CT (214)	CC (107)	445	0.481	0.499	0.438
rs4952222	31799863	Intron	-	CC (445)	AC (0)	AA (0)	445	0.000	0.000	1.000
rs11675297	31793419	Intron	-	GG (353)	AG (83)	AA (6)	442	0.107	0.192	0.657
rs2208532	31788989	Intron	-	GG (143)	AG (211)	AA (91)	445	0.442	0.493	0.416
rs2300697	31786637	Intron	-	CC (138)	CT (208)	TT (97)	443	0.454	0.496	0.266
rs12467911	31782791	Intron	-	TT (122)	CT (215)	CC (107)	444	0.483	0.499	0.521
rs2268796	31782280	Intron	-	AA (187)	AG (195)	GG (63)	445	0.361	0.461	0.293
rs2268794	31779404	Intron	-	TT (347)	AT (90)	AA (8)	445	0.119	0.210	0.446
rs4952220	31765556	Intron	-	CC (206)	AC (185)	AA (54)	445	0.329	0.442	0.215
rs12470143	31763558	Intron	-	CC (209)	CT (183)	TT (52)	444	0.323	0.437	0.223
rs11892064	31759286	Intron	-	TT (344)	CT (92)	CC (8)	444	0.122	0.214	0.525
rs28383048	31758781	CDS	L113V	CC (445)	CG (0)	GG (0)	445	0.000	0.000	1.000
rs2281546	31757024	Intron	-	TT (343)	GT (94)	GG (8)	445	0.124	0.217	0.599
rs9332961	31754468	CDS	G203S	GG (445)	AG (0)	AA (0)	445	0.000	0.000	1.000
rs9332963	31754404	CDS	L224H	TT (445)	AT (0)	AA (0)	445	0.000	0.000	1.000
rs11889731	31752857	Intron	-	TT (343)	GT (93)	GG (8)	444	0.123	0.215	0.564
rs9332975	31750417	3'UTR	-	AA (345)	AG (92)	GG (8)	445	0.121	0.213	0.520

SNP, single-nucleotide polymorphism; BPH, benign prostatic hyperplasia; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; UTR, untranslated region; CDS, coding DNA sequence.