



Genetic Polymorphism of Nerve Injury-induced Protein 1 in Prostate Cancer

Jae Young Joung¹, Sang Jin Lee², Aesun Shin³, Weon Seo Park¹, Jeong Eun Kim¹, Ho Kyung Seo¹, Jinsoo Chung¹, Jung-Ah Hwang⁴, Seung-Hyun Hong⁴, Jeongseon Kim⁵, Kang Hyun Lee¹ and Yeon-Su Lee^{*}

¹Center for Prostate Cancer, National Cancer Center, Goyang, Korea

²Genitourinary Cancer Branch, National Cancer Center, Goyang, Korea

³Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea

⁴Functional Genomics Branch, National Cancer Center, Goyang, Korea

⁵Molecular Epidemiology Branch, National Cancer Center, Goyang, Korea

Abstract

Objective: To investigate the association of genetic variants of nerve injury-induced protein 1 (NINJ1) with risk of prostate cancer in Korean men, we performed this association study using single nucleotide polymorphism (SNP).

Materials and methods: We enrolled 383 patients with prostate cancer and 373 healthy controls. Twenty-six candidate SNPs of the NINJ1 gene were selected for genotype analysis. The distribution of each genotype and haplotype was analyzed, and their association with the incidence of prostate cancer was evaluated.

Results: None of the SNPs and haplotypes showed significant associations with prostate cancer risk in our subjects. In relation to the genotype frequency, 14 out of the 24 characterized SNPs revealed monomorphic features in cases and controls.

Conclusions: Although no association was observed between SNPs of the NINJ1 gene and prostate cancer risk, this study is meaningful because it is the first report to investigate the genetic epidemiology of the NINJ1 gene in relation to the development of prostate cancer. In addition, we observed monomorphic features of several SNPs of the NINJ1 gene in Korean men, and this finding was similar to that observed in Chinese and Japanese men based on the review of SNP database.

Keywords: NAFLD; Leptin; Adiponectin prostate cancer; Nerve injury-induced protein 1; Single nucleotide polymorphism

Abbreviations and Acronyms: NINJ1: Nerve Injury-Induced Protein 1; SNP: Single Nucleotide Polymorphism; GWAS: Genome-Wide Association Study; HWE: Hardy-Weinberg Equilibrium; CIs: Confidence Intervals; LD: Linkage Disequilibrium

Introduction

Prostate cancer is generally considered as a heterogeneous disease due to its etiology and development. In addition to environmental factors such as a high fatty diet, prostate cancer is related to various inherited genetic factors. Therefore, many studies have endeavored to identify the risk factors for prostate cancer, by mainly focusing on target gene approaches, which have confirmed the effect of known tumor-associated genes [1-4]. So far, a number of association studies including genome-wide association studies (GWAS) have identified significant associations between many single nucleotide polymorphisms (SNPs) and prostate cancer [5-9].

Nerve injury-induced protein 1 (NINJ1) is a cell surface protein that was first identified in Schwann cells following nerve injury [10]. This protein has been found to be involved in neuro-inflammatory processes because it plays roles in cell adhesion and nerve regeneration following nerve injury. A recent study showed that NINJ1 is involved in the development and progression of multiple sclerosis, which is the most well-known autoimmune inflammatory disease of the central nervous system [11]. The expression of NINJ1 has been identified in many human tissues including heart, brain, placenta, lungs, liver, skeletal muscles, kidneys, pancreas, spleen, thymus, prostate, testis, ovaries, small intestine, colon, blood, and adrenal glands, in addition to dorsal root ganglia [10]. The gene encoding NINJ1 is located in the 9q22 chromosomal region with four exons covering less than 10 kb,

and it is considered to be linked to hereditary sensory neuropathy type I, a degenerative neurological disorder. Besides, the genetic location of NINJ1 was also linked to the cancer predisposition syndrome multiple self-healing squamous epitheliomata [12]. Thus, there are some studies showing that NINJ1 is associated with a few malignancies such as hepatocellular carcinoma, acute lymphoblastic leukemia, and high-grade bladder cancer [13-17]. It is known that p53 plays a crucial role in carcinogenesis as a tumor suppressor gene by contributing to the process of DNA repair and programmed cell death. Interestingly, NINJ1 has been reported to be up-regulated by p53 [18]. Furthermore, in prostate cancer, p53 nuclear accumulation has been shown to be related to tumor progression [19-21].

With regard to genetic variations of NINJ1, there are some studies that investigated the association of NINJ1 polymorphism with protection in leprosy nerve damage [22]. Polymorphism of the NINJ1 gene was reported to be associated with increased risk of high-grade bladder cancer [16].

To the best of our knowledge, there is no report assessing the genetic variations of the NINJ1 gene in prostate cancer and the

***Corresponding author:** Yeon-Su Lee, Ph.D, Cancer Genomics Branch, National Cancer Center, Korea, Tel: +82-31-920-2550; E-mail: yslee2@ncc.re.kr

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clinical significance of inherited NINJ1 variation in prostate cancer. We performed an analysis of candidate SNPs of the NINJ1 gene to determine the potential association of specific variations of the NINJ1 gene with risk of developing prostate cancer.

Experimental Section

Patients and methods

We performed a hospital-based case-control study of prostate cancer. Both prostate cancer patients and controls were ethnic Koreans residing in Korea. Patients with histologically confirmed prostate cancer were enrolled at the National Cancer Centre in Korea between January 2005 and February 2012. Controls were confirmed free of prostate cancer by determining the blood PSA level and by performing digital rectal examination. In 5 subjects of the control group with an abnormal PSA level (serum PSA level > 4 ng/mL), prostate needle biopsy was performed to confirm the absence of prostate cancer. The requirements and purpose of the study were explained to all of the study participants who signed informed consent forms to express their willingness to participate in the study. The study subjects donated blood voluntarily, and the blood samples were stored at -70°C on-site until use for genotype analysis. Information on demographic characteristics was obtained through personal questionnaires. This study was approved by the Institutional Review Board of the National Cancer Center in Korea (NCCNCS05-049). Subject's informed consent has to be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Single nucleotide polymorphism (SNP) selection and genotyping

The target SNPs of NINJ1 were selected from the National Center for Biotechnology Information (NCBI) database (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). We collected the information on all of the coding SNPs in NINJ1 with heterozygosity; a total of 26 SNPs were identified (Table 1). Among these SNPs, we excluded the SNP, rs148685363 because of inconsistent results from two consecutive experiments. Two additional SNPs (rs140126462 and rs1106192) were also excluded because of assay design failure to create suitable primers. Finally, primers for 23 SNPs were designed using DESIGNER (Sequenom, CA, USA) software (Supplementary Table 1). Genomic DNA was prepared from 200 µl of peripheral blood using the QIAamp Blood Kit (QIAGEN, Valencia, CA, USA) according to the manufacturer's instructions. Genotyping was performed according to the previously described method [1], and the resulting genotype data were obtained by Typer (version 4.0, Sequenom) and were subjected to statistical analysis.

Statistical analyses

The demographic and clinical characteristics of the study population and controls were analyzed using a chi-square test for categorical variables and an independent t-test for continuous variables. Hardy-Weinberg Equilibrium (HWE) was determined separately in cases and controls for each SNP. SNPs that deviated from the HWE in the control group were excluded (χ^2 test at p-value < 0.001). The association between NINJ1 polymorphisms and prostate cancer risk was evaluated on the basis of genotypic frequencies of each SNP using Cochran-Armitage trend test. The unconditional logistic regression model was also used to analyze the odds ratios (ORs) and their 95% confidence intervals. The haplotype estimation was carried out using

the PHASE program (version 2.1; www.stat.washington.edu/stephens/software.html), which implements a Bayesian statistical method for reconstructing haplotypes. An unconditional logistic regression was used to determine the association between NINJ1 haplotypes and prostate cancer risk, considering the haplotypic frequencies of each haplotype and the haplotype pair of each person. Additionally, the associations between genotypes and clinical parameters were determined using the polytomous logistic regression. All other statistical analyses were performed using SAS (version 9.1 SAS Institute, NC, USA). The reported p-values are two-sided, and a significance level < 5% was considered statistically significant.

Results

Characteristics of the study subjects

The demographic and clinical features of 383 prostate cancer patients and 373 healthy controls are presented in Table 2. With respect to age, PSA level, body mass index (BMI), alcohol consumption status, and family history of prostate cancer, significant differences were observed between the cases and controls. Patients with prostate cancer were older, had higher PSA levels, and were more likely to have a family history of prostate cancer. On the other hand, controls tended to be regular consumers of alcohol compared with patients.

Distribution of alleles and genotypes of NINJ1 polymorphisms

Distribution of genotypes of the target 23 SNPs of NINJ1 and their association with the risk of developing prostate cancer are shown in Table 3. None of the significant SNPs had any genotypes in terms of an association with risk of prostate cancer. In relation to genotypic frequencies of the 24 characterized SNPs, 14 SNPs showed monomorphic features with only 1 predicted genotype in both cases and controls. Based on the NCBI database, genetic characteristics of 14 SNPs showing the monomorphic genotype are included in Table 1. Among these 14 SNPs, the genotype frequencies of 5 SNPs that showed monomorphic features in our study were reviewed in different populations. Monomorphic features of these 5 SNPs were observed in Asians including Han Chinese and Japanese, which is the same as our result. Notably, similar results were observed in Puerto Ricans and Toscani in Italia (Supplementary Table 2).

Haplotype analysis of NINJ1 gene polymorphisms

Table 4 shows the frequency distribution and association analysis of haplotypes for 6 SNPs in NINJ1. Two haplotype blocks were constructed. In comparison to the individuals with the [TG/TG] haplotype consisting of 2 SNPs (rs7033638 and rs12238760), the individuals with the [TG/CA] haplotype tended to have a higher risk of prostate cancer, but it was not statistically significant (adjusted OR, 1.26; 95% CI, 0.90-1.77). In the other haplotype block consisting of the other 4 SNPs, subjects with the [AGTA/AGTC] haplotype also tended to have a higher risk of prostate cancer than subjects with the [AGTA/AGTA] haplotype; however, it was not significant (adjusted OR, 1.42; 95% CI, 0.81-2.50).

Association of the genotypes and haplotypes with PSA value, GS, and pathologic stage of prostate cancer

We determined the association of SNPs with clinical factors, including PSA value, GS, and pathologic stage (pT). For association analysis, the patients were divided into two subgroups based on their tumor GS from needle biopsy (GS < 7 and GS ≥ 7). The PSA value was analyzed as a categorical variable in 2 PSA categories (< 10 ng/ml

rs number	SNP position	Reference Alleles	Variant Alleles	Amino acid change	Amino acid position	Function	Remarks	Reference MAF Caucasian	Asian (Japan or china)	Result MAF (Korean)
rs7033638	95883785	T	A/C			3' UTR		C (0.0183)	C (0.142)	C (0.219)
rs12238760	95883846	G	A			3' UTR		NA	A (0.167)	A (0.218)
rs1127857	95883865	C*	G*			3' UTR		G (0.150)	G (0)	G (0.001)
rs1127851	95883958	T*	A*			3' UTR		T (0.142)	T (0.150)	T (0.090)
rs116415036***	95884297	G	A			3' UTR		NA	NA	A (0)
rs28722632***	95884421	G	A			3' UTR		NA	NA	A (0)
rs28399238***	95884443	G	C			3' UTR		NA	NA	C (0)
rs3750555	95884501	A	C/G			3' UTR		A (0)	A (0.15)	A (0.091)
rs141593889***	95887201	G	A	P/S	150	Exon		A (0)	NA	A (0)
rs61755996***	95887232	G	A	F/F	139	Exon		A (0.002)	NA	A (0)
rs138077782***	95887239	G	A	T/M	137	Exon		A (0)	NA	A (0)
rs148685363	95887304	C	T	L/L	115	Exon	n.i**	T (0.007)	NA	NA
rs2275848	95887320	G	T	A/D	110	Exon		G (0.142)	G (0.158)	G (0.087)
rs150605482***	95887323	G	A	P/L	109	Exon		A (0)	NA	A (0)
rs11546432***	95887345	G*	C*			Intron		NA	NA	C (0)
rs144669023***	95888815	C	T	A/T	61	Exon		T (0)	NA	T (0)
rs140126462	95888817	T	C	N/S	60	Exon	Design Fail	C (0.003)	NA	NA
rs79209251***	95888830	G	A	L/L	56	Exon		NA	NA	A (0)
rs145421928***	95888872	C	T	A/T	42	Exon		T (0)	NA	T (0)
rs1106192	95896586	C	G			Promoter	Design Fail	NA	NA	NA
rs112480392***	95897334	C	A			Promoter		NA	NA	A (0)
rs73651368***	95897380	C	T			Promoter		NA	NA	T (0)
rs13286331	95897425	C	A			Promoter		A (0.200)	NA	A (0.001)
rs1419232	95897564	C*	A*			Promoter		C (0.013)	C (0.192)	C (0.139)
rs79615670***	95897653	G	A			Promoter		A (0.033)	NA	A (0)
rs117006920	95897665	C	T			Promoter		NA	T (0.017)	T (0.004)

SNP, single nucleotide polymorphism; NA, not available in SNP database; MAF, minor allele frequency; *Reference allele s are represented as reverse strand; **Not included because of different results between 2 consecutive tests; ***Monomorphic features (MAF=0) in Korean; Design Fail, unable to read sequences with designed primers.

Table 1: SNPs investigated in this study.

Variables	Cases (n = 383)		Controls (n = 373)		P-value*
AGE, years (mean ± standard deviation)	65.38 ± 6.75		61.56 ± 4.39		<0.001
Serum PSA (ng/ml)					<0.001
<4	15	-3.90%	357	-95.70%	
4-10 (≥4 to <10)	191	-50.00%	15	-4.00%	
10-20 (≥10 to <20)	76	-19.90%	1	-0.30%	
≥20	100	-26.20%	0	0.00%	
BMI, kg/m ²					0.014
<25	245	-64.00%	206	-55.20%	
≥25	138	-36.00%	167	-44.80%	
Smoking status					0.196
Never	69	-20.00%	87	-24.00%	
Ever	276	-80.00%	275	-76.00%	
Alcohol consumption habit					<0.001

Never	130	-33.90%	68	-18.60%	
Ever	253	-66.10%	297	-81.40%	
Family history of prostate cancer among first-degree relatives					<0.001
No	369	-96.30%	372	-99.70%	
Yes	14	-3.70%	1	-0.30%	
Gleason score					
6-Feb	194	-50.60%			
7	123	-32.10%			
10-Aug	66	-17.20%			
pTstage					
pT0	6	-1.60%			
pT2a	65	-17.20%			
pT2b	6	-1.60%			
pT2c	168	-44.40%			
pT3a	70	-18.50%			
pT3b	62	-16.40%			
pT4	1	-0.30%			

PSA, prostate specific antigen; BMI, body mass index; *Pearson's χ^2 test for categorical variables and independent *t*-test for continuous variables; two-sided *p*-value.

Table 2: Demographic and clinical characteristics of the subjects, n (%).

SNP	Genotype	Cases (%)		Controls (%)		$P_{\text{trend}}^{\dagger}$	Crude	Adjusted
							OR (95% CI)	OR (95% CI) ^a
rs7033638	T/T	226	59.5	239	64.6	0.212	1	1
	T/C	131	34.5	110	29.7		1.26 (0.92-1.72)	1.26 (0.91-1.77)
	C/C	23	6	21	5.7		1.16 (0.62-2.15)	1.38 (0.72-2.66)
	T/C + C/C	154	40.5	131	35.4	0.149	1.24 (0.92-1.67)	1.29 (0.93-1.77)
rs12238760	G/G	226	59.5	242	64.9	0.164	1	1
	G/A	131	34.5	111	29.8		1.25 (0.91-1.70)	1.24 (0.88-1.73)
	A/A	23	6	20	5.3		1.21 (0.65-2.27)	1.47 (0.76-2.85)
	G/A + A/A	154	40.5	131	35.1	0.126	1.26 (0.94-1.69)	1.29 (0.94-1.78)
rs1127857	C/C	381	99.7	368	100	1	1	1
	C/G	1	0.3	0	0		-	-
rs1127851	A/A	319	84	304	81.5	0.311	1	1
	A/T	59	15.5	65	17.4		0.86 (0.58-1.26)	0.83 (0.54-1.25)
	T/T	2	0.5	4	1.1		0.47 (0.09-2.60)	0.46 (0.07-2.91)
	A/T + T/T	61	16	69	18.5	0.375	0.84 (0.58-1.23)	0.81 (0.54-1.23)
rs3750555	G/G	317	83.6	302	81.4	0.299	1	1
	G/A	61	16.1	65	17.5		0.89 (0.61-1.30)	0.86 (0.57-1.30)
	A/A	1	0.3	4	1.1		0.24 (0.03-2.13)	0.18 (0.02-1.82)
	G/A + A/A	62	16.4	69	18.6	0.419	0.86 (0.59-1.25)	0.83 (0.55-1.24)

rs2275848	T/T	316	84.5	304	82.4	0.365	1	1
	G/T	56	15	61	16.5		0.87 (0.59-1.29)	0.82 (0.54-1.26)
	G/G	2	0.5	4	1.1		0.47 (0.09-2.61)	0.46 (0.07-2.92)
	G/T + G/G	58	15.5	65	17.6	0.439	0.86 (0.58-1.26)	0.81 (0.53-1.24)
rs13286331	C/C	377	99.7	372	100	1	1	1
	A/C	1	0.3	0	0		-	-
rs1419232	A/A	282	74.4	275	74.1	0.593	1	1
	C/A	92	24.3	85	22.9		1.05 (0.75-1.47)	1.05 (0.73-1.51)
	C/C	5	1.3	11	3		0.44 (0.15-1.28)	0.42 (0.13-1.31)
	C/A+ C/C	97	25.6	96	25.9	0.929	0.98 (0.71-1.37)	0.98 (0.69-1.40)
rs117006920	C/C	377	98.7	372	99.7	0.23	1	1
	C/T	5	1.3	1	0.3		4.93 (0.57-42.42)	2.95 (0.30-28.51)

†Calculated from Cochran-Armitage trend test.
 ‡Adjusted for age, alcohol consumption habit, BMI and family history of prostate cancer.

Table 3: NINJ1 polymorphisms and association with prostate cancer risk.

Haplotypes	Cases (%)		Controls (%)		P†	Crude OR (95% CI)	Adjusted OR (95% CI)‡
Block 1							
TG/TG	228	-59.5	242	-64.9	0.314	1	1
TG/CA	131	-34.2	110	-29.5		1.26 (0.93-1.73)	1.26 (0.90-1.77)
CA/CA or CA/CG or TG/CG	24	-6.3	21	-5.6		1.21 (0.66-2.24)	1.48 (0.77-2.83)
Block 2							
AGTA/AGTA	282	-73.6	276	-74	0.5	1	1
AGTA/TAGC	54	-14.1	58	-15.6		0.91 (0.61-1.37)	0.89 (0.57-1.37)
AGTA/AGTC	38	-9.9	27	-7.2		1.38 (0.82-2.32)	1.42 (0.81-2.50)
Others*	9	-2.4	12	-3.2		0.73 (0.30-1.77)	0.72 (0.28-1.85)

OR, odds ratio; CI, confidence interval; ‡Adjusted for age, alcohol consumption habit, BMI and family history of prostate cancer; †Chi-square test; NINJ1 haplotypes consisted with the following SNPs: block 1- rs7033638-rs12238760, block2-rs1127851-rs750555-rs2275848-rs1419232; *Other haplotype pairs includes AGTA/TAGA (3 cases and 1 control), AGTC/TAGC (3 cases and 6 controls), TAGC/TAGC (1 case and 4 controls), AGTC/AGTC (1case and 1 control), and TGGA/TAGC (1case).

Table 4: Frequency of NINJ1 haplotypes and their associations with prostate cancer risk.

and > 10 ng/ml). Patients were divided into 2 subgroups depending on the pathologic tumor stage (stage ≤ pT2b and stage ≥ pT2c). However, none of the 6 SNPs and haplotypes was significantly associated with the PSA value, GS, and pathologic stage (Supplementary Table 3).

Discussion

In this study, we evaluated the association between genetic variations of the NINJ1 gene and prostate cancer risk among 383 cases and 373 controls. Overall, no association was observed between candidate SNPs of the NINJ1 gene and risk of prostate cancer. With respect to genotype frequency, 14 SNPs showed only 1 predicted genotype in both case and control groups, which was similar to that in an Asian population including the Han Chinese and Japanese men. This result indicates that these nucleotide sites may not show polymorphic genotypes among Asians. Instead, these sites are highly likely to show

monomorphic genotypes in Asian populations.

To date, studies identifying the genetic variations of NINJ1 in terms of prostate cancer risk or prognosis have not been published. Although no association was observed between SNPs of NINJ1 and prostate cancer risk, this study is meaningful because it is the first report to investigate the genetic epidemiology of the NINJ1 gene in relation to the development of prostate cancer. With respect to the polymorphism of NINJ1 and clinical features of prostate cancer, our study provides the pathologic data of surgical specimens as well as the clinical data of prostate cancer cases. In previous studies, we identified some relationships between pathologic factors for prostate cancer and specific polymorphisms of other candidate genes including the PSCA gene, 8q24, and AMACR [1,2]. However, we could not detect any significant relationship between pathologic factors for prostate cancer and polymorphism of the NINJ1 gene in the present study.

In the dorsal root ganglion, NINJ1 is up-regulated after nerve injury; and it plays a role in nerve regeneration [23]. In human carcinogenesis, NINJ1 was linked with the cancer predisposition syndrome multiple self-healing squamous epitheliomata [12], which is characterized by a predisposition to multiple squamous cell cancers of the skin [24]. In hematologic malignancies, NINJ1 expression was increased in acute lymphocytic leukemia. NINJ1 was also identified by cDNA microarrays as a marker of B-lineage acute lymphoblastic leukemia [15].

In solid tumors, NINJ1 was, at first, confirmed to be up-regulated in hepatocellular carcinoma associated with viral infection or liver cirrhosis, which suggested that NINJ1 might be involved in carcinogenesis of hepatocellular carcinoma [13]. In non-muscle invasive bladder cancer, NINJ1 expression was associated with tumor progression based on immunohistochemical staining using tissue microarray [17]. Recently, the cDNA microarray results demonstrated that NINJ1 expression was associated with non-muscle invasive bladder cancer recurrence [25].

Notably, a genetic screening study using microarray showed that tumor suppressor protein p53 increases NINJ1 expression, and this finding has resulted in an increased interest in the potential role of NINJ1 in carcinogenesis [18]. In prostate cancer, some studies have demonstrated an association between p53 nuclear accumulation due to alteration and poor differentiation, progression, metastasis, and androgen-independent growth [19-21].

NINJ1 gene is located near the D95S12 gene at 9q22.3 that encompasses the loci for the ESS1 gene, which is known as one of the tumor suppressor loci in bladder cancer [26]. A study using the DNA fingerprinting technique showed that altered regions were found at many cytobands including 9q22.32 in the prostate specimens [27]. All of the patients with polymorphism in 9q22.32 consistently showed high grade PIN and carcinoma foci in prostate specimens, which suggests that this region may harbor putative genes that play important roles in the development and early progression of prostate cancer. The NINJ1 gene may be considered as one of the candidate genes in this surrounding area that may possibly harbor mutations that change normal prostatic cells to progress into their tumor stages. In addition, the NINJ1 gene is situated close to the PCA 3 gene that is located on 9q21-22. Currently, it is well known that the PCA 3 gene is predominantly expressed in prostate tissues, and it is widely used as diagnostic and prognostic marker in prostate cancer [28,29].

Regarding the association study of the NINJ1 gene in benign neurologic disorders, the SNP rs2275848 of the NINJ1 gene was found to be associated with protection from nerve damage in patients with leprosy [22]. The SNP of the NINJ1 gene was found to be associated with higher risk for high-grade bladder cancer [16], and it was suggested that the polymorphism could identify the subjects with higher risk for bladder cancer occurrence and progression.

In our study, 14 SNPs showed monomorphic features in Korean men. Theoretically, we could not detect rare alleles because of uncertainty in the technical accuracy of DNA pooling and data sequencing process. However, considering that the SNPs have already been mapped in the complete human genome sequence as a reference, monomorphic genotypes of specific sites could be differently observed in each population with reference to the SNP database [30]. Considering that the minor allele frequency was zero compared with that in the reference SNP database, our results imply that these sites are completely monomorphic rather than polymorphic in Korean men, which shows that genetic variations are closely associated with

population characteristics such as ethnicity. In this study, we also found that three Asian populations show complete monomorphic features in 5 SNPs of the NINJ1 gene. In the literature review about the estimated rate of polymorphism, Marth et al. reported that only less than 15% of the SNPs in the database have been proven to be polymorphic in any population and the allele frequency estimates can be different among results by about 5% [31]. Potentially, we can get different results for genetic variations of specific genes depending on the study population. Based on this fact, an SNP study is preferred if a candidate SNP with an appropriate minor allele frequency is common in each population.

Our study has several fundamental limitations since it was a hospital-based study. Firstly, because of the relatively small number of cases and controls and differences in characteristics between the two groups, the power of this study is limited. To minimize the effect of the different distribution in cases and controls, we adjusted for the age, BMI, alcohol consumption habit, and family history of prostate cancer in the statistical analysis. Secondly, we examined only a small number of SNPs in the NINJ1 gene with respect to risk of prostate cancer. Therefore, we cannot completely rule out the association of the NINJ1 gene with prostate cancer based on our negative results. Finally, many SNPs were excluded from our association analysis due to monomorphic features. SNPs with appropriate minor allele frequencies in our population should have been selected as candidate SNPs, but it is not easy to estimate appropriateness of allele frequencies of SNPs during the study design stage.

Authors Contributions

JYJ and SJL designed study and wrote the manuscript. JK participated in study design. WSP helped to draft the manuscript. AS performed a statistical analysis for clinical factors of patients. JEK managed and analyzed the raw data of characteristics of patients. WSP, HKS, JC helped to do study design and draft manuscript. JAH and SHH did genotyping. KHL and YSL did study design and supervised this study. HKS and JC reviewed the previous data.

All authors read and approved the final manuscript.

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