Int J Clin Exp Med 2016;9(12):23530-23540
www.ijcem.com /ISSN:1940-5901/IJCEM0030074

Original Article

AMACR polymorphisms are associated with prostate cancer risk and aggressiveness in a Korean study population

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Received April 7, 2016; Accepted October 8, 2016; Epub December 15, 2016; Published December 30, 2016

Abstract: To investigate the potential relationship between sequence variants in the *AMACR* gene and prostate cancer risk in a Korean study cohort. We evaluated the association between 21 single nucleotide polymorphisms (SNPs) in the *AMACR* gene and prostate cancer risk as well as clinical characteristics (pathological stage and Gleason score) in Korean men (272 prostate cancer patients and 173 benign prostatic hyperplasia patients who underwent a prostate biopsy, which was negative for malignancy) using unconditional logistic regression. 8 *AMACR* sequence variants (*rs3195676, rs10941112, rs4866402, rs34678, rs10941110, rs34676, rs16892096,* and *rs250414*) had a significant association with prostate cancer risk (age-adjusted odds ratio [OR]=0.74, P=0.05; OR=0.74, P=0.04; OR=0.64, P=0.03; OR=1.45, P=0.01; OR=0.74, P=0.04; OR=1.46, P=0.01; OR=0.65, P=0.05; and OR=0.72, P=0.03, respectively). 2 haplotypes (*AMACR_B1_ht1* and *AMACR_B1_ht2*) showed a significant association with prostate cancer risk (OR=0.70, P=0.02; and OR=1.49, P=0.01, respectively). 8 SNPs (*rs3195676, rs10941112, rs10941110, rs168803, rs16892096, rs10472909, rs2652130, and rs12659370)* and 1 haplotype (*AMACR_B2_ht2*) were significantly associated with pathological stage, 3 SNPs (*rs16892066*, *rs16892064,* and *rs840380*) and 2 haplotypes (*AMACR_B2_ht3* and *AMACR_B2_ht4*) were also significantly related to Gleason score. Some *AMACR* gene polymorphisms in Korean men might not only be associated with prostate cancer risk but also significantly related to pathologic stage and Gleason score. However, current limitation for small cohort with not-healthy control group might have false positive effects. These results should be validated via further large-scale studies.

Keywords: AMACR, polymorphism, genetic variants, prostate cancer, prostate cancer biomarker

Introduction

Prostate cancer remains the second leading cause of cancer deaths in the Western world [1]. Similarly, in Korea, the incidence rate of prostate cancer has rapidly increased during the last decade [2]. Prostate cancer is also one of the major contributors to cancer-related morbidity. Although epidemiological investigations over several decades have studied exogenous risk factors for prostate cancer, including diet, occupation, and sexually transmitted agents, the only established risk factors for this disease are age, ethnicity, and family history of prostate cancer [3]. Western diet has been associated with a higher relative risk of prostate cancer, and fat is a principal and distinguishing component of the Western diet. Alpha-methylacyl-CoA racemase (*AMACR*) metabolizes dietary fatty acids [4] and is a well-established prostate cancer tissue biomarker [5].

The *AMACR* gene is normally expressed in several tissues including the prostate and plays a critical role in the metabolism of branched-chain fatty acid molecules [4, 6, 7]. *AMACR* expression has been shown to be highest in localized prostate cancer and subsequent decreases in metastatic prostate cancer are associated with progression and cancer-specific death [8, 9].

Evidence has been presented to suggest that polymorphisms within the *AMACR* gene may be associated with prostate cancer risk. A number of genome-wide linkage studies in hereditary prostate cancer (HPC) families implicate 5p13, the chromosomal region of *AMACR*, as a candidate susceptibility locus [10-15].

Two studies have been conducted to investigate whether sequence variants of *AMACR* alter the risk for familial prostate cancer [16, 17]. Zheng et al. [16] found four missense changes had significantly different genotype frequencies between HPC cases and unaffected controls and haplotype analysis of the M9V and D175G single nucleotide polymorphisms (SNPs) provided stronger evidence for an association. Subsequent to this initial investigation, a study of brothers discordant for the diagnosis of prostate cancer from familial and early-onset prostate cancer families, found significant evidence for prostate cancer association with the M9V polymorphism [17].

Recently, three additional studies have been conducted to investigate the association between sporadic prostate cancer and *AMACR* gene variants [18, 19]. Lindstrom et al. [18] screened 1,461 cases and 796 controls from Sweden for 46 polymorphisms including four *AMACR* variants. No association was observed for any of the AMACR variants investigated, regardless of whether an additive, dominant, or recessive genetic model was used [18]. The Cancer Genetic Markers of Susceptibility (CGEMS) project genotyped 1,177 cases and 1,105 controls for 19 SNPs across the AMACR gene region and found no association with prostate cancer (http://cgems.cancer.gov). Daugherty et al. [19] screened 1,318 cases and 1,842 controls from multiple centers throughout the United States for 5 non-synonymous and two intronic *AMACR* variants. While no statistically significant associations with prostate cancer were noted, risks for prostate cancer tended to be lower in homozygote white carriers of the variant alleles at M9V, D175G, S201L, and K277E among regular ibuprofen users [19]. Lee et al. [20] assessed 194 cases and 169 controls for 17 SNPs in the *AMACR* gene in Korean men, and found rs2278008 (E227K) tended to lower prostate cancer risk.

In this study, we investigated the potential relationship between sequence variants in the *AMACR* gene and sporadic prostate cancer risk in a Korean study cohort known to be an ethnically homogenous population [21].

Materials and methods

Study population

This study was approved by the institutional review board of Chung-Ang University Hospital and Seoul National University Bundang Hospital (IRB nos. C2008035 and B-0905/075-011, respectively). Both the prostate cancer and BPH groups comprised a population of older men treated for urological problems at Chung-Ang University Hospital (Seoul, Korea) and Seoul National University Bundang Hospital (Gyeonggi, Seoul, Korea). We excluded patients who had undergone prior biopsies or the surgical treatment of prostate disease before receiving a biopsy. Peripheral blood leukocyte samples were obtained before the prostate biopsy for genotyping from 445 men (prostate cancer =272; BPH=173) and stored at -80°C. All 445 men underwent multi (≥12)-core transrectal ultrasound-guided biopsy for the evaluation of elevated PSA levels (≥3 ng/ml), abnormal digital rectal exams or hypoechoic lesions, as detected using prostate ultrasound. In all men, the prostate was routinely biopsied bilaterally near the base, mid-gland region and apex, with at least six biopsies per side. If necessary, additional biopsies were obtained to evaluate suspicious lesions. Among 173 patients enrolled in the BPH group, which was negative for malignancy in prostate biopsy, 135 patients underwent TURP owing to lower urinary tract symptoms.

After TURP, all specimens were shown to be benign by a pathological examination. BPH samples obtained from patients and confirmed to be pathologically negative were used as the control group for reducing selection bias. Most of the 272 prostate cancer patients underwent radical prostatectomy, and eight patients who had metastatic lesions in a preoperative radiologic evaluation underwent hormonal therapy plus external radiotherapy. Five patients with prostate cancer were enrolled in a watchful waiting protocol owing to their poor medical condition. Written informed consent was obtained from all study participants. Blood samples were collected in tubes containing sodium EDTA. The QIAamp Blood Extraction kit (Qiagen,

Table 1. Study characteristics of prostate cancer cases and controls

	Cases (Prostate cancer)	Controls (BPH)	*P*-value
N	272	173	
Age (year) ± SD	68.2 ± 6.8	67.3 ± 8.8	0.85
BMI (kg/m^2) ± SD	24.1 ± 3.3	24.0 ± 3.0	0.41
Prostate volume (cm^3) ± SD	37.2 ± 18.6	48.4 ± 26.2	0.02
PSA (ng/ml) ± SD	48.2 ± 192.8	5.2 ± 6.7	<0.01
Gleason score, n (%)			
≤6	29 (11)		
7	202 (75)		
≥8	39 (14)		
Clinical stage, n (%)			
Localized	252 (92.6)		
Locally advanced	10 (3.7)		
Metastatic	8 (2.9)		
Unknown	2 (0.8)		
Pathologic stage, n (%)			
Localized (T2)	152 (60.3)		
Advanced (≥T3)	100 (39.7)		

BPH, benign prostatic hyperplasia; BMI, body mass index; PSA, prostate specific antigen.

Seoul, Korea) was used for DNA extraction. The PSA level was classified as low (PSA<4 ng/ml), intermediate (4≤PSA<10 ng/ml) and high (10 ng/ml≤PSA). The Gleason score was classified as low (≤6), intermediate (7) or high (8≤). The pathological stages were categorized as localized (T1 or T2 N0M0), locally advanced (T3 or T4 N0M0) and metastatic (TxN+ or M+) on the basis of pathological and/or radiological reports. The clinical characteristics of the cases were similar to a previous Korean study [22].

SNP selection and genotyping

In this study, we selected 21 SNPs from two international databases (International HapMap and NCBI dbSNPs). SNP selection from the International HapMap database (Han Chinese and Japanese) was carried out as follows: (1) extraction of all genotypes from CHB and JPN populations in the *AMACR* gene region using HapMart of the International HapMap database (version: release #27; http://www.hapmap.org); (2) the calculation of minor allele frequency (MAF) and linkage disequilibrium (LD) using Haploview software (Cambridge, USA; http://www.broad.mit.edu/mpg/haploview); and (3) selection of SNPs having MAF>0.05 and tagging SNPs if several SNPs showed high LD>0.98. Furthermore, we added the SNPs from NCBI dbSNPs in the *AMACR* gene region. The selection criteria included location (SNPs in exons were preferred) and amino acid changes (non-synonymous SNPs were preferred).

Genotyping was performed at the multiplex level using the Illumina Golden Gate genotyping system [23]. Briefly, approximately 250 ng genomic DNA extracted from the blood of each individual was used to genotype each sample that underwent DNA activation, binding to paramagnetic particles, hybridization to oligonucleotides, washing, extension, ligation, amplification by PCR and hybridization to the Beadplate in an appropriate hybridization buffer. Image intensities were scanned by BeadXpress Reader, and genotyped using the Genome Studio software (Illumina Inc., USA). The genotype quality score for retaining data was set at 0.25. A total of 21 SNPs were successfully genotyped in the 445 DNA samples. All SNPs showed a call rate higher than 98% in cases or controls. Ten samples were randomly selected for genotyping in duplicate. Concordance among duplicate samples was 100%. The overall call rate for all SNPs was 99.8%.

Statistics

SNP genotype frequencies were examined for Hardy-Weinberg equilibrium (HWE) using the χ^2 statistic and all were found to be consistent (P>0.05) with HWE among Korean controls (**Table 2**). Data were analyzed using unconditional logistic regression to calculate an odds ratio as an estimate of relative risk of prostate cancer associated with SNP genotypes [24].

To determine the association between the genotype and haplotype distributions of patients and controls, logistic regression analysis was carried out to control for age (continuous value) as a covariate to eliminate or reduce any conflicts that might influence the findings. The significant associations are shown in bold face (P≤0.05). In analyzing a model in which a codominant (additive) effect of the variant (V)

Table 2. Frequencies of *AMACR* single-nucleotide polymorphisms in prostate cancer patients and normal controls in the Korean Population

SNPID	Position	AA Change	Alleles	Major	Hetero	Minor	Total	MAF	Heterozygosity	HWE
rs194125	Promoter	.	C>A	323	110	10	443	0.147	0.250	0.861
rs3195676	CDS	V9M	G>A	171	204	60	435	0.372	0.467	0.946
rs34689	Intron	.	T>G	335	89	12	436	0.130	0.226	0.047
rs34687	Intron	.	G>A	342	89	13	444	0.130	0.225	0.019
rs10941112	CDS	G175D	G>A	174	210	60	444	0.372	0.467	0.789
rs4866402	Intron	.	C>A	329	109	7	445	0.138	0.238	0.551
rs34678	Intron	.	T>C	187	198	60	445	0.357	0.459	0.510
rs10941110	Intron	.	G>A	174	210	60	444	0.372	0.467	0.789
rs34677	CDS	Q239H	G>T	342	88	14	444	0.131	0.227	0.007
rs34676	Intron	.	T>G	187	197	61	445	0.358	0.460	0.430
rs168803	Intron	.	T>G	244	161	40	445	0.271	0.395	0.077
rs840409	Intron	.	C>G	336	95	14	445	0.138	0.238	0.029
rs253190	Intron	.	C>T	335	95	14	444	0.139	0.239	0.029
rs16892096	Intron	.	T>C	341	98	6	445	0.124	0.217	0.727
rs10472909	Intron	.	A>T	173	210	60	443	0.372	0.467	0.767
rs2652130	Intron	.	A>C	253	163	29	445	0.248	0.373	0.692
rs250414	Intron	.	C>T	173	211	58	442	0.370	0.466	0.613
rs12659370	3' UTR	.	C>A	255	165	24	444	0.240	0.365	0.687
rs16892066	3' UTR	.	G>A	329	105	9	443	0.139	0.239	0.854
rs16892064	3' UTR	.	G>A	330	105	9	444	0.139	0.239	0.848
rs840380	3' UTR	.	A>G	289	134	22	445	0.200	0.320	0.213

Abbreviations: MAF, Minor allele frequencies; HWE, Hardy-Weinberg equilibrium.

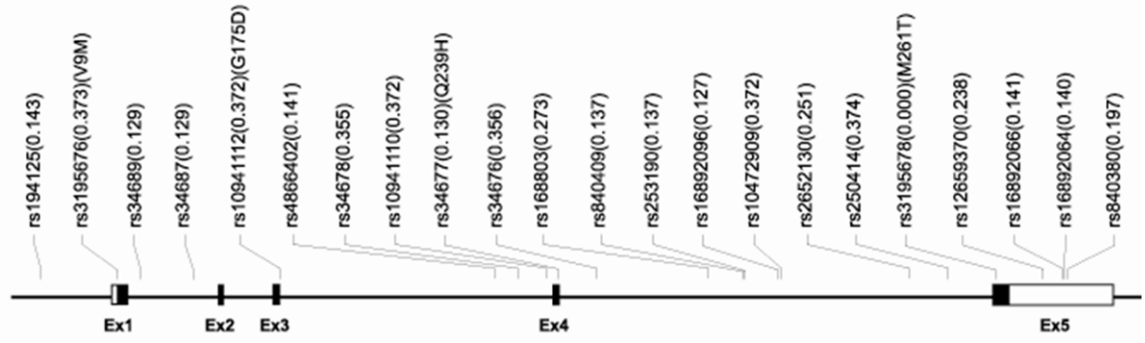
allele was assumed, the genotypes wild (W)/W, W/V and V/V were coded as 0, 1 and 2, respectively. When a dominant effect was assumed, genotype W/W was coded as 0, and W/V and V/V were coded as 1, whereas W/V and V/V were scored as 0 and V/V was scored as 1 in a model that assumed a recessive effect [25]. Lewontin's D' (|D'|) and the LD coefficient r^2 were examined to measure LD between all pairs of biallelic loci [26]. The haplotypes were inferred from the successfully genotyped SNPs using PHASE algorithm ver. 2.0 [27], using SAS version 9.1 (SAS, Cary, NC, USA). The effective number of independent marker loci was calculated to correct multiple testing, using the software SNPSpD (http://www.genepi.qimr.edu.au/general/daleN/SNPSpD/), which is based on the spectral decomposition of matrices of pairwise LD between SNPs [28]. The resulting number of independent marker loci (23.1) was applied to correct for multiple testing. All *P*-values from the results were corrected for multiple testing by controlling for the false discovery rate [29].

Results

Twenty-one sequence variants in the *AMACR* gene were examined in this study; 1 was located in the promoter; 13 in introns; 3 in exons; and 4 in the 3'-untranslated region (UTR) (**Figure 1A**). The measured LD among 21 SNPs was determined by calculating Lewontin's D' and r^2 values; the results showed that these SNPs were divided into haplotype blocks (**Figure 1B** and **1C**). The clinical characteristics of the prostate cancer case and controls are shown in **Table 1**.

The genotype frequencies for each polymorphism in both the prostate cancer group and the control group were analyzed using a logistic regression model (**Table 3**). Among the 21 polymorphisms examined, the 8 polymorphisms (*rs3195676, rs10941112, rs4866402, rs34678, rs10941110, rs34676, rs16892096,* and *rs250414*) were found to be significantly associated with prostate cancer risk. The *rs3195676* (age-adjusted odds ratio [OR]=0.74, P=0.05), *rs10941112* (OR=0.74, P=0.04), *rs4866402*

A **Map of AMACR(alpha-methylacyl-CoA racemase) on chromosome 5p13(20.3 kb)**



B **Haplotypes in AMACR**

Block 1

Hap.	*rs3195676*	*rs34689*	*rs34687*	*rs10941112*	*rs4866402*	*rs34678*	*rs10941110*	*rs34677*	*rs34676*	*rs168803*	*rs840409*	*rs253190*	*rs16892096*	*rs10472909*	*rs2652130*	*rs250414*	Freq.
ht1	A	T	G	A	C	T	A	G	T	T	C	C	T	T	A	T	0.337
ht2	G	T	G	G	C	C	C	G	G	T	C	C	T	A	A	C	0.306
ht3	G	T	G	G	A	T	G	G	T	G	C	C	C	A	C	C	0.111
ht4	G	G	A	G	C	T	G	T	T	G	G	T	T	A	C	C	0.111
ht5	G	T	G	G	C	C	G	G	G	T	C	C	T	A	A	T	0.024
ht6	A	T	G	A	C	T	A	G	T	T	C	C	T	T	A	C	0.023
ht7	G	T	G	G	A	T	G	G	T	G	C	C	T	T	A	C	0.022
ht8	G	G	A	G	C	T	G	T	T	G	G	T	T	A	A	C	0.014
ht9	G	T	G	G	C	C	G	G	G	T	C	C	C	A	C	C	0.013
Others.	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	0.040

Block2

Hap.	*rs12659370*	*rs16892066*	*rs16892064*	*rs840380*	
ht1	C	G	G	A	*0.425*
ht2	A	G	G	A	*0.238*
ht3	C	G	G	G	*0.197*
ht4	C	A	A	A	*0.140*

C **LDs among AMACR polymorphisms**

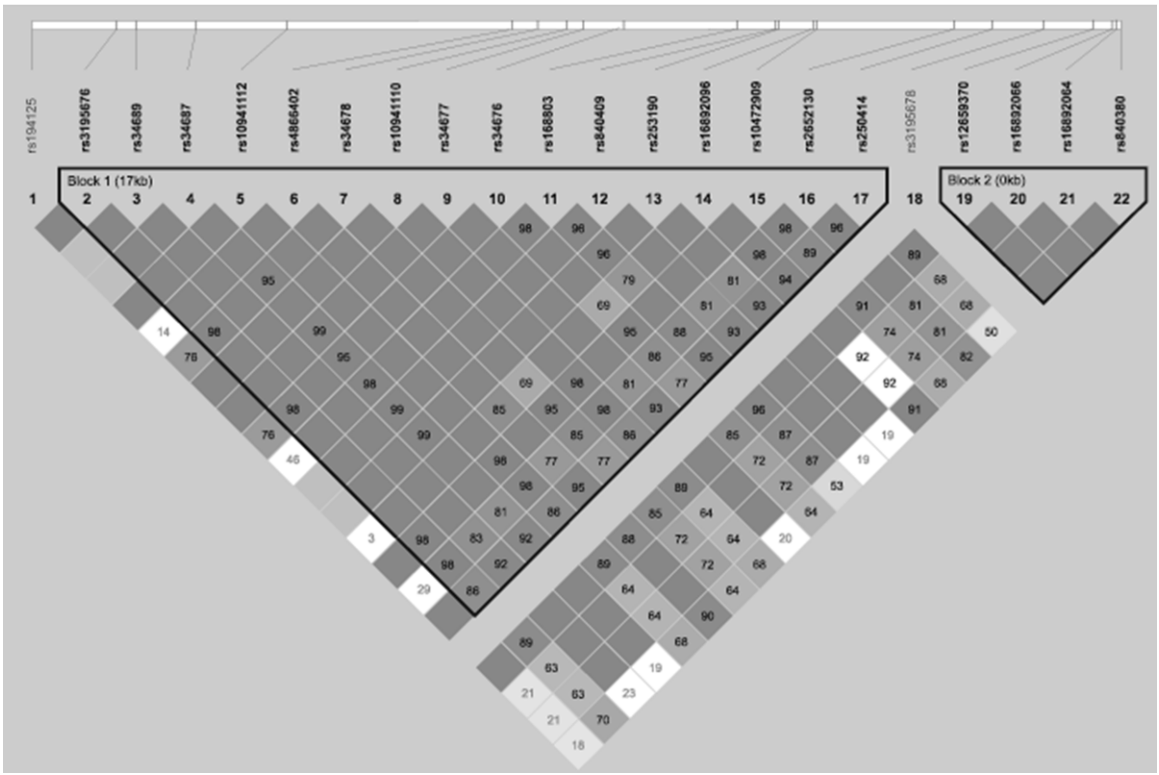


Figure 1. A. Genetic map of *AMACR* (alpha-methylacyl-CoA racemase) on chromosome 5p13. Coding exons are marked by black blocks, and 5' and 3' UTRs by white blocks. B. Haplotypes of *AMACR*. 'Others' category contains rare haplotypes. C. Linkage disequilibrium (LD) among *AMACR* polymorphisms.

Table 3. Logistic regression analysis of *AMACR* single-nucleotide polymorphisms with the risk of prostate cancer in the Korean Population

SNPID	Minor Allele Frequency		Co-dominant		Dominant		Recessive	
	Pca (n=272)	BPH (n=173)	Age adjusted OR (95% CI)	*P*-value	Age adjusted OR (95% CI)	*P*-value	Age adjusted OR (95% CI)	*P*-value
rs194125	0.150	0.142	1.00 (0.67-1.48)	0.99	0.97 (0.62-1.51)	0.88	1.34 (0.33-5.48)	0.68
rs3195676	0.345	0.415	0.74 (0.56-1.00)	**0.05**	0.65 (0.43-0.99)	**0.04**	0.73 (0.41-1.30)	0.28
rs34689	0.142	0.111	1.28 (0.85-1.94)	0.24	1.31 (0.81-2.11)	0.27	1.65 (0.43-6.34)	0.47
rs34687	0.142	0.110	1.30 (0.86-1.95)	0.22	1.32 (0.82-2.12)	0.26	1.76 (0.47-6.68)	0.40
rs10941112	0.343	0.416	0.74 (0.55-0.98)	**0.04**	0.65 (0.43-0.97)	**0.04**	0.72 (0.41-1.27)	0.26
rs4866402	0.121	0.165	0.64 (0.42-0.95)	**0.03**	0.59 (0.38-0.92)	**0.02**	0.82 (0.17-3.92)	0.81
rs34678	0.388	0.309	1.45 (1.08-1.95)	**0.01**	1.76 (1.18-2.63)	**0.006**	1.35 (0.75-2.44)	0.32
rs10941110	0.343	0.416	0.74 (0.55-0.98)	**0.04**	0.65 (0.43-0.97)	**0.04**	0.72 (0.41-1.27)	0.26
rs34677	0.144	0.110	1.31 (0.87-1.97)	0.19	1.33 (0.82-2.14)	0.25	1.94 (0.52-7.23)	0.32
rs34676	0.390	0.309	1.46 (1.09-1.95)	**0.01**	1.76 (1.18-2.63)	**0.006**	1.38 (0.77-2.49)	0.28
rs168803	0.267	0.277	0.90 (0.67-1.22)	0.51	0.86 (0.58-1.28)	0.46	0.93 (0.47-1.85)	0.83
rs840409	0.151	0.118	1.31 (0.88-1.95)	0.19	1.32 (0.83-2.10)	0.25	1.93 (0.52-7.21)	0.33
rs253190	0.151	0.119	1.30 (0.87-1.94)	0.20	1.31 (0.82-2.08)	0.26	1.92 (0.51-7.14)	0.33
rs16892096	0.108	0.147	0.65 (0.43-1.00)	**0.05**	0.62 (0.39-0.99)	**0.04**	0.66 (0.13-3.50)	0.63
rs10472909	0.351	0.407	0.79 (0.59-1.06)	0.12	0.73 (0.49-1.10)	0.13	0.76 (0.43-1.34)	0.34
rs2652130	0.239	0.263	0.85 (0.62-1.17)	0.31	0.86 (0.58-1.28)	0.46	0.66 (0.30-1.44)	0.29
rs250414	0.338	0.419	0.72 (0.53-0.96)	**0.03**	0.66 (0.44-0.99)	**0.04**	0.63 (0.36-1.13)	0.12
rs12659370	0.220	0.272	0.76 (0.55-1.06)	0.11	0.70 (0.47-1.05)	0.08	0.81 (0.34-1.92)	0.64
rs16892066	0.153	0.116	1.38 (0.91-2.09)	0.13	1.40 (0.89-2.23)	0.15	1.88 (0.38-9.37)	0.44
rs16892064	0.153	0.116	1.39 (0.91-2.11)	0.13	1.41 (0.89-2.24)	0.14	1.90 (0.38-9.47)	0.44
rs840380	0.217	0.173	1.31 (0.92-1.85)	0.13	1.34 (0.89-2.04)	0.17	1.66 (0.62-4.45)	0.31
AMACR_B1_ht1	0.303	0.384	0.70 (0.52-0.94)	**0.02**	0.60 (0.40-0.90)	**0.01**	0.69 (0.38-1.27)	0.23
AMACR_B1_ht2	0.342	0.260	1.49 (1.09-2.02)	**0.01**	1.76 (1.18-2.62)	**0.005**	1.35 (0.68-2.67)	0.39
AMACR_B1_ht3	0.099	0.121	0.76 (0.49-1.18)	0.22	0.74 (0.46-1.20)	0.22	0.66 (0.13-3.50)	0.63
AMACR_B1_ht4	0.116	0.104	1.08 (0.70-1.67)	0.74	1.13 (0.69-1.84)	0.63	0.77 (0.18-3.39)	0.73
AMACR_B2_ht1	0.412	0.439	0.87 (0.66-1.16)	0.35	0.82 (0.53-1.24)	0.34	0.87 (0.52-1.46)	0.59
AMACR_B2_ht2	0.219	0.272	0.76 (0.55-1.06)	0.10	0.70 (0.47-1.04)	0.08	0.81 (0.34-1.91)	0.63
AMACR_B2_ht3	0.217	0.173	1.31 (0.92-1.85)	0.13	1.34 (0.89-2.04)	0.17	1.66 (0.62-4.45)	0.31
AMACR_B2_ht4	0.153	0.116	1.38 (0.91-2.10)	0.13	1.41 (0.89-2.23)	0.15	1.89 (0.38-9.45)	0.44

Minor allele frequencies and *P*-values for logistic analyses of three alternative models (co-dominant, dominant, and recessive) controlling for age as covariate are shown. Significant associations are shown in boldface (*P*-value ≤0.05). Abbreviations: CI, confidence interval; OR, odds ratio; PCa, prostate cancer.

(OR=0.64, P=0.03), *rs10941110* (OR=0.74, P=0.04), *rs16892096* (OR=0.65, P=0.05) and *rs250414* (OR=0.72, P=0.03) had negative correlation with prostate cancer compared with the control group. The *rs34678* (OR=1.45, P=0.01) and *rs34676* (OR=1.46, P=0.01) had positive correlation with prostate cancer compared with the control group (**Table 3**). No significant association was found between the presence of prostate cancer and the other 13 SNPs. In addition, a haplotype association test was performed on 8 common haplotypes (freq. >0.05) within the 2 haplotype blocks. The 2 haplotypes, *AMACR_B1_ht* (OR=0.70, P=0.02) and *AMACR_B1_ht2* (OR=1.49, P=0.01) showed a significant association with risk of prostate cancer (**Table 3**). In the analysis of logistic regression model of *AMACR* polymorphisms according to pathological stage, the 8 SNPs (*rs3195676, rs10941112, rs10941110, rs16-8803, rs16892096, rs10472909, rs26521-30, and rs12659370)* and the 1 haplotype

Table 4. Logistic analysis of *AMACR* polymorphisms according to pathological stage criteria

SNP ID	Minor Allele Frequency		Co-dominant		Dominant		Recessive	
	T2 (n=100)	≥T3 (n=152)	Age adjusted OR (95% CI)	*P*-value	Age adjusted OR (95% CI)	*P*-value	Age adjusted OR (95% CI)	*P*-value
rs194125	0.161	0.138	1.19 (0.72-1.96)	0.51	1.08 (0.61-1.93)	0.79	3.23 (0.58-18.05)	0.18
rs3195676	0.411	0.309	1.56 (1.06-2.30)	**0.02**	1.62 (0.95-2.76)	0.08	2.20 (1.01-4.79)	**0.05**
rs34689	0.109	0.155	0.69 (0.40-1.16)	0.16	0.59 (0.32-1.12)	0.11	0.88 (0.20-3.77)	0.86
rs34687	0.108	0.154	0.68 (0.40-1.15)	0.15	0.59 (0.31-1.10)	0.10	0.89 (0.21-3.83)	0.87
rs10941112	0.412	0.309	1.58 (1.07-2.32)	**0.02**	1.63 (0.96-2.76)	0.07	2.26 (1.04-4.92)	**0.04**
rs4866402	0.082	0.137	0.56 (0.31-1.04)	0.07	0.59 (0.31-1.13)	0.11	.	.
rs34678	0.397	0.390	1.04 (0.71-1.53)	0.84	0.90 (0.53-1.53)	0.69	1.42 (0.69-2.94)	0.34
rs10941110	0.412	0.309	1.58 (1.07-2.32)	**0.02**	1.63 (0.96-2.76)	0.07	2.26 (1.04-4.92)	**0.04**
rs34677	0.108	0.158	0.67 (0.40-1.13)	0.14	0.59 (0.31-1.11)	0.10	0.74 (0.18-3.06)	0.68
rs34676	0.397	0.393	1.03 (0.70-1.50)	0.90	0.90 (0.53-1.53)	0.69	1.34 (0.65-2.74)	0.43
rs168803	0.191	0.297	0.58 (0.38-0.89)	**0.01**	0.52 (0.30-0.88)	**0.02**	0.43 (0.15-1.22)	0.11
rs840409	0.124	0.160	0.75 (0.46-1.25)	0.27	0.70 (0.38-1.28)	0.24	0.75 (0.18-3.08)	0.69
rs253190	0.124	0.160	0.75 (0.46-1.25)	0.27	0.70 (0.38-1.28)	0.24	0.75 (0.18-3.08)	0.69
rs16892096	0.067	0.127	0.50 (0.26-0.96)	**0.04**	0.51 (0.25-1.02)	0.06	.	.
rs10472909	0.418	0.319	1.56 (1.06-2.29)	**0.02**	1.63 (0.96-2.77)	0.07	2.11 (0.98-4.54)	0.06
rs2652130	0.186	0.263	0.63 (0.40-0.98)	**0.04**	0.58 (0.34-0.99)	**0.05**	0.49 (0.15-1.60)	0.24
rs250414	0.387	0.313	1.40 (0.95-2.06)	0.09	1.31 (0.77-2.21)	0.32	2.26 (1.02-5.05)	**0.05**
rs12659370	0.268	0.198	1.56 (1.00-2.41)	**0.05**	1.50 (0.89-2.55)	0.13	3.25 (0.95-11.18)	0.06
rs16892066	0.124	0.168	0.69 (0.41-1.18)	0.18	0.58 (0.32-1.05)	0.07	2.35 (0.38-14.44)	0.36
rs16892064	0.124	0.168	0.69 (0.41-1.18)	0.17	0.58 (0.32-1.05)	0.07	2.35 (0.38-14.44)	0.36
rs840380	0.227	0.220	1.06 (0.70-1.62)	0.78	1.01 (0.60-1.72)	0.96	1.38 (0.48-3.97)	0.54
AMACR_B1_ht1	0.351	0.277	1.41 (0.96-2.07)	0.08	1.33 (0.79-2.22)	0.28	2.37 (1.04-5.44)	**0.04**
AMACR_B1_ht2	0.361	0.333	1.16 (0.78-1.72)	0.47	1.01 (0.60-1.70)	0.97	1.89 (0.82-4.36)	0.14
AMACR_B1_ht3	0.062	0.113	0.53 (0.27-1.03)	0.06	0.55 (0.26-1.13)	0.10	.	.
AMACR_B1_ht4	0.098	0.123	0.75 (0.43-1.33)	0.33	0.62 (0.32-1.20)	0.16	2.16 (0.35-13.24)	0.41
AMACR_B2_ht1	0.381	0.417	0.83 (0.57-1.20)	0.32	0.70 (0.41-1.20)	0.20	0.94 (0.46-1.90)	0.86
AMACR_B2_ht2	0.268	0.197	1.57 (1.01-2.43)	**0.05**	1.52 (0.90-2.57)	0.12	3.28 (0.95-11.25)	0.06
AMACR_B2_ht3	0.227	0.220	1.06 (0.70-1.62)	0.78	1.01 (0.60-1.72)	0.96	1.38 (0.48-3.97)	0.54
AMACR_B2_ht4	0.124	0.167	0.70 (0.41-1.19)	0.19	0.58 (0.32-1.06)	0.08	2.37 (0.39-14.54)	0.35

Minor allele frequencies and *P*-values for logistic analyses of three alternative models (co-dominant, dominant, and recessive) controlling for age as covariate are shown. Significant associations are shown in boldface (*P*-value ≤0.05). Abbreviations: CI, confidence interval; OR, odds ratio.

(*AMACR_B2_ht2*) were found to be significantly associated with pathological stage (**Table 4**). The *rs3195676* (OR=1.56, P=0.02), *rs10941112* (OR=1.58, P=0.02), *rs10941110* (OR=1.58, P=0.02), *rs10472909* (OR=1.56, P=0.02), *rs12659370* (OR=1.56, P=0.05) and the *AMACR_B2_ht2* (OR=1.57, P=0.05) had positive correlation with higher pathological stage. The *rs168803* (OR=0.58, P=0.01), *rs16892096* (OR=0.50, P=0.04) and *rs2652130* (OR=0.63, P=0.04) had negative correlation with pathological stage. In the analysis of logistic regression model of *AMACR* polymorphisms according to Gleason score, the 3 SNPs (*rs16892066*, *rs16892064,* and *rs840380*) and the 2 haplotypes (*AMACR_B2_ht3* and *AMACR_B2_ht4*) were found to be significantly associated with Gleason score (**Table 5**). The *rs840380* (OR=1.65, P=0.03) and the *AMACR_B2_ht3* (OR=1.65, P=0.03) had positive correlation with higher Gleason score. The *rs16892066* (OR=0.55, P=0.03), *rs16892064* (OR=0.54, P=0.03) and the *AMACR_B2_ht4* (OR=0.55, P=0.03) had negative correlation

Table 5. Logistic analysis of *AMACR* polymorphisms according to Gleason score criteria

SNP ID	Minor Allele Frequency			Co-dominant		Dominant		Recessive	
	≥8 (n=39)	7 (n=202)	≤6 (n=29)	Age adjusted OR (95% CI)	*P*-value	Age adjusted OR (95% CI)	*P*-value	Age adjusted OR (95% CI)	*P*-value
rs194125	0.149	0.138	0.149	1.08 (0.63-1.84)	0.79	1.12 (0.61-2.07)	0.72	0.85 (0.15-4.78)	0.86
rs3195676	0.327	0.370	0.345	1.17 (0.78-1.77)	0.45	1.10 (0.63-1.93)	0.74	1.59 (0.69-3.65)	0.28
rs34689	0.146	0.111	0.139	1.00 (0.58-1.70)	0.99	0.86 (0.45-1.64)	0.64	2.18 (0.52-9.14)	0.29
rs34687	0.147	0.121	0.139	0.95 (0.57-1.60)	0.85	0.88 (0.46-1.66)	0.69	1.34 (0.33-5.52)	0.69
rs10941112	0.326	0.362	0.344	1.20 (0.80-1.80)	0.37	1.14 (0.66-1.98)	0.64	1.61 (0.71-3.68)	0.26
rs4866402	0.131	0.121	0.122	0.74 (0.41-1.34)	0.32	0.72 (0.38-1.39)	0.33	0.70 (0.07-6.83)	0.76
rs34678	0.389	0.397	0.389	0.99 (0.67-1.48)	0.97	1.07 (0.61-1.88)	0.81	0.85 (0.39-1.84)	0.68
rs10941110	0.326	0.362	0.344	1.20 (0.80-1.80)	0.37	1.14 (0.66-1.98)	0.64	1.61 (0.71-3.68)	0.26
rs34677	0.149	0.121	0.141	0.96 (0.57-1.59)	0.86	0.88 (0.47-1.67)	0.70	1.29 (0.33-5.00)	0.72
rs34676	0.391	0.397	0.391	0.99 (0.67-1.47)	0.96	1.07 (0.61-1.88)	0.81	0.85 (0.40-1.82)	0.67
rs168803	0.282	0.241	0.265	0.84 (0.55-1.27)	0.40	0.79 (0.46-1.37)	0.40	0.79 (0.31-2.04)	0.63
rs840409	0.156	0.121	0.148	1.01 (0.61-1.67)	0.98	0.96 (0.51-1.79)	0.89	1.29 (0.33-5.01)	0.72
rs253190	0.156	0.121	0.148	1.01 (0.61-1.67)	0.98	0.96 (0.51-1.79)	0.89	1.29 (0.33-5.01)	0.72
rs16892096	0.124	0.069	0.109	0.88 (0.47-1.63)	0.68	0.79 (0.40-1.56)	0.50	2.84 (0.28-29.17)	0.38
rs10472909	0.336	0.362	0.351	1.20 (0.80-1.80)	0.37	1.14 (0.66-1.99)	0.63	1.60 (0.71-3.62)	0.26
rs2652130	0.265	0.138	0.237	0.98 (0.63-1.54)	0.94	0.90 (0.52-1.57)	0.72	1.39 (0.45-4.32)	0.57
rs250414	0.328	0.357	0.339	1.11 (0.73-1.67)	0.63	0.98 (0.56-1.70)	0.93	1.65 (0.71-3.87)	0.25
rs12659370	0.209	0.207	0.219	1.35 (0.85-2.14)	0.21	1.40 (0.80-2.45)	0.24	1.65 (0.48-5.64)	0.42
rs16892066	0.157	0.224	0.154	0.55 (0.32-0.93)	**0.03**	0.56 (0.30-1.03)	0.06	0.21 (0.04-1.00)	**0.05**
rs16892064	0.157	0.224	0.154	0.54 (0.32-0.93)	**0.03**	0.56 (0.30-1.03)	0.06	0.21 (0.04-1.00)	**0.05**
rs840380	0.203	0.190	0.219	1.65 (1.05-2.59)	**0.03**	1.66 (0.94-2.93)	0.08	2.97 (1.02-8.64)	**0.05**
AMACR_B1_ht1	0.359	0.287	0.345	1.08 (0.72-1.62)	0.71	0.93 (0.54-1.60)	0.78	1.78 (0.75-4.26)	0.19
AMACR_B1_ht2	0.359	0.337	0.362	1.03 (0.68-1.55)	0.90	1.11 (0.64-1.93)	0.71	0.86 (0.36-2.05)	0.73
AMACR_B1_ht3	0.051	0.116	0.052	0.89 (0.47-1.68)	0.71	0.80 (0.40-1.60)	0.53	2.84 (0.28-29.17)	0.38
AMACR_B1_ht4	0.090	0.124	0.069	1.04 (0.58-1.87)	0.90	0.88 (0.45-1.73)	0.72	4.06 (0.68-24.12)	0.12
AMACR_B2_ht1	0.308	0.433	0.379	0.77 (0.52-1.14)	0.19	0.70 (0.39-1.24)	0.22	0.72 (0.34-1.52)	0.39
AMACR_B2_ht2	0.282	0.208	0.207	1.35 (0.85-2.15)	0.21	1.40 (0.80-2.46)	0.24	1.66 (0.48-5.66)	0.42
AMACR_B2_ht3	0.321	0.203	0.190	1.65 (1.05-2.59)	**0.03**	1.66 (0.94-2.93)	0.08	2.97 (1.02-8.64)	**0.05**
AMACR_B2_ht4	0.090	0.156	0.224	0.55 (0.32-0.93)	**0.03**	0.56 (0.30-1.04)	0.06	0.21 (0.04-1.00)	**0.05**

Minor allele frequencies and *P*-values for logistic analyses of three alternative models (co-dominant, dominant, and recessive) controlling for age as covariate are shown. Significant associations are shown in boldface (*P*-value ≤0.05). Abbreviations: CI, confidence interval; OR, odds ratio.

with Gleason score. There were no associations detected between the 21 SNPs examined and PSA level in this study (data not shown).

Discussion

AMACR is a key enzyme in the β-oxidative catabolic metabolism of fatty acids and has been found to be upregulated in a variety of cancers, including prostate cancer [5]. The mechanism by which *AMACR* affects prostate cancer risk is not fully understood. One possibility is that the reactive oxygen species created from the enzymatic activity of *AMACR* leads to DNA damage [30]. Alternatively, *AMACR* may impact carcinogenesis by affecting levels of the androgen receptor and IGF-1 [31].

Sequence variants of AMACR have been previously investigated to find their association with prostate cancer risk [16-20, 32, 33]. In a Korean population, we found that the 2 SNPs (*rs34678* and *rs34676*) and 1 haplotype (*AMACR_B1_ht2*) had a significant positive association with risk of prostate cancer. We also found that the 6 *AMACR* polymorphisms (*rs3195676*, *rs10941112*, *rs4866402, rs10941110, rs16892096,* and *250414*) and 1 haplotype (*AMACR_B1_ht*) had a significant negative correlation with risk of prostate cancer. Among them, the2 SNPs (*rs3195676* and *rs10941112*) are coding non-synonymous SNPs that result in an amino acid change at position 9 (valine to methionine) and at position 175 (glycine to aspartate). An Australian study

found that the two *AMACR* SNPs (*rs3195676* and *rs10941112*) were associated with reduced risks of sporadic prostate cancer [33]. Consistent with the Australian study, we found the same 2*AMACR* SNPs (*rs3195676* and *rs10941112*) were associated with reduced risks for prostate cancer in Korean men. In this study, we found the 8 SNPs (*rs3195676, rs10941112, rs10941110, rs168803, rs16892096, rs10472909, rs2652130, and rs12659370)* and 1 haplotype (*AMACR_B2_ht2*) were found to be significantly associated with pathological stage and the 3 SNPs (*rs16892066*, *rs16892064,* and *rs840380*) and 2 haplotypes (*AMACR_B2_ht3* and *AMACR_B2_ht4*) were found to be significantly associated with Gleason score. Wright et al. [32] reported a reduction in the relative risk of less aggressive prostate cancer (localized stage, Gleason 2-7(3+4), PSA<20 ng/ml at diagnosis) with the1 AMACR polymorphism (rs2287939), but this polymorphism was not included in our study. The literature on *AMACR* SNPs and prostate cancer risk presents conflicting results. In two studies [16, 17], *rs2287939* was associated with a risk reduction in familial, but not sporadic, prostate cancer. The ORs for sporadic disease were similar, although non-significant in both studies. Two other studies found no significant associations between prostate cancer and *AMACR* SNPs [18, 19]. Lee et al. [20] assessed 194 cases and 169 controls for 17 SNPs in the *AMACR* gene in Korean men, and found the rs2278008 tended to lower prostate cancer risk. But this polymorphism was not evaluated in our study.

Our study had several limitations. Our analysis was based on a comparison of samples from patients with prostate cancer and samples from patients with non-malignant BPH as controls. Although our control group was proven as benign via a previous prostate biopsy, all the men in the BPH group were potentially at risk for the development of prostate cancer and may have had latent prostate cancer at the time of their designation as controls, leading to disease misclassification. In this study, we had limitation of only adjusting the age as covariate in logistic analysis, it should be necessary for controlling other health related factors.

Conclusions

Logistic regression analyses of this study suggested that some *AMACR* gene polymorphisms were associated with a significantly elevated risk of prostate cancer when compared with healthy controls. These results suggest that *AMACR* gene polymorphisms may alter susceptibility to prostate cancer and may possibly be used as biomarkers for the disease.

As racial/ethnic differences may exist, our study demonstrating an association between prostate cancer and *AMACR* gene polymorphisms is one of the efforts in an Asian population. Outside validation of these findings should be performed, especially to fish the relationships between several SNPs and prostate cancer-related factors that correlated with prognostic outcomes.

Acknowledgements

This research was supported by the Agriculture, Food and Rural Affairs Research Center Support Program, Ministry of Agriculture, Food and Rural Affairs.

Disclosure of conflict of interest

None.

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References

[1] Jemal A, Siegel R, Xu J and Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60: 277-300.

[2] Park SK, Sakoda LC, Kang D, Chokkalingam AP, Lee E, Shin HR, Ahn YO, Shin MH, Lee CW, Lee DH, Blair A, Devesa SS and Hsing AW. Rising prostate cancer rates in South Korea. Prostate 2006; 66: 1285-1291.

[3] Chan JM, Holick CN, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ and Giovannucci EL. Diet after diagnosis and the risk of prostate cancer progression, recurrence, and death (United States). Cancer Causes Control 2006; 17: 199-208.

[4] Wanders RJ, Vreken P, Ferdinandusse S, Jansen GA, Waterham HR, van Roermund CW and Van Grunsven EG. Peroxisomal fatty acid al-

pha- and beta-oxidation in humans: enzymology, peroxisomal metabolite transporters and peroxisomal diseases. Biochem Soc Trans 2001; 29: 250-267.

[5] Rubin MA, Zhou M, Dhanasekaran SM, Varambally S, Barrette TR, Sanda MG, Pienta KJ, Ghosh D and Chinnaiyan AM. alpha-Methylacyl coenzyme A racemase as a tissue biomarker for prostate cancer. JAMA 2002; 287: 1662-1670.

[6] Amery L, Fransen M, De Nys K, Mannaerts GP and Van Veldhoven PP. Mitochondrial and peroxisomal targeting of 2-methylacyl-CoA racemase in humans. J Lipid Res 2000; 41: 1752-1759.

[7] Ferdinandusse S, Denis S, L IJ, Dacremont G, Waterham HR and Wanders RJ. Subcellular localization and physiological role of alpha-methylacyl-CoA racemase. J Lipid Res 2000; 41: 1890-1896.

[8] Kuefer R, Varambally S, Zhou M, Lucas PC, Loeffler M, Wolter H, Mattfeldt T, Hautmann RE, Gschwend JE, Barrette TR, Dunn RL, Chinnaiyan AM and Rubin MA. alpha-Methylacyl-CoA racemase: expression levels of this novel cancer biomarker depend on tumor differentiation. Am J Pathol 2002; 161: 841-848.

[9] Rubin MA, Bismar TA, Andren O, Mucci L, Kim R, Shen R, Ghosh D, Wei JT, Chinnaiyan AM, Adami HO, Kantoff PW and Johansson JE. Decreased alpha-methylacyl CoA racemase expression in localized prostate cancer is associated with an increased rate of biochemical recurrence and cancer-specific death. Cancer Epidemiol Biomarkers Prev 2005; 14: 1424-1432.

[10] Camp NJ, Farnham JM and Cannon Albright LA. Genomic search for prostate cancer predisposition loci in Utah pedigrees. Prostate 2005; 65: 365-374.

[11] Goddard KA, Witte JS, Suarez BK, Catalona WJ and Olson JM. Model-free linkage analysis with covariates confirms linkage of prostate cancer to chromosomes 1 and 4. Am J Hum Genet 2001; 68: 1197-1206.

[12] Hsieh CL, Oakley-Girvan I, Balise RR, Halpern J, Gallagher RP, Wu AH, Kolonel LN, O'Brien LE, Lin IG, Van Den Berg DJ, Teh CZ, West DW and Whittemore AS. A genome screen of families with multiple cases of prostate cancer: evidence of genetic heterogeneity. Am J Hum Genet 2001; 69: 148-158.

[13] Maier C, Herkommer K, Hoegel J, Vogel W and Paiss T. A genomewide linkage analysis for prostate cancer susceptibility genes in families from Germany. Eur J Hum Genet 2005; 13: 352-360.

[14] Smith JR, Freije D, Carpten JD, Gronberg H, Xu J, Isaacs SD, Brownstein MJ, Bova GS, Guo H, Bujnovszky P, Nusskern DR, Damber JE, Bergh A, Emanuelsson M, Kallioniemi OP, Walker-Daniels J, Bailey-Wilson JE, Beaty TH, Meyers DA, Walsh PC, Collins FS, Trent JM and Isaacs WB. Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science 1996; 274: 1371-1374.

[15] Wiklund F, Gillanders EM, Albertus JA, Bergh A, Damber JE, Emanuelsson M, Freas-Lutz DL, Gildea DE, Goransson I, Jones MS, Jonsson BA, Lindmark F, Markey CJ, Riedesel EL, Stenman E, Trent JM and Gronberg H. Genome-wide scan of Swedish families with hereditary prostate cancer: suggestive evidence of linkage at 5q11.2 and 19p13.3. Prostate 2003; 57: 290-297.

[16] Zheng SL, Chang BL, Faith DA, Johnson JR, Isaacs SD, Hawkins GA, Turner A, Wiley KE, Bleecker ER, Walsh PC, Meyers DA, Isaacs WB and Xu J. Sequence variants of alpha-methylacyl-CoA racemase are associated with prostate cancer risk. Cancer Res 2002; 62: 6485-6488.

[17] Levin AM, Zuhlke KA, Ray AM, Cooney KA and Douglas JA. Sequence variation in alpha-methylacyl-CoA racemase and risk of early-onset and familial prostate cancer. Prostate 2007; 67: 1507-1513.

[18] Lindstrom S, Zheng SL, Wiklund F, Jonsson BA, Adami HO, Balter KA, Brookes AJ, Sun J, Chang BL, Liu W, Li G, Isaacs WB, Adolfsson J, Gronberg H and Xu J. Systematic replication study of reported genetic associations in prostate cancer: strong support for genetic variation in the androgen pathway. Prostate 2006; 66: 1729-1743.

[19] Daugherty SE, Shugart YY, Platz EA, Fallin MD, Isaacs WB, Pfeiffer RM, Welch R, Huang WY, Reding D and Hayes RB. Polymorphic variants in alpha-methylacyl-CoA racemase and prostate cancer. Prostate 2007; 67: 1487-1497.

[20] Lee SJ, Joung JY, Yoon H, Kim JE, Park WS, Seo HK, Chung J, Hwang JA, Hong SH, Nam S, Park S, Kim J, Lee KH and Lee YS. Genetic variations of alpha -methylacyl-CoA racemase are associated with sporadic prostate cancer risk in ethnically homogenous Koreans. Biomed Res Int 2013; 2013: 394285.

[21] Consortium HP-AS, Abdulla MA, Ahmed I, Assawamakin A, Bhak J, Brahmachari SK, Calacal GC, Chaurasia A, Chen CH, Chen J, Chen YT, Chu J, Cutiongco-de la Paz EM, De Ungria MC, Delfin FC, Edo J, Fuchareon S, Ghang H, Gojobori T, Han J, Ho SF, Hoh BP, Huang W, Inoko H, Jha P, Jinam TA, Jin L, Jung J, Kangwanpong D, Kampuansai J, Kennedy GC, Khurana P, Kim HL, Kim K, Kim S, Kim WY, Kimm K, Kimura R, Koike T, Kulawonganunchai S, Kumar V, Lai PS, Lee JY, Lee S, Liu ET, Majumder PP, Mandapati KK, Marzuki S, Mitchell W, Mukerji M, Naritomi K, Ngamphiw C, Niikawa N, Nishida N, Oh B,

Oh S, Ohashi J, Oka A, Ong R, Padilla CD, Palittapongarnpim P, Perdigon HB, Phipps ME, Png E, Sakaki Y, Salvador JM, Sandraling Y, Scaria V, Seielstad M, Sidek MR, Sinha A, Srikummool M, Sudoyo H, Sugano S, Suryadi H, Suzuki Y, Tabbada KA, Tan A, Tokunaga K, Tongsima S, Villamor LP, Wang E, Wang Y, Wang H, Wu JY, Xiao H, Xu S, Yang JO, Shugart YY, Yoo HS, Yuan W, Zhao G, Zilfalil BA; Indian Genome Variation Consortium. Mapping human genetic diversity in Asia. Science 2009; 326: 1541-1545.

[22] Song SY, Kim SR, Ahn G and Choi HY. Pathologic characteristics of prostatic adenocarcinomas: a mapping analysis of Korean patients. Prostate Cancer Prostatic Dis 2003; 6: 143-147.

[23] Oliphant A, Barker DL, Stuelpnagel JR and Chee MS. BeadArray technology: enabling an accurate, cost-effective approach to high-throughput genotyping. Biotechniques 2002; Suppl: 56-58, 60-1.

[24] Morris JA and Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. Br Med J (Clin Res Ed) 1988; 296: 1313-1316.

[25] Lewis CM. Genetic association studies: design, analysis and interpretation. Brief Bioinform 2002; 3: 146-153.

[26] Hedrick PW. Gametic disequilibrium measures: proceed with caution. Genetics 1987; 117: 331-341.

[27] Stephens M, Smith NJ and Donnelly P. A new statistical method for haplotype reconstruction from population data. Am J Hum Genet 2001; 68: 978-989.

[28] Nyholt DR. A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. Am J Hum Genet 2004; 74: 765-769.

[29] Benjamini Y, Drai D, Elmer G, Kafkafi N and Golani I. Controlling the false discovery rate in behavior genetics research. Behav Brain Res 2001; 125: 279-284.

[30] Tamatani T, Hattori K, Nakashiro K, Hayashi Y, Wu S, Klumpp D, Reddy JK and Oyasu R. Neoplastic conversion of human urothelial cells in vitro by overexpression of H2O2-generating peroxisomal fatty acyl CoA oxidase. Int J Oncol 1999; 15: 743-749.

[31] Takahara K, Azuma H, Sakamoto T, Kiyama S, Inamoto T, Ibuki N, Nishida T, Nomi H, Ubai T, Segawa N and Katsuoka Y. Conversion of prostate cancer from hormone independency to dependency due to AMACR inhibition: involvement of increased AR expression and decreased IGF1 expression. Anticancer Res 2009; 29: 2497-2505.

[32] Wright JL, Neuhouser ML, Lin DW, Kwon EM, Feng Z, Ostrander EA and Stanford JL. AMACR polymorphisms, dietary intake of red meat and dairy and prostate cancer risk. Prostate 2011; 71: 498-506.

[33] FitzGerald LM, Thomson R, Polanowski A, Patterson B, McKay JD, Stankovich J and Dickinson JL. Sequence variants of alpha-methylacyl-CoA racemase are associated with prostate cancer risk: a replication study in an ethnically homogeneous population. Prostate 2008; 68: 1373-1379.