

# Validation of the novel susceptibility loci for prostate cancer in a Chinese population

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**Abstract.** The present study evaluated 23 newly identified susceptibility loci for prostate cancer (PCa) in a Chinese population and assessed whether any validated loci were associated with the genetic risk score (GRS) of PCa in a Chinese population. A total of 1,417 patients with PCa and 1,008 controls were recruited in the present study. The association of each single nucleotide polymorphism (SNP) with PCa risk and PCa aggressiveness was analyzed. The predictive ability of two GRSs based on 30 SNPs (GRS30) and the 9 most significant SNPs (GRS9) in the Chinese population were also compared. Among the 19 SNPs evaluated, 1 SNP (rs7153648 at 14q23) was associated with PCa risk [odds ratio (OR)=1.206, P<0.05] and 1 SNP (rs636291 at 1p23) was associated with PCa aggressiveness (OR=1.123, P<0.05). GRS30 and GRS9 were significantly increased in patients with PCa compared with that among non-PCa controls. The areas under receiver operating

characteristic curves of GRS9 and GRS 30 were similar (0.792 for GRS9 vs. 0.7994 for GRS30, P=0.138). To conclude, among the 19 SNPs evaluated, only 1 SNP was associated with PCa risk in the Chinese population. SNPs that were weakly associated with PCa were unlikely to improve the predictive ability of existing GRS in the Chinese population.

## Introduction

Prostate cancer (PCa) is the second most common cancer and one of the leading causes of mortality among males worldwide by 2012 (1). The incidence of PCa in China is considered reduced compared with that in Western countries; however, it has been progressively increasing over the past 30 years (2).

Genetic susceptibility to PCa has been well established and almost 100 common risk loci have been identified by genome wide association studies (GWAS) among European, African-American, Japanese and Chinese populations (3,4). However, only 10 of these loci were initially identified from GWAS in Japanese and Chinese populations. Among previous evaluation and validation studies, a part of the loci was revealed to be associated with PCa risk in Chinese population (5). Since these risk-associated single nucleotide polymorphisms (SNPs) exhibited a cumulative effect on PCa risk, the genetic risk scores (GRS) derived from PCa risk-associated SNPs were able to evaluate an individual's risk of PCa. The GRS based on the Chinese population is established and demonstrated to be a significant predictor of biopsy outcome in previous studies (5-9).

With an increasing sample size used in GWAS through combined data, a meta-analysis of a multi-ethnic population, which included 87,040 individuals, identified 23 new susceptibility loci for PCa (including 15 in European, 7 in

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multiethnic and 1 in the early onset analysis) (10). These PCa risk-associated alleles exhibited decreased effects with odds ratios (ORs) ranging between 1.06 and 1.14 (10). However, since the Chinese population was not included in the study, the effects of these 23 novel risk variants in individuals of Chinese descent remains unknown.

The objective of the present study was to evaluate the 23 newly identified susceptibility loci for PCa in a Chinese population and assess whether any validated loci contributed to the GRS in predicting the risk of PCa in a Chinese population.

## Materials and methods

**Population.** The baseline characteristics of the present study subjects were summarized (Table I). A total of 2,425 subjects including 1,417 patients with PCa and 1,008 controls were recruited in the present study. All patients were part of the China PCa consortium from the southeast of China (11-13) recruited during January 2010 and December 2011, from which data were obtained. All cases were pathologically diagnosed with primary PCa and all the controls were recruited from the community or selected from subjects who had undergone routine physical examination in local hospitals. Written informed consent was obtained from subjects for their participation in the present study and a blood sample was taken from each subject at the time of recruitment for DNA extraction. The present study was reviewed and approved by the Institutional Review Board of every participating institution.

**Genotyping and quality control.** DNA samples were genotyped in the Center for Cancer Genomics at Wake Forest University (Winston-Salem, NC, USA) using the Illumina HumanOmniExpress BeadChips (Illumina, Inc., San Diego, CA, USA), which included 731,458 SNPs. For PCa risk-associated SNPs that were not included in the GWAS array, imputation was performed using IMPUTE 2.2.2 based on the combined data of the 1,000 Genomes project and HapMap3 data (14). A posterior probability of >0.9 was applied to call imputed genotypes. Imputed SNPs were excluded if they exhibited: i) A call rate <95%; ii) a minor allele frequency <0.05; or iii)  $P < 1 \times 10^{-3}$  in a Hardy-Weinberg equilibrium test in controls, as previously described (13).

**Assessment of genetic risk.** A GRS was calculated for each subject based on genotypes of the SNPs and weighted by their ORs and risk allele frequency, as described previously (15). GRS was calculated as

$$\text{GRS} = \prod_{i=1}^n \frac{OR_i^{g_i}}{W_i},$$

where  $g_i$  is the genotype of SNP  $i$  for an individual (0, homozygous of non-risk allele; 1, heterozygous; 2 homozygous of risk allele).  $OR_i$  is the OR of SNP  $i$  estimated from external study (16),  $W_i$  is the average population risk of SNP  $i$ , calculated as  $W_i = f_i^2 OR_i^2 + 2f_i(1-f_i) OR_i + (1-f_i)^2$ , where  $f_i$  is the risk allele frequency of SNP  $i$  based on the 1,000 Genome Project of the CHB (Han Chinese in Beijing, China) population (17). Therefore, a GRS value of 1.0 represents a population average risk.

Table I. Characteristics of study population.

Variables	PCa cases (n=1,417)	Controls (n=1,008)
Age, years <sup>a,b</sup>	71.3±8.1	62.1±10.0
PSA, ng/ml <sup>a,c</sup>		
0-3.99	54 (4.0)	965 (95.9)
4-9.99	187 (14.0)	32 (3.2)
10-19.99	305 (22.8)	6 (0.6)
≥20	791 (59.2)	3 (0.3)
Missing	80 (5.6)	2 (0.2)
Gleason score <sup>c</sup>		
≤7	809 (60.1)	N/A
≥8	537 (39.9)	N/A
Missing	71 (5)	N/A

<sup>a</sup>At the time of diagnosis for cases or at recruitment for controls. <sup>b</sup>Data are presented as the mean ± standard deviation. <sup>c</sup>Data are presented as n (%). PSA, prostate-specific antigen; N/A, not applicable; PCa, prostate cancer.

**Statistical analysis.** A logistic regression model was used to analyze the association of each SNP with PCa risk, assuming an additive genetic model, which was implemented in PLINK version 1.07 (18). ORs and 95% confident intervals (CIs) were estimated from logistic regression analysis with adjustment for age and the highest eigen value. Student's t-tests were used to analyze the differences in means of normally distributed variables between 2 groups. For variables that were not normally distributed, 2 tests were performed: i) A nonparametric method using the Wilcoxon rank sum test and ii) Student's t-tests for different means between 2 groups following log-transformation. Differences in binary variables were investigated using  $\chi^2$  tests. Area under the receiver operating characteristic curve (AUC) was used to evaluate the performance of GRS in discriminating between 2 groups of subjects. The difference between two AUCs was determined using Delong's test (19).  $P < 0.05$  was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS 19.0 (SPSS; IBM Corporation, Armonk, NY, USA).

## Results

**SNPs and PCa risk.** The present study evaluated 19 newly reported SNPs. Among the 19 SNPs, only 1 (rs7153648 at 14q23) was associated with PCa risk in the China PCa cohort (OR=1.206,  $P < 0.05$ ). The direction of the effect was consistent with the previous multiethnic meta-analysis (10). The other 18 SNPs that had previously demonstrated genome-wide significance in European ancestry meta-analysis and multiethnic meta-analysis (Table II) either were not associated with PCa risk or did not demonstrate the same magnitude of effect in the Chinese population investigated in the present study.

**SNPs and PCa aggressiveness.** The association between the 19 SNPs and PCa aggressiveness was also investigated (cases with a Gleason score ≥7; Table III). The results did not demonstrate

Table II. Association results for 19 novel risk variants for PCa in Chinese males.

Origin of GWAS	SNP ID	Chromosome position <sup>a</sup>	Region	Gene	Alleles	Risk allele	Risk allele frequency		Odds ratio	P-value
							PCA cases	Controls		
European	rs636291	1p35	Intron	PEX14	A/G	G	0.254	0.241	1.12	0.148
European	rs17599629	1q21	Intron	GOLPH3L	G/A	G	0.103	0.098	1.03	0.780
Multi-ethnic	rs1775148	1q32	Intergenic	SLC41A1	C/T	C	0.508	0.486	1.13	0.109
European	rs9287719	2p25	Intergenic	NOL10	C/T	C	0.372	0.350	1.14	0.075
European	rs10009409	4q13	Intergenic	COX18	T/C	C	0.484	0.468	1.07	0.310
European	rs4713266	6p24	Intron	NEDD9	C/T	C	0.187	0.177	1.11	0.263
European	rs115457135	6p22	Intron	TRIM31	A/G	A	0.144	0.161	1.03	0.903
European	rs115306967	6p21	Intergenic	HLA-DRB6	G/C	C	0.135	0.126	1.12	0.570
Multi-ethnic	rs9443189	6q14	Intron	MYO6	G/A	A	0.633	0.632	1.03	0.728
European	rs56232506	7p12	Intron	TNS3	A/G	A	0.383	0.383	1.02	0.764
European	rs17694493	9p21	Intron	CDKN2B-AS1	G/C	G	0.030	0.029	1.13	0.575
European	rs76934034	10q11	Intron	41706	T/C	T	1.000	0.999	1.00	0.999
European	rs11214775	11q23	Intron	HTR3B	G/A	G	0.798	0.796	0.97	0.756
Multi-ethnic	rs7153648	14q23	Intergenic	SIX1	C/G	C	0.178	0.153	1.21	0.045
European	rs8014671	14q24	Intergenic	TTC9	G/A	G	0.300	0.298	0.99	0.904
Multi-ethnic	rs12051443	16q22	Intron	PHLPP2	A/G	A	0.762	0.758	0.91	0.243
Multi-ethnic	rs12480328	20q13	Intron	ADNP	T/C	T	0.924	0.919	0.94	0.616
Multi-ethnic	rs1041449	21q22	Intergenic	TMPPRSS2	G/A	G	0.164	0.161	1.05	0.674
Multi-ethnic	rs2238776	22q11	Intron	TBX1	G/A	G	0.515	0.515	1.07	0.376

<sup>a</sup>Genome Build 37. PCA, prostate cancer; SNP, single nucleotide polymorphism; GWAS, genome wide association study.

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Table III. Association results for 19 novel risk variants for aggressive PCa in Chinese males.

Origin of GWAS	SNP ID	Chromosome position <sup>a</sup>	Region	Gene	Alleles	Risk allele	Risk allele frequency		
							PCa cases	Controls	P-value
European	rs636291	1p35	Intron	PEX14	A/G	G	0.262	0.239	0.049
European	rs17599629	1q21	Intron	GOLPH3L	G/A	G	0.102	0.100	0.984
Multi-ethnic	rs1775148	1q32	Intergenic	SLC41A1	C/T	C	0.508	0.490	0.148
European	rs9287719	2p25	Intergenic	NOL10	C/T	C	0.373	0.356	0.303
European	rs10009409	4q13	Intergenic	COX18	T/C	C	0.477	0.475	0.746
European	rs4713266	6p24	Intron	NEDD9	C/T	T	0.820	0.818	0.862
European	rs115457135	6p22	Intron	TRIM31	A/G	A	0.139	0.132	0.790
European	rs115306967	6p21	Intergenic	HLA-DRB6	G/C	C	0.142	0.124	0.308
Multi-ethnic	rs9443189	6q14	Intron	MYO6	G/A	G	0.378	0.362	0.141
European	rs56232506	7p12	Intron	TNS3	A/G	A	0.388	0.379	0.374
European	rs17694493	9p21	Intron	CDKN2B-AS1	G/C	G	0.031	0.029	0.565
European	rs76934034	10q11	Intron	41706	T/C	T	1.000	1.000	0.999
European	rs11214775	11q23	Intron	HTR3B	G/A	G	0.800	0.796	0.661
Multi-ethnic	rs7153648	14q23	Intergenic	SIX1	C/G	C	0.171	0.161	0.571
European	rs8014671	14q24	Intergenic	TTC9	G/A	G	0.305	0.294	0.407
Multi-ethnic	rs12051443	16q22	Intron	PHLPP2	A/G	A	0.767	0.760	0.286
Multi-ethnic	rs12480328	20q13	Intron	ADNP	T/C	T	0.929	0.919	0.352
Multi-ethnic	rs1041449	21q22	Intergenic	TMPRSS2	G/A	A	0.840	0.834	0.647
Multi-ethnic	rs2238776	22q11	Intron	TBX1	G/A	G	0.517	0.512	0.875

<sup>a</sup>Genome Build 37. PCa, prostate cancer; SNP, single nucleotide polymorphism; GWAS, genome wide association study.

Table IV. Genetic score and prostate biopsy outcomes.

Parameter	9 SNPs	30 SNPs
Genetic score <sup>a</sup>		
PCa	1.26±0.72	1.44±1.18
Non-PCa	0.99±0.53	0.96±0.73
P-value	3.71x10 <sup>-28</sup>	7.44x10 <sup>-41</sup>
Association with PCa <sup>b</sup>		
Genetic score ≤1.0	1	1
Genetic score >1.0	2.47 (2.05-2.97)	2.25 (1.96-2.58)
P-value	6.90x10 <sup>-22</sup>	2.97x10 <sup>-31</sup>
Discrimination of PCa		
AUC	0.792	0.799
P-value		0.138
(AUC comparison)		

<sup>a</sup>Data presented as the mean ± standard deviation. <sup>b</sup>Data presented as odds ratio (95% confidence interval). PCa, prostate cancer; AUC, areas under receiver operating characteristic curves; SNP, single nucleotide polymorphism.

a significant association between rs7153648 and PCa aggressiveness, whereas rs636291 at 1p23 was significantly associated with PCa aggressiveness (OR=1.123, P<0.05).

**SNPs, GRS and PCa.** GRS was calculated using rs7153648 and 29 previously implicated SNPs (10). The mean GRS based on the 30 SNPs (GRS30) was significantly increased in patients with PCa compared with that among non-PCa individuals (1.439 vs. 0.961, P=7.44x10<sup>-41</sup>; Table IV). As reported in a previous study, it would be more efficient and reliable to calculate GRS using race-specific disease-associated SNPs that demonstrated genome-wide significance (20). Therefore, in the present study, GRS was also calculated based on the 9 strongest SNPs previously reported in individuals of Asian descent (GRS9; Table V) (16). The mean GRS based on 9 SNPs was 1.26 in patients with PCa and 0.99 in non-PCa controls (P=3.71x10<sup>-28</sup>).

Following adjustment for age (Table IV), GRS9 and GRS30 remained significantly associated with PCa (all P<0.01). The OR of the GRS30 for the prediction of PCa risk was 2.25 (95% CI, 1.976-2.598; P=2.97x10<sup>-31</sup>), decreased compared with that of GRS9 (OR=2.468; 95% CI, 2.053-2.967; P=6.9x10<sup>-22</sup>), although no significant differences were identified. When comparing the predictive ability of the GRS9 and GRS30, the AUCs were similar (0.792 for GRS9 vs. 0.7994 for GRS30, P=0.138).

## Discussion

Genetic susceptibility is a major risk factor for PCa and is estimated to account for 42% of variation in the disease (21). In the past few years, GWAS and meta-analysis of combined data have identified 99 genomic variants associated with PCa in multiple populations of European, African-American, Japanese, Latino and Chinese ancestry (10). In the present study, 23 novel susceptibility loci detected in European

Table V. Most significant SNPs previously reported in Asian individuals<sup>a</sup>.

SNP	Locus	Position <sup>b</sup>	Nearby gene	Reported SNPs in meta-analysis			Frequency in 1,000 Genome-CHB	
				Allele <sup>c</sup>	OR	P-value		
rs12653946	5p15.33	1895829	IRX4	G/A	0.78	1.94x10 <sup>-12</sup>	0.103	TC
rs339331	6q22.2	1.17x10 <sup>8</sup>	RFX6	C/T	0.78	4.27x10 <sup>-11</sup>	0.103	CT
rs1512268	8p21.2	23526463	NKX3-1	C/T	0.76	1.40x10 <sup>-13</sup>	0.113	TC
rs16901979	8q24.21	1.28x10 <sup>8</sup>	POU5F1B	C/A	0.72	1.00x10 <sup>-16</sup>	0.052	AC
rs6983267	8q24.21	1.28x10 <sup>8</sup>	POU5F1B	G/T	1.23	8.36x10 <sup>-9</sup>	0.113	GT
rs1447295	8q24.21	1.28x10 <sup>8</sup>	LOC727677	C/A	0.65	3.92x10 <sup>-23</sup>	0.010	AC
rs10993994	10q11	51549496	MSMB	C/T	0.83	3.58x10 <sup>-8</sup>	0.165	TC
rs12791447	11p15.4	7556577	PPFIBP2	C/T	1.23	3.59x10 <sup>-8</sup>	0.010	GA
rs58262369	14q23.2	64693912	ESR2	C/T	0.78	6.05x10 <sup>-10</sup>	0.031	TC
							0.474	CC
							0.485	TT
							0.526	CC
							0.392	CC
							0.526	TT
							0.237	CC
							0.505	CC
							0.155	AA
							0.216	CC

<sup>a</sup>According to reference 16. <sup>b</sup>On the basis of the National Center for Biotechnology Information (NCBI) database, build 37. <sup>c</sup>Effect/non-effect allele. OR, odds ratio; SNP, single nucleotide polymorphism.



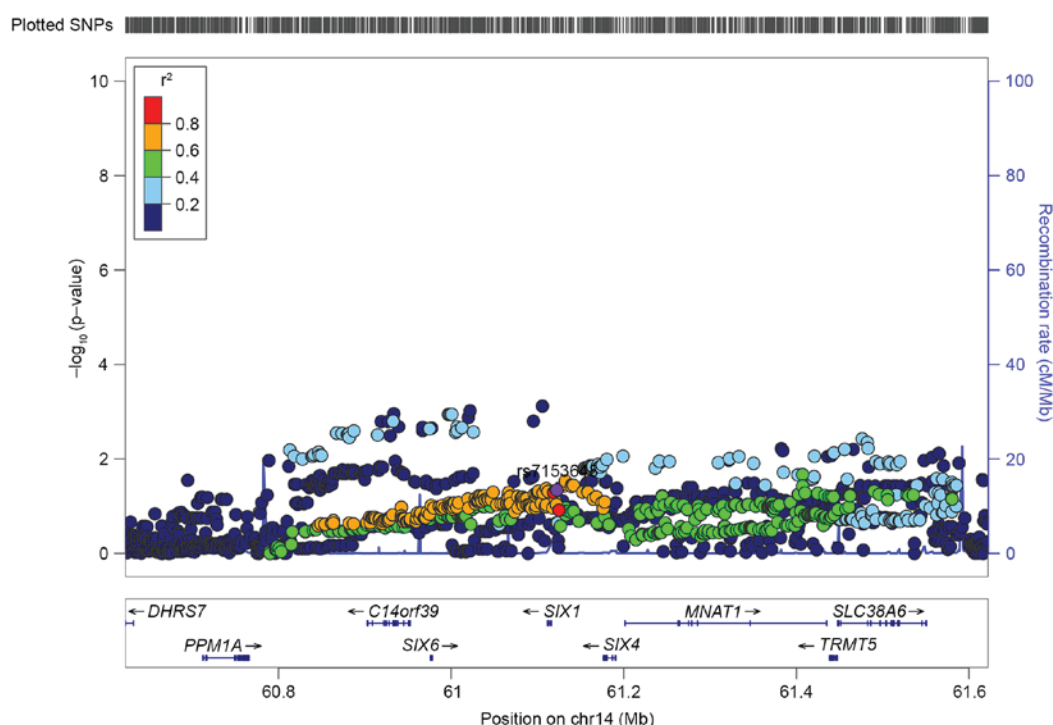


Figure 1. Regional information of rs7153648 at 14q23 (build: hg19). SNP, single nucleotide polymorphism.

ancestry or multi-ethnic analysis were investigated and their association in a Chinese population was evaluated.

Of the 19 SNPs evaluated in the present study, only 1 was identified to be associated with PCa. The estimate of risk of this SNP in the Chinese population was similar to that in European and multi-ethnic populations (10). Despite reaching genome-wide significance in European or multi-ethnic populations, the other 18 loci were not identified to be significant in the population of the present study. The discrepancy may be explained in multiple ways. First, since the effects of 18 SNPs (not including rs636291 at 1p36) were relatively low, with ORs ranging between 1.06 and 1.13, the present study may not possess the power to identify the small effects of these SNPs. This was also one of the reasons why rs7153648 did not reach a significant level following Bonferroni correction ( $P=0.05/19$ ). Second, the risk allele frequencies in European and Chinese ancestry differed between SNPs evaluated (Table II); this difference may also influence the detection of significant effects of these SNPs in populations of Chinese ancestry. Finally, besides the different genetic backgrounds between European ancestry (or other populations) and Chinese ancestry, environmental factors, dietary-habit and other non-genetic factors may also affect the penetrance of these alleles, which may result in the difference of risk profiles.

When evaluating the association between the 19 SNPs and aggressive PCa (Gleason score,  $\geq 7$ ), the results demonstrated that rs636291 at 1p36 reached a significant level ( $P<0.05$ ). This SNP reached genome-wide significance in early onset disease in European ancestry (10); however, a similar analysis could not be performed in the present study due to the lack of cases (only 34 patients with PCa were diagnosed  $<55$  years of age). Nevertheless, this result may indicate that this risk variant was associated with more advanced PCa and should be further validated in an independent study.

In the comparison of the two GRS-based risk models, the results revealed that the performance was approximately the same between the two models. This may be attributed to the fact that certain risk variants were not strongly associated with PCa and others conferred a decreased effect to the risk of PCa in Chinese population compared with that in European whites. In a previous study, the plateau effect of PCa risk-associated SNPs was evaluated in predicting PCa in a Chinese population and it was identified that the predictive performance increased when the top 13 highest impact PCa risk-associated SNPs were included in the GRS (9). The results were similar in the present study; therefore, this may indicate that further SNPs weakly associated with PCa may not improve the predictive performance of GRS for PCa. Therefore, GRS only including the strongest SNPs may be appropriate while balancing the predictive performance and economic benefit.

In the present study, the variant rs7153648 at 14q23 that we demonstrated to be associated with PCa is located in the intergenic region of SIX homeobox 1. The regional information of the confirmed SNP (rs7153648) was presented (Fig. 1). In the LocusZoom plots of this loci, multiple SNPs located upstream of rs7153648 demonstrated marked association ( $P<0.01$ ) but a weak correlation (dark blue circles), which may suggest the presence of multiple potential independent association signals. Variant rs636291 at 1p36, which was associated with early-onset PCa in European ancestry and was identified to be associated with aggressive PCa in Chinese ancestry in the current study, is located in intron 2 of peroxisomal biogenesis factor 14 and is associated with a variant (rs616488) reported in a GWAS of breast cancer (22).

There were multiple limitations to the present study. First, only 19 SNPs, rather than 23 of the novel identified loci, were genotyped or imputed due to 4 SNPs not being included in the GWAS panel and failing to impute using the CHB population

of the 1,000 Genome project. Among the 4 SNPs, rs80130819 at 12q13 was not polymorphous in the CHB population, while the remaining 3 were polymorphous in the CHB population. Second, due to the open nature of the China PCa cohort, the clinical characterization of the cases was not consistent between distinct hospitals (e.g., Gleason score diagnosis in the present study), which limited further analysis of clinical phenotypes.

To conclude, by evaluating 19 PCa risk-associated SNPs identified in a large meta-analysis of GWAS from a European and multiethnic population, the results of the present study identified 1 SNP that was associated with PCa risk and 1 that was associated with aggressive PCa in a Chinese population. However, the validated small-effect SNP and other SNPs that weakly associated with PCa are not likely to improve the predictive ability of existing GRS in Chinese populations.

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