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Prostate Cancer Risk Alleles Significantly Improve Disease Detection and are Associated with Aggressive Features in Patients with a "Normal" Prostate Specific Antigen and Digital Rectal Exam

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Abstract

Background—Several reports suggest that a combination of risk alleles may be associated with prostate cancer (CaP) risk and tumor features. However, their ability to detect CaP and tumor characteristics in patients with a "normal" PSA (<4 ng/ml) and non-suspicious digital rectal examination (DRE) remains to be determined.

Methods—We examined 203 men of European ancestry with clinical stage T1c CaP diagnosed at a "normal" PSA and 611 healthy volunteer controls. The genotypes for 17 different risk alleles were compared between CaP cases and controls. Additional analyses were used to compare the pathologic features between carriers and non-carriers (defined using best-fit genetic model) of these variants.

Results—All risk alleles were present at an increased frequency in cases with "normal" PSA values and DRE compared to controls. Amongst CaP patients, carriers of an increasing number of genetic risk factors (i.e., alleles and positive family history) were at a significantly increased risk of CaP (P-trend <0.001). Specifically, men with >10 genetic risk factors had an 11.2-fold risk (95% CI 4.3-29.2) of having the disease compared to men with ≤5 variants. There also was a higher frequency of many the variants amongst men with adverse pathologic features.

Conclusions—A substantial proportion of biopsy-detectable CaP occurs in men with "normal" PSA levels and negative DRE. In this population, CaP risk alleles and family history are significantly associated with CaP risk and may help predict aggressive disease. Future studies are warranted to determine the utility of incorporating these variants into CaP screening programs.

Keywords

Cumulative; adverse features; prostate cancer detection

Introduction

Serum prostate specific antigen (PSA) and the digital rectal exam (DRE) are considered the standard components employed for prostate cancer (CaP) screening and early detection programs (1). The widespread use of these screening tools has resulted in a stage migration, as a greater proportion of tumors are now detected at lower PSA levels. In fact, data obtained from the Prostate Cancer Prevention Trial suggests that up to 15% of men with a "normal" screening test (i.e., PSA value < 4.0 ng/ml and non-suspicious DRE) have biopsy-detectable CaP (2). Further analyses of the data from this trial demonstrated that CaP was

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present in 10% of men with a PSA <1 ng/ml and a negative DRE (3). However, the common use of PSA as a screening tool, and in particular within "normal" ranges < 4.0 ng/ml, has led to a concern regarding the over-diagnosis of potentially indolent cancers (4). Thus, other biomarkers that could help assist in evaluating patients at increased risk of CaP are needed.

While CaP continues to be the most common non-cutaneous cancer among U.S. men, its etiology remains poorly understood. In recent years, genome-wide association, linkage analysis and fine-mapping studies have identified more than 30 different single nucleotide polymorphims (SNPs) that are reproducibly associated with CaP risk in large cohorts of men of European ancestry and other racial populations (5-15). Although each individual risk allele is only moderately associated with CaP susceptibility (O.R. ~1.1-1.8), a strong cumulative effect between the alleles has been reported and confirmed in several studies (16-18). However, the cumulative risk of the susceptibility alleles in patients who are considered at low risk of developing CaP (i.e., PSA values <4.0ng/ml) remains to be determined.

Many of the risk alleles described have now been evaluated for a potential association with aggressive clinico-pathologic features such as early age at onset, familial aggregation and higher tumor grades and stages (5,9,13,19-23). While most studies have reported that the aggressive forms of the disease are influenced by many of the same risk alleles associated with CaP susceptibility, others have not (24-26). In fact, a recent genome-wide association study that specifically compared the frequency of the risk alleles in patients with high grade and stage CaP to those with low grade and stage tumors identified a specific risk allele that may distinguish aggressive disease (27). Taken together, while all of the variants appear to predispose to the development of CaP, many studies are beginning to identify those that also predict aggressive tumor characteristics.

It is also unknown whether these alleles can provide information regarding aggressive tumor characteristics in this same population of men with seemingly indolent CaP. Therefore, the present study examined the performance of the susceptibility alleles in prediction models for CaP risk and tumor aggressiveness in patients with "normal" screening results.

Materials and Methods

Our initial study cohort included 1459 men of European ancestry who underwent radical prostatectomy from 1997 to 2009. Of these patients, 203 (n=13 from Washington University, St. Louis, MO; n=190 from Northwestern University, Chicago, IL) had a "normal" screening exam at the time of CaP diagnosis: clinical stage TIC, PSA <4.0 ng/ml, and non-suspicious DRE. Of these men, 97.5% were treated by a single surgeon (WJC) and the rest by other urologists from the Northwestern University Specialized Program of Research Excellence (SPORE) group. In addition, we identified 611 men of European ancestry (controls) with a PSA level <4.0ng/ml, normal digital rectal examination, and no prior history of a prostate biopsy. Of these men, 611 were recruited as healthy control subjects for genetic studies from the National Prostate Cancer Coalition (NPCC) screening study (2007), as previously described (5). The study received IRB approval, and all participants provided informed consent.

Patient demographics, biopsy and prostatectomy findings were documented for CaP patients, including pre-operative PSA, first-degree family history of CaP (n=195/203), clinical stage, pathologic stage, surgical margin status, and presence of extracapsular tumor extension, seminal vesicle invasion or lymph node metastases. Organ-confined disease was defined as a tumor confined to the prostate with negative surgical margins (Stage pT2RO). Men with extraprostatic tumor extension (≥pT3), positive surgical margins (R1), seminal

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vesicle invasion or lymph node metastases (N1) were categorized as having non-organ confined disease.

DNA samples were isolated from whole blood, and the genotypes for 17 different risk alleles were available for all participants, as previously described (5,10-13). In particular, we assayed for 5 susceptibility alleles along 8q24: the A allele of single nucleotide polymorphism (SNP) rs1447295, the A allele of SNP rs16901979, the G allele of SNP rs16902094, the T allele of SNP rs45114, and the G allele of SNP rs6983267. Genotypes were also determined for the A allele of SNP rs721048 along 2p15; the A allele of SNP rs10934853 along chromosome 3q21; the A allele of SNP rs2736098 along chromosome 5; the C allele of SNP rs401681 along chromosome 5p15; the T allele of SNP rs10993994 along chromosome 10q11; the A allele of SNP rs11228565 and the G allele of SNP rs10896450 along 11q13; the G allele of SNP rs11649743 along chromosome 17q12; the A allele of rs4430796 on 17q12; the G allele of SNP rs1859962 on 17q24; the C allele of SNP rs8102476 on chromosome 19q13; and the A allele of SNP rs5945572 on chromosome Xp11. Genotyping for all cases and controls was performed by deCODE Genetics, Inc., as previously described. The quality control and genotyping accuracy of the risk alleles has previously been reported (5,10-13). Tests for Hardy–Weinberg equilibrium were performed for each SNP separately among control subjects with the use of Fisher's exact test.

The frequencies of the risk alleles amongst cases and controls were determined. The genotype information was compared using Akaike's information criteria to choose the best-fit genetic model (dominant or recessive) in a larger population of patients as previously described (18). Carriers were defined using the best-fit genetic model as previously described (31). The cumulative risk was determined using all 17 of the risk alleles as well as only the risk alleles that were significantly over-represented in the present studied population of cases and controls. For some analyses, data was restricted to patients with available information regarding first degree family history of CaP (n=195 cases; n=348 controls). In addition, receiver operating characteristic (ROC) curves were constructed with and without adjustment for age using the carrier number of all 17 susceptibility alleles as a continuous variable and family history. The Fisher's exact and Kruskal-Wallis tests were used to compare the frequency of clinical-pathologic features amongst carriers of the 17 different susceptibility alleles. A p-value <0.05 was considered significant. All statistical analysis was performed using SAS 9.2 (Cary, NC).

Results

The clinical and pathologic characteristics of the 203 CaP cases and 611 healthy control subjects are shown in Table 1. The mean age of the cases and controls were 57.7±7.6 years and 58.5 ±10.4 years, respectively. The specific age distribution by quartiles and PSA range are shown Table 1. Although the mean PSA of CaP cases (3.0±0.8 ng/ml) was significantly higher than controls (1.0±0.6 ng/ml), all cases had a serum PSA value <4.0 ng/ml. Consequently, all cases were ultimately diagnosed with CaP for reasons other than an absolute PSA value >4.0 ng/ml (e.g. increased PSA velocity, PSA above age-specific median, etc). As expected, a significantly increased proportion of cases reported a first-degree relative with CaP compared to controls [$p<0.0001$, OR 3.3 (2.2-4.9)].

The genotypes and frequencies of the 17 different risk alleles were determined for all cases and controls (Table 2) and found to be in Hardy–Weinberg equilibrium (data not shown). In addition, all of the CaP risk alleles were present at increased frequencies amongst cases compared to controls. However, given the relatively small population of cases and controls, only 6 of the susceptibility alleles were significantly ($p<0.05$) overrepresented in CaP cases (Table 2).

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We next determined the best-fit genetic model (dominant or recessive) for each risk allele (Table 2) and used this to define carrier status. The cumulative risk of being a carrier of multiple variants was then assessed using all 17 susceptibility alleles (Table 3a). Similar to prior reports, we observed a strong cumulative effect of the risk variants. Compared to men who were carriers of four or fewer risk alleles, men who carried 6, 7, 8, 9, or 10 variants had an odds ratio of 1.0, 1.4, 1.4, 2.5, 3.1 and 10.6, respectively (p-trend <0.001; Table 3a). When the presence of family history was included in the analyses, we found that carriers of >10 genetic risk factors (i.e., risk alleles and/or family history) had an 11.2-fold increased risk of having CaP (p<0.0001; 95% C.I. 4.3-29.2; Table 3b) compared with men who were carriers of ≤ 5 risk alleles.

We next restricted our analyses to the 6 different risk alleles that were significantly over-represented in the present study populations. Table 3c shows that men who were carriers of 1, 2, 3, or 4 or more alleles had progressively increasing odds of CaP, as compared with carriers of only one or none of the risk alleles (p- trend <0.0001). Specifically, carriers of ≥4 risk variants had a 6.8-fold increased risk of having CaP, even though their serum PSA concentration was <4.0 ng/ml, and they had a non-suspicious DRE. Finally, when we included family history into the restricted model, we found that carriers of ≥4 genetic risk factors had a 9.3-fold increased risk of having the disease (Table 3d).

ROC curves were next used to assess the ability of the variants to detect CaP in patients with a “normal” PSA and DRE. The AUC for the model including all the carrier numbers of all 17 risk variants was 0.655 [p<0.0001, OR 1.4 (1.3-1.6)], which was not significantly different after adjustment for age (AUC=0.623). However, there was a significant improvement in the AUC when family history was included in the analysis with the risk alleles (p<0.001; AUC=0.706).

Using the best-fit genetic models, we also compared the frequency of adverse clinical and pathologic features amongst carriers and non-carriers of the 17 risk alleles in the present population of men with clinical stage T1c CaP and a PSA value <4.0 ng/ml. There was an increased frequency of carriers for many of the risk alleles amongst men with an increased (i.e., Gleason ≥7) clinical and pathologic Gleason grade disease (Table 4). Given the relatively small number of men with high grade clinical (n=38) and pathologic (n=66) disease in the CaP case population, it is not surprising that statistical significance was not obtained for any of the alleles. However, the frequency of carriers of SNP rs16901979 along chromosome 8q24 reached marginal significance amongst men with increased clinical (p=0.15) and pathologic grade disease (p=0.10; Table 4). In general, there were no significant associations between the risk alleles and other adverse clinical and pathologic features (data not shown). However, a significantly higher proportion of carriers of SNP rs16901979 along 8q24 also had seminal vesicle invasion (8.7%) compared to non-carriers (0.6%; p=0.034).

Discussion

This study examined the performance of 17 independent risk alleles and family history amongst men of European ancestry with “normal” PSA and DRE examination. In addition, it determined their associations with tumor features. We found that an increasing number of genetic risk factors can progressively distinguish CaP, even amongst patients who would otherwise be considered “low risk” of developing the disease. Furthermore, the frequency of the risk alleles along chromosome 8q24 was marginally associated with adverse clinico-pathologic features in this relatively small population of men.

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A cumulative association of 5 risk alleles along 8q24 and 17q with CaP susceptibility has been previously described (16,18). Subsequent studies have identified additional chromosomal regions that are independently associated with increased CaP risk and also contribute to the cumulative risk of developing the disease (6-8,12,14,23,28-30). In this regard, we recently demonstrated that additional variants significantly improve risk stratification (31). The present study suggests that a panel of 17 of the risk alleles can be used to help assess the risk of CaP in men who otherwise present with no overt clinical features that may alert a treating physician to suspect CaP (e.g., “normal” PSA and DRE). In particular, men who were carriers of more than 10 of the risk alleles had an almost 11-fold risk of having CaP. Even using a limited model involving only 6 of the alleles, men who were carriers of 4 or more CaP alleles had a 6.8-fold risk of having the disease. When family history was included in these cumulative analyses, we found that men who had >10 genetic risk factors had an 11.2-fold risk of having CaP. Furthermore, ROC curves demonstrated that a model that includes the risk alleles and family history can moderately distinguish the presence of CaP in this population of men with a “normal” PSA and DRE. In the future, we would expect an increased ability to predict CaP in this population of men, as genetic risk alleles continue to be identified and are included in a cumulative risk model.

Many prior studies, have suggested that specific risk alleles are over-represented in patients with adverse clinical features (5,9,13,19-23,32). Recently, a genome-wide association study identified a risk variant located along 17p12 that was found to be present at a significantly greater frequency in men with advanced grade and stage disease (27). In the current study, we examined the relationships between the 17 risk alleles and pathologic tumor features. We found that the rs16901979 allele along 8q24 was marginally associated with higher Gleason grade disease, even in a population of men who are generally considered at low risk of having advanced CaP. In addition, this allele was over-represented in patients with seminal vesicle invasion. This finding supports the results of other recent studies demonstrating that the rs16901979 risk allele is associated with a significantly increased risk of high grade disease and adverse features (19,20). However, there were no other obvious associations between many of the other risk alleles and adverse pathology. A possible explanation for the lack of these robust findings is perhaps the relatively small population of men with CaP who had adverse pathologic features. Alternatively, despite their association with overall CaP risk, many risk alleles may not provide additional information about CaP aggressiveness amongst men of European descent with a normal PSA value.

Several limitations of our study deserve mention. Our study population was limited to a relatively small number of men of European descent. Since prior studies have shown that allele frequencies differ among different ethnic groups (8,9,33), further studies are needed to examine the cumulative effects of these alleles in other populations. In addition, since there are now more than 30 different CaP susceptibility alleles identified, perhaps many of these other alleles could be incorporated into models to assist in both risk stratification and identifying the presence of adverse pathologic features. Finally, it is important to note that while ~25% of cases carried >10 risk factors, this population was relatively small (n=49/203) and therefore may have over-estimated the risk of CaP. Therefore, future studies in larger populations of men of different ethnicities are needed to more accurately assess their association with disease susceptibility and adverse pathology.

Conclusion

In conclusion, a panel of 17 risk alleles and family history of CaP is associated with a progressive increase in the risk of the disease, even amongst patients with “normal” PSA and DRE. Alleles along 8q24 can assist in the identification of some adverse tumor features in this population. However, larger studies are warranted to evaluate the contribution of

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additional risk alleles to CaP risk stratification and to identify alleles that can better distinguish aggressive disease.

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Table 1

Clinico-pathologic Characteristics Prostate Cancer Cases and Healthy Volunteer Controls

	Cases (n=203) %	Controls (n=611) %
European Ancestry	100	100
Age (years) in Quartiles*		
≤51	22.2	26.0
52-57	23.1	23.7
58-64	39.9	26.0
≥65	14.8	24.2
First Degree Family History of CaP**	36.4	14.9
Serum PSA (ng/ml)*		
0.0 - < 2.5	17.7	97.5
2.5 - < 4.0	82.3	2.5
Percent Clinical Stage (≤T1c)	100	-
Percent Biopsy Gleason Score		
≤6	81.3	-
≥7	18.7	-
Percent Organ Confined Disease (≤T2)	92.1	-
Percent Prostatectomy Gleason Score		
≤6	67.5	-
≥7	32.5	-
Percent Positive Surgical Margins	9.9	-
Percent Extracapsular Extension	7.9	-
Percent Seminal Vesicle Invasion	1.5	-
Percent Lymph Node Metastases	0.5	-

* Statistically significant difference ($p<0.001$) in distribution among cases and controls tested using χ^2 test.

** Analyses were limited to subjects with available family history information including 195 cases and 348 controls. The frequency of a positive family history was significantly over-represented in cases compared to controls (P<0.001, O.R. 3.3 (95% CI 2.2-4.9).

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Table 2

Comparison of the Frequencies of the Risk alleles (Single Nucleotide Polymorphisms) in Prostate Cancer Cases with a “Normal” PSA and DRE and Healthy Volunteer Controls

SNP	Chrom. Location	Allele	Percent of		P Value	OR (95% CI)	Best-Fit Genetic Model
			Cases	Controls			
rs721048	2p15	A	18.5	16.7	0.40	1.1 (0.8-1.5)	Recessive
rs10934853	3q21	A	31.8	27.1	0.07	1.3 (.10-1.6)	Dominant
rs2736098	5p15	A	31.8	26.0	0.029	1.3 (1.0-1.7)	Recessive
rs401681	5p15	C	57.1	54.0	0.27	1.1 (0.9-1.4)	Dominant
rs16901979	8q24	A	5.9	4.0	0.13	1.5 (0.9-2.5)	Dominant
rs16902094	8q24	G	15.3	13.8	0.46	1.1 (0.8-1.5)	Dominant
rs445114	8q24	T	63.6	63.3	0.95	1.0 (0.8-1.3)	Dominant
rs6983267	8q24	G	59.4	50.5	0.002	1.4 (1.1-1.8)	Dominant
rs1447295	8q24	A	14.3	8.6	0.002	1.8 (1.3-2.5)	Dominant
rs10993994	10q11	T	48.8	39.3	0.0009	1.5 (1.2-1.8)	Recessive
rs11228565	11q13	A	25.6	19.4	0.009	1.4 (1.1-1.9)	Dominant
rs10896450	11q13	G	57.6	49.5	0.005	1.4 (1.1-1.7)	Dominant
rs11649743	17q12	G	83.7	82.5	0.60	1.1 (0.8-1.5)	Recessive
rs4430796	17q12	A	54.7	51.6	0.28	1.1 (0.9-1.4)	Dominant
rs1859962	17q24	G	53.2	49.0	0.15	1.2 (0.9-1.5)	Recessive
rs8102476	19q13	C	60.6	57.8	0.32	1.1 (0.9-1.4)	Dominant
rs5945572	Xp11	A	42.4	37.3	0.21	1.2 (0.9-1.7)	Dominant

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Table 3a

Cumulative relationship between risk alleles with prostate cancer susceptibility amongst CaP patients with a "normal" PSA and DRE and healthy volunteer controls

Cumulative risk model including all 17 risk alleles

Carrier of Variants #	Case N=203 N= (%)	Control N=611 N= (%)	OR (95%C.I.)	p-value
0-4	3 (1.5)	17 (2.8)	--	
5	12 (5.9)	43 (7.0)	1.6 (0.4-6.3)	0.52
6	18 (8.9)	103 (16.9)	1.0 (0.3-3.7)	0.99
7	32 (15.8)	133 (21.8)	1.4 (0.4-4.9)	0.64
8	35 (17.2)	144 (23.6)	1.4 (0.4-5.0)	0.62
9	43 (21.2)	98 (16.0)	2.5 (0.7-8.9)	0.16
10	32 (15.8)	58 (9.5)	3.1 (0.9-11.5)	0.08
>10	28 (13.8)	15 (2.5)	10.6 (2.7-42.0)	0.0008

* P-trend <0.001

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Table 3b

Cumulative risk model including all 17 risk alleles and a positive family history*

Carrier of Variants #	Case N=195 N= (%)	Control N=348 N= (%)	OR (95%C.I.)	p-value
0-5	11 (5.6)	35 (10.1)	--	
6	9 (4.6)	59 (17.0)	0.5 (0.2-1.3)	0.15
7	33 (16.9)	66 (19.0)	1.6 (0.7-3.5)	0.25
8	36 (18.5)	89 (25.6)	1.3 (0.6-2.8)	0.53
9	30 (15.4)	56 (16.1)	1.7 (0.8-3.8)	0.20
10	37 (19.0)	32 (9.2)	3.7 (1.6-8.4)	0.002
>10	39 (20.0)	11 (3.2)	11.2 (4.3-29.2)	<0.0001

* P-trend<0.001

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Table 3c

Cumulative risk model limited to the risk alleles that were significantly over-represented in CaP patients with a “normal” PSA and DRE (i.e. SNP rs2736098 along chromosome 5p15, SNP rs6983267 along 8q24, SNP rs1447295 along 8q24, SNP rs10993994 along 10q11, SNP rs11228565 along 11q13, rs1089649742 along 11q13)

Carrier of Variants #	Case N=203 N= (%)	Control N=611 N= (%)	OR (95%C.I.)	p-value
0	3 (1.5)	24 (3.9)	--	
1	21 (10.3)	134 (21.9)	1.3 (0.3-4.5)	0.73
2	65 (32.0)	211 (34.5)	2.5 (0.7-8.4)	0.15
3	65 (32.0)	184 (30.1)	2.8 (0.8-9.7)	0.10
4-6	49 (24.1)	58 (9.5)	6.8 (1.9-23.8)	0.003

* P-trend <0.001

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Table 3d

Cumulative risk model limited to the risk alleles that were significantly over-represented in CaP patients with a “normal” PSA and DRE and a positive family*

Carrier of Variants #	Case N=195 N= (%)	Control N=348 N= (%)	OR (95%C.I.)	p-value
0	3 (1.5)	18 (5.2)	--	
1	13 (6.7)	65 (18.7)	1.2 (0.3-4.6)	0.79
2	44 (22.6)	118 (33.9)	2.2 (0.6-8.0)	0.21
3	64 (32.8)	101 (29.0)	3.8 (1.1-13.4)	0.038
4-7	71 (36.4)	46 (13.2)	9.3 (2.6-33.2)	<0.0001

* P-trend <0.001

* Analyses were limited to cases (n=195) and controls (n=338) with available family history information

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Table 4

The Frequency of High Gleason Grade Disease Amongst Carriers and Non-Carriers (Defined by Best-Fit Genetic Model) of the Risk Alleles

SNP	Chrom. Location	Percent of Men with Clinical Gleason ≥7 (n=38)			Percent of Men with Pathologic Gleason ≥7 (n=66)		
		Carriers	NC	p-value	Carriers	NC	p-value
rs721048	2p15	25.0 (2/8)	18.5 (2/8)	0.65	25.0 (2/8)	32.8 (64/195)	0.99
rs10934853	3q21	15.3 (16/105)	22.5 (16/105)	0.21	31.4 (33/105)	33.7 (33/98)	0.77
rs2736098	5p15	26.3 (5/19)	17.9 (33/184)	0.36	26.3 (5/19)	33.2 (61/184)	0.62
rs401681	5p15	18.5 (30/162)	19.5 (8/41)	0.83	33.3 (54/162)	29.3 (12/41)	0.71
rs16901979	8q24	30.4 (7/23)	17.2 (31/180)	0.15	47.8 (11/23)	30.6 (55/180)	0.10
rs16902094	8q24	21.7 (13/60)	17.5 (25/143)	0.55	31.7 (19/60)	32.9 (47/143)	0.99
rs445114	8q24	19.7 (35/178)	12.0 (3/25)	0.58	33.2 (59/178)	28.0 (7/25)	0.66
rs6983267	8q24	17.8 (31/174)	24.1 (7/29)	0.44	32.8 (57/174)	31.0 (9/29)	0.99
rs1447295	8q24	18.2 (10/55)	18.9 (28/148)	0.99	36.4 (20/55)	31.1 (46/148)	0.50
rs10993994	10q11	11.3 (6/53)	21.3 (32/150)	0.15	34.0 (18/53)	32.0 (48/150)	0.86
rs11228565	11q13	18.2 (16/87)	19.0 (22/116)	0.99	37.9 (33/87)	28.5 (33/116)	0.17
rs10896450	11q13	18.5 (30/162)	19.5 (8/41)	0.83	31.5 (51/162)	36.6 (15/41)	0.58
rs11649743	17q12	17.9 (25/140)	20.6 (13/63)	0.70	30.7 (43/140)	36.5 (23/63)	0.43
rs4430796	17q12	19.8 (31/157)	15.2 (7/46)	0.67	31.9 (50/157)	34.8 (16/46)	0.72
rs1859962	17q24	16.3 (10/62)	19.9 (28/141)	0.70	25.8 (16/62)	35.5 (50/141)	0.20
rs8102476	19q13	18.5 (32/173)	20.0 (6/30)	0.80	34.1 (59/173)	23.3 (7/30)	0.30
rs5945572	Xp11	16.3 (14/86)	20.5 (24/117)	0.47	25.6 (22/86)	37.6 (44/117)	0.10