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Association of 17 Prostate Cancer Susceptibility Loci with Prostate Cancer Risk in Chinese Men

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Abstract

Background—Several genome-wide association studies (GWAS) in populations of European descent have identified more than a dozen common genetic variants that are associated with prostate cancer risk.

Methods—To determine whether these variants are also associated with prostate cancer risk in the Chinese population, we evaluated 17 prostate cancer susceptibility loci in a population-based case-control study from Shanghai, including 288 prostate cancer cases and 155 population controls.

Results—After adjusting for age, two of the 17 loci were significantly associated with prostate cancer risk, while the other 15 loci were suggestively associated with prostate cancer risk in this population. The strongest associations were found for chromosome 8q24 Region 2 (rs1016343: OR=2.07, 95% CI: 1.35-3.20, P=9.4×10^{-4}) and 8q24 Region 1 (rs10090154: OR=2.07, 95% CI: 1.31-3.28, P=0.002); additional single nucleotide polymorphisms (SNPs) assessed in these two 8q24 regions were also significant ($OR_{Region2}$=1.92-2.05, P=9.4×10^{-4}-0.003, and $OR_{Region1}$=1.77-1.81, P=0.01 for all SNPs).

Conclusions—Our study shows that multiple prostate cancer risk loci identified in European populations using GWAS are also associated with prostate cancer risk in Chinese men, a low-risk population with mostly clinically relevant cancers. Larger studies in Chinese and Asian populations are needed to confirm these findings and the role of these risk loci in prostate cancer etiology in Asian men.

Keywords

prostate cancer; association; Asian; Chinese; 8q24

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Introduction

Recent genome-wide association studies (GWAS) in 4 different study populations, all of which in European descents, have revealed more than a dozen loci associated with prostate cancer risk [1-9]. Confirmation of these risk loci among European descents has been reported extensively, but there are few studies in other racial/ethnic groups [10-19]. Most published studies in populations not of European descent were on the 8q24 loci in African American, Japanese American, Taiwanese, Latino American, Native Hawaiians, and Asian Indian populations [11-19]. Considering the fact that there are substantial differences in genetic background and lifestyles between racial groups, association studies in multiple race/ethnic populations may provide important insight into the role of genetics and gene-environmental interactions in prostate cancer etiology [20].

To date, recent GWAS have revealed 17 loci associated with prostate cancer risk in various populations worldwide [1-8,10,12-17], including 3 loci on chromosomal band 8q24 [represented by single nucleotide polymorphism (SNP) rs1447295 (Region 1), rs16901979 (Region 2), and rs6983267 (Region 3)] and 2 loci on chromosomal band 17q12 [represented by rs4430796 (Region 1) and rs11649743 (Region 2)] as well as 12 loci in other regions of the genome. To determine whether these risk loci also affect prostate cancer risk in Asian men, where prostate cancer risk is much lower but is rising steadily, we evaluated their relationship with prostate cancer risk in a population-based study conducted in Shanghai, China.

Materials and Methods

Study population

Details of this population-based case-control study have been reported elsewhere [21-23]. Briefly, cases were permanent residents of Shanghai who were newly diagnosed with prostate cancer between 1993 and 1995, identified through a rapid reporting system in 28 collaborating hospitals in urban Shanghai. The rapid reporting system captured > 95% of the cases diagnosed in urban Shanghai during the study period. Pathology material from cancer cases was reviewed by study pathologists in Shanghai and subsequently confirmed by pathologists at the Armed Forces Institute of Pathology in the USA. Based on records maintained at the Shanghai Resident Registry, male controls with no history of cancer were selected at random from the 6.5 million permanent Shanghai residents >18 years of age and frequency-matched to cancer cases by age (5-year intervals). Over 75% of the study subjects provided overnight fasting blood samples. DNA was extracted from the buffy coat fractions at the American Type Culture Collection (Manassas, VA). Only subjects with sufficient DNA available were included in the study for genotyping. In total, 288 prostate cancer cases and 155 population controls were included. There was no difference in demographic characteristics between those with and without DNA samples. This study was approved by the Institutional Review Boards at the National Cancer Institute and the Shanghai Cancer Institute and written informed consent was obtained from all study subjects.

Additional population controls

To increase the sample size of population controls for allele-based analysis, we included genotyping information from the Chinese subjects from the HapMap project in the study, including 162 Han Chinese from Beijing (CHB) and 140 Chinese from Metropolitan Denver, Colorado (CHD) [24-26]. Both CHB and CHD subjects were unrelated individuals who identified themselves as having at least three out of four Han Chinese grandparents. Data were pooled with Shanghai population controls for further analysis only if SNP allele

frequencies were similar in both the Shanghai controls and HapMap subjects, as suggested by HapMap guidelines [24-26].

Selection of SNPs for evaluation and genotyping

We selected one SNPs from each of the 17 loci that were significantly associated with prostate cancer risk ($P < 10^{-8}$) in four previous GWAS [1-8] and one followed-up fine mapping follow-up study [27]. These loci included three independent loci at 8q24 (Region 1 rs1447295, Region 2 rs16901979, and Region 3 rs6983267), two independent loci at 17q12 (Region 1 rs4430796 and Region 2 rs11649743), and one locus each at 2p15, 3p12, 6q25, 7p15, 7q21, 9q33, 10q11, 10q26, 11q13, 17q24.3, 19q13, and Xp11. We also selected 8 additional SNPs at 8q24 where prostate cancer associations have been reported in two fine mapping studies [15,28]. These include two additional SNPs in 8q24 Region 1 (rs4242382 and rs10090154), three additional SNPs in 8q24 Region 2 (rs1016343, rs13254738, and rs6983561), and 2 additional SNPs in 8q24 Region 3 (rs7837328 and rs7000448) as well as a SNP centromeric to the three 8q24 risk regions (rs979200).

The 25 SNPs were genotyped for all study subjects using a MassARRAY iPLEX system (Sequenom, Inc. San Diego, CA). Two duplicates and two water samples were included in each 96-well plate as PCR-negative controls. All assays were performed in a blinded fashion. The genotype call rates for these SNPs were 98% and the average concordance rate between samples was 100% among the duplicated quality control samples.

Statistical methods

Tests for Hardy-Weinberg Equilibrium (HWE) were performed for each autosomal SNP separately among control subjects, using Pearson's χ^2 test. Unadjusted allelic odds ratios (ORs) and the associated 95% confidence interval (95% CI) were calculated for each risk allele (R) versus non-risk allele (N); risk alleles were defined based on European populations. Logistic regression analysis was used to test for the association between prostate cancer and the genotypes as well as for calculating ORs and 95% CI in models that were adjusted for age (4 categories: <65, 65-69, 70-74, and ≥75). Due to the limited size of the study, autosomal SNPs were modeled in a dominant mode of inheritance (NN vs NR +RR) if the risk allele frequency was less than 50% in the controls and in a recessive mode of inheritance (NN+NR vs RR) if the risk allele frequency was greater than 50% in the controls. Significant results are defined as $P<0.05$ (unadjusted and age-adjusted models) and $P<0.002$ (Bonferroni corrected for age-adjusted models). For SNPs on 8q24, pair-wise linkage disequilibrium (LD) was estimated in control subjects using Haploview [30]. Haplotype blocks were inferred using the default option of the Gabriel method [31].

Results

Table I shows selected demographic characteristics of study participants. Case and control subjects were of similar age and body size; over half of the subjects were in the normal body mass index (BMI) category (BMI of 18.5-22.9 kg/m^2) as defined by the World Health Organization recommendations for Asian populations [29]. Over 55% of cases had PSA levels above 4 ng/ml. The median total PSA level for cases was 8.1 ng/mL with an interquartile range of 0.38 to 90.0 ng/mL and the median total PSA level for controls was 1.5 ng/mL with an interquartile range of 1.0 to 2.8 ng/mL. Because screening is relatively uncommon during our study period, only about 46% of the cases were localized, while over half were regional or remote. The majority of the cases (91%) were moderately or poorly differentiated.

All autosomal SNPs were in HWE ($P \geq 0.05$) among control subjects (Table II). Of the 17 loci evaluated (Table II, top panel), two were significantly associated with prostate cancer in unadjusted models, including 8q24 Region 2 rs16901979 (OR=1.93, 95% CI, 1.39-2.70) and 8q24 Region 1 rs1447295 (OR=1.52, 95% CI, 1.06-2.18), while 13 other loci were suggestively associated with prostate cancer risk. Because allele frequencies for all SNPs were very similar between our controls and HapMap subjects (CHB and CHD), we combined our controls with those from HapMap and used this larger combined control group for further analysis to increase the statistical power of the study. Analysis of allele frequencies of the cases and the combined controls showed that four of the 17 loci, including the two 8q24 regions described above, 7p15 rs10486567 (P=0.009), and 10q11 rs10993994 (P=0.04), were significantly associated with prostate cancer risk. The effect of both 8q24 Regions 1 and 2 persisted after further adjustment for age using logistic regression analysis; further adjustment for BMI did not change the results. In addition, although not statistically significant, 11 other loci were suggestively associated with increased risk (ORs after age-adjustment ranged from 1.11-2.02) and 4 loci were suggestively associated with decreased risk (ORs ranged from 0.82-0.96). In general, directions of the effects as well as effect sizes for both significant and non-significant loci are the same as that seen in the European populations in almost all risk regions examined.

Additional SNPs genotyped in the three 8q24 risk regions (Table II, bottom panel and Figure 1a) show all SNPs in 8q24 Regions 1 and 2 were significantly associated with prostate cancer risk (P<0.05) in both unadjusted and adjusted models. The strongest associations were found for the additional three SNPs in Region 2 (rs1016343, rs13254738, and rs6983561; $P_{adjusted}$ ranged from 9.4×10^{-4}-0.003), followed by the additional two SNPs in Region 1 (rs4242382, and rs10090154; $P_{adjusted}$ ranged from 0.002-0.01). The additional SNPs at region 3 (rs7837328, and rs7000448) were not significantly associated with prostate cancer similar to rs6983267, nor was rs979200 at the centromeric boundary of 8q24 ($P_{adjusted}$>0.05). All SNPs within the same region were in significant LD with one another (Figure 1b). Among all 25 SNPs typed, three SNPs in the 8q24 Region 2 (rs16901979, rs1016343, and rs13254738) as well as one SNP in 8q24 Region 1 (rs10090154) remained significant after Bonferroni correction (P<0.002) in adjusted models.

Discussion

In this population-based study of prostate cancer in Chinese men, we systematically evaluated 17 reported prostate cancer risk loci identified through GWAS in populations of European descent. We found that two of the 17 loci (8q24 Regions 1 and 2) were significantly associated with prostate cancer risk in Chinese men in all statistical models. These results suggest that some prostate cancer risk variants identified in populations of European descent are also relevant for Chinese men, a low-risk population with mostly clinically relevant cancers.

Evaluation of additional SNPs at the 3 risk loci on 8q24 in this Chinese population showed that SNPs in Regions 1 and 2 were significantly associated with prostate cancer risk while associations for SNPs in Region 3 were mostly null, although this result could be due to limited power related to minor allele frequencies of SNPs on Region 3. These results are consistent with those from three previous studies of 8q24 in Asian populations [12,16,17], which found significant associations with Regions 1 and 2 while results for Region 3 were mixed. Taken together, these results suggest that risk Regions 1 and 2 of 8q24 may be more important than Region 3 of 8q24 in relation to prostate cancer risk in Asian populations, although larger studies are needed to confirm these findings.

There are several notable advantages to replicating GWAS findings from populations of European descent in other racial/ethnic groups, including minority populations. First, most of the cases had aggressive prostate tumors, since PSA screening in China was relatively uncommon during the early 1990s in China when the parent study was conducted. Second, this is an efficient and cost-effective approach for identifying high-risk variants in minority populations. Targeted evaluations of a dozen high-risk loci for prostate cancer, identified from GWAS in European populations, in minority populations are feasible and efficient because smaller numbers of SNPs need to be typed and evaluated, thus incurring a lower cost. The identification of several regions associated with prostate cancer risk in this small Chinese study population successfully demonstrated the benefit. Third, genetic association studies in multi-ethnic populations provide important information in distinguishing true from false associations. For example, confirming the same risk loci in populations that have substantially different genetic backgrounds and lifestyle provides further support for the observed associations. For the SNPs that fail to be confirmed in other racial/ethnic groups given sufficient power, the substantially different genetic backgrounds and environmental exposures between the populations may provide a unique opportunity to study gene-gene and gene-environmental interaction in the disease risk [20].

Limitations of the study should be noted. The statistical power of this small study was limited. For example, we had only 80% power to detect SNPs with allelic OR ≥ 1.6 and minor allele frequency (MAF) ≥ 20% in this study population [32]. Therefore, caution should be exercised in interpreting these results (i.e., we could not exclude the possibility that some of the non-significant SNPs in this study may still be modestly associated with prostate cancer risk in the Chinese population). False positive associations due to multiple testing are likely. After adjustment for 25 tests, only four SNP in 8q24 remained significant after Bonferroni correction. Finally, although our cases and controls came from a relatively homogenous Chinese population in Shanghai, we could not rule out the possibility that some observed associations in the study may have been subject to potential population stratification, since the genetic background (i.e., ancestry informative markers) in our subjects had not been measured and controlled for.

Conclusions

In summary, we found that multiple prostate cancer risk-associated loci identified in populations of European descent using GWAS may be associated with prostate cancer risk in the Chinese population. Our study demonstrated an efficient and cost-effective approach to confirming in a Chinese population the genetic variants implicated in other study populations. Larger studies in the Chinese population are needed to confirm these findings and further evaluate additional genetic variants, especially those with a modest effect. Identification of variants associated with prostate cancer may improve our understanding of the disease etiology and have potential implications for the early detection, diagnosis, and treatment of prostate cancer.

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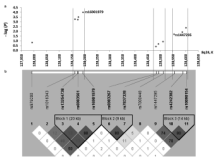

Figure 1.
A schematic view of genetic association between SNPs at 8q24 and prostate cancer risk. (Upper panel) Allelic association tests for SNPs at 8q24 (127,950,000-128,600,000) and prostate cancer risk in the Shanghai population. (Lower panel) Pair-wise LD and inferred haplotype blocks of SNPs at this region based on the control subjects in the Shanghai population. The color of each square represents the pair-wise D′; the darker dhases corresponding to stronger D′, with the brightest red representing D′=1 and pure white represents D′=0. The number in the square represents r^2.

Table I
Selected demographic characteristics of study subjects

	Prostate Cancer Cases N=288		Controls N=155	
Characteristic	**n**	**%**	**n**	**%**
Age (years)				
< 65	29	11.9	29	18.7
65-69	42	17.3	26	16.8
70-74	75	30.9	45	29.0
≥ 75	97	39.9	55	35.5
Body mass index (BMI; kg/m^2)[a]				
Underweight (<18.5)	17	13.1	16	10.4
Normal (18.5-22.9)	67	51.5	87	56.5
Overweight (23-27.5)	35	26.9	38	24.7
Obese (>27.5)	11	8.5	13	8.4
Prostate specific antigen (PSA; ng/ml)				
Normal (≤ 4)	128	44.6	129	83.2
Elevated (> 4)	159	55.4	26	16.8
Clinical Stage of Cancer				
Localized	102	35.4	-	-
Regional	56	19.4	-	-
Remote	64	22.2	-	-
Unstaged	66	22.9	-	-
Histological phenotype				
Well differentiated	18	6.3	-	-
Moderately differentiated	76	26.4	-	-
Poorly differentiated	111	38.5	-	-
Unknown	83	28.8	-	-

[a] BMI categories are based on the World Health Organization recommendations for Asian populations [29]

Table II

Association of SNPs with prostate cancer risk in a Chinese population

					Controls n=155					HapMap[d] N=302	Prostate Cancer Cases n=288											
						Genotypes[b]					Unadjusted Allelic OR[e]					Genotypes[b]			Age-adjusted OR[g]			
Chr	SNP	Locus	Non-risk allele (N)	Risk allele (R)[a]	Risk allele frequency	NN	NR	RR	HWE P[c]	Risk allele frequency	Risk allele frequency	OR	95% CI	P	P[f]	NN	NR	RR	Model[h]	OR	95% CI	P
Prostate cancer risk loci identified in populations of European descent																						
2	rs721048	2p15	G	A	0.033	142	10	0	*0.68*	0.033	0.039	1.18	0.56 - 2.50	*0.67*	*0.60*	263	20	1	D	0.94	0.41 - 2.17	*0.89*
3	rs2660753	3p12	C	T	0.314	70	70	13	*0.44*	0.323	0.310	0.99	0.74 - 1.32	*0.92*	*0.64*	142	105	35	D	0.82	0.54 - 1.23	*0.34*
6	rs9364554	6q25	C	T	0.310	72	63	15	*0.82*	0.344	0.308	0.99	0.74 - 1.34	*0.95*	*0.19*	138	117	29	D	0.96	0.64 - 1.45	*0.84*
7	**rs10486567**	**7p15**	**T**	**C**	**0.128**	**116**	**35**	**2**	***0.72***	**0.126**	**0.181**	**1.47**	**1.00 - 2.17**	***0.05***	***0.009***	192	73	14	D	1.53	0.97 - 2.43	*0.07*
7	rs6465657	7q21	T	C	0.860	5	32	112	*0.17*	0.875	0.850	0.90	0.61 - 1.33	*0.59*	*0.13*	7	74	203	R	0.83	0.52 - 1.34	*0.45*
8	**rs16901979**	**8q24 (Region 2)**	**C**	**A**	**0.235**	**85**	**52**	**8**	***0.99***	**0.264**	**0.366**	**1.93**	**1.39 - 2.70**	***1.0×10^{-4}***	***2.0×10^{-4}***	**110**	**139**	**34**	**D**	**2.03**	**1.33 - 3.10**	***0.001***
8	rs6983267	8q24 (Region 3)	T	G	0.428	51	72	29	*0.69*	0.434	0.457	1.12	0.85 - 1.48	*0.41*	*0.42*	86	134	62	D	1.11	0.72 - 1.72	*0.64*
8	**rs1447295**	**8q24 (Region 1)**	**C**	**A**	**0.156**	**110**	**35**	**6**	***0.15***	**0.130**	**0.222**	**1.52**	**1.06 - 2.18**	***0.02***	***3.7×10^{-5}***	**173**	**96**	**15**	**D**	**1.81**	**1.16 - 2.83**	***0.009***
9	rs1571801	9q33	G	T	0.036	142	11	0	*0.64*	0.054	0.063	1.80	0.90 - 3.62	*0.10*	*0.55*	246	33	1	D	1.75	0.84 - 3.63	*0.13*
10	rs10993994	10q11	C	T	0.434	43	77	24	*0.29*	0.443	0.504	1.32	0.99 - 1.75	*0.06*	***0.04***	75	130	77	D	1.12	0.70 - 1.77	*0.64*
10	rs4962416	10q26	A	G	0.007	146	2	0	*0.93*	0.007	0.012	1.85	0.38 - 9.03	*0.45*	*0.39*	276	7	0	D	2.02	0.41 - 9.92	*0.38*
11	rs10896449	11q13	A	G	0.086	122	21	2	*0.33*	0.084	0.111	1.35	0.82 - 2.23	*0.24*	*0.12*	221	63	0	D	1.53	0.89 - 2.64	*0.13*
17	rs11649743	17q12 (Region 2)	A	G	0.660	19	64	67	*0.55*	0.654	0.700	1.22	0.91 - 1.64	*0.19*	*0.064*	28	110	143	R	1.35	0.89 - 2.05	*0.15*
17	rs4430796	17q12 (Region 1)	C	T	0.720	11	63	78	*0.72*	0.724	0.740	1.14	0.83 - 1.56	*0.43*	*0.42*	17	110	155	R	1.18	0.78 - 1.78	*0.43*
17	rs1859962	17q24.3	T	G	0.391	55	75	22	*0.66*	0.405	0.457	1.31	0.98 - 1.74	*0.07*	*0.072*	83	136	59	D	1.31	0.85 - 2.03	*0.22*
19	rs2735839	19q13	A	G	0.580	24	79	47	*0.34*	0.596	0.610	1.14	0.85 - *1.52*	*0.38*	*0.69*	46	131	107	R	1.15	0.66 - 2.00	*0.63*
X	rs5945619	Xp11	A	G	0.059	144[i]		9[i]		0.053	0.086	1.51	0.68 - 3.33	*0.31*	*0.16*	255[i]		24[i]		1.82	0.82 - 4.06	*0.14*
Additional SNPs genotyped at 8q24[j]																						
8	rs979200	8q24	T	C	0.510	36	76	39	*0.93*	0.498	0.459	0.82	0.62 - 1.08	*0.16*	*0.18*	84	134	61	R	0.77	0.47 - 1.25	*0.29*
8	**rs1016343**	**8q24 (Region 2)**	**C**	**T**	**0.330**	**66**	**65**	**16**	***1.00***	**0.341**	**0.453**	**1.76**	**1.29 - 2.41**	***3.7×10^{-4}***	***1.0×10^{-4}***	**76**	**159**	**49**	**D**	**2.07**	**1.35 - 3.20**	***9.4×10^{-4}***
8	**rs13254738**	**8q24 (Region 2)**	**A**	**C**	**0.697**	**11**	**70**	**71**	***0.26***	**0.303**	**0.801**	**1.82**	**1.32 - 2.56**	***0.001***	***5.9×10^{-4}***	**9**	**92**	**176**	**R**	**2.05**	**1.34 - 3.13**	***9.4×10^{-4}***
8	**rs6983561**	**8q24 (Region 2)**	**A**	**C**	**0.245**	**80**	**53**	**8**	***0.84***	**0.245**	**0.368**	**1.85**	**1.33 - 2.59**	***2.9×10^{-4}***	***3.1×10^{-4}***	**109**	**141**	**34**	**D**	**1.92**	**1.25 - 2.93**	***0.003***

					Controls n=155				HapMap[d] N=302	Prostate Cancer Cases n=288											
						Genotypes[b]					Unadjusted Allelic OR[e]					Genotypes[b]			Age-adjusted OR[g]			
Chr	SNP	Locus	Non-risk allele (N)	Risk allele (R)[a]	Risk allele frequency	NN	NR	RR	HWE P[c]	Risk allele frequency	Risk allele frequency	OR	95% CI	P	P[f]	NN	NR	RR	Model[h]	OR	95% CI	P
8	rs7837328	8q24 (Region 3)	G	A	0.372	59	64	22	*0.50*	0.381	0.417	1.20	0.90 - 1.59	*0.22*	*0.20*	99	133	52	D	1.18	0.77 - 1.81	*0.45*
8	rs7000448	8q24 (Region 3)	C	T	0.307	75	55	18	*0.12*	0.307	0.360	1.26	0.93 - 1.70	*0.13*	*0.12*	114	133	35	D	1.43	0.94 - 2.16	*0.09*
8	**rs4242382**	**8q24 (Region 1)**	**G**	**A**	**0.168**	**108**	**37**	**7**	***0.11***	**0.140**	**0.241**	**1.56**	**1.09 - 2.22**	***0.01***	***1.0×10^{-5}***	**163**	**105**	**16**	**D**	**1.77**	**1.15 - 2.75**	***0.01***
8	**rs10090154**	**8q24 (Region 1)**	**C**	**T**	**0.142**	**112**	**30**	**6**	***0.04***	**0.142**	**0.223**	**1.70**	**1.17 - 2.48**	***0.006***	***0.004***	**170**	**98**	**14**	**D**	**2.07**	**1.31 - 3.28**	***0.0019***

[a] Risk alleles are defined based on European populations

[b] NN=homozygous non-risk alleles; NR=heterozygous; RR=homozygous risk alleles

[c] HWE=Hardy-Weinberg Equilibrium

[d] Chinese subjects from the HapMap Project: CHB (N=162) & CHD (N=140)

[e] Based on analysis of Shanghai prostate cancer cases versus Shanghai controls; OR=Odds Ratio; CI=confidence interval

[f] Based on analysis of Shanghai prostate cancer cases versus all controls (Shanghai controls, CHB and CHD; N=457)

[g] Based on logistic regression analysis of Shanghai prostate cancer cases versus Shanghai controls adjusting for age (4 categories: <65, 65-69, 70-74, and ≥75)

[h] D=dominant mode of inheritance; R=recessive mode of inheritance

[i] Haploid

[j] Additional SNPs were selected to be genotyped from previous fine mapping studies of 8q24 to provide better coverage of this region. These include two additional SNPs at Region 1, three additional SNPs at region 2, two additional SNPs at Region 3, and 1 SNP centromeric to the risk regions.