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Pathologic Outcomes Associated with the 17q Prostate Cancer Risk Variants

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Abstract

Purpose—Recent studies have identified 2 distinct genetic variants along chromosome 17 (allele T of SNP rs4430796 on 17q12 and allele G of SNP rs1859962 on 17q24) that have been linked to prostate cancer (CaP) risk. Less is known about tumor pathology features in carriers of these variants.

Materials and Methods—Genotypes for regions 17q12 and 17q24 were determined for 759 Caucasian men with CaP and compared to 790 healthy control volunteers using logistic regression. For CaP patients, Fisher's Exact tests or Kruskal-Wallis tests, when appropriate, were used to assess the relationship(s) between clinical and pathologic characteristics with 17q carrier status.

Results—The frequencies of the 17q12 and 17q24 genetic variants were significantly higher in CaP patients compared to controls (OR 1.32 and 1.15, respectively). Eighty-three percent and 77% of CaP patients, as well as 75% and 75% of controls were carriers of the 17q12 and 17q24 variants, respectively. Carriers of the 17q12 risk variants were significantly more likely to have high-grade disease using an additive best-fit genetic model. In addition, there were trends for adverse pathologic features associated with 17q12 independent of the best-fit genetic model.

Conclusions—Sequence variants along 17q12 and 17q24 are present in a significantly higher proportion of our CaP cases than among our controls. Adverse pathologic features, including higher Gleason grade and pathologic stage, were more frequent among 17q12 carriers. Since these alleles may act in conjunction with variants on other chromosomes to influence CaP risk, additional research is required to determine the cumulative associations of genetic risk variants with prognosis.

Keywords

chromosome 17; genetics; prostate cancer

INTRODUCTION

Within the past few years, sequence variants located along chromosome 8q24 have been described that are significantly associated with an increased risk for prostate cancer (CaP). More specifically, single nucleotide polymorphisms (SNPs) contained within at least 3

different regions of a 600 kB region along 8q24 independently and significantly contribute to CaP risk^{1–5}. This discovery has been considered a major breakthrough in CaP genetics.

Although it has been estimated that the 8q24 genetic variants may explain up to 30% to 40% of CaP cases in the population, they do not explain the entire incidence of CaP¹. In fact, other regions on chromosomes 2, 3, 6, 7, 10, 11, 17, 19 and X also have been implicated in CaP susceptibility^{6–10}. Many of these other newly identified genetic variants have yet to be independently validated. This is not the case for the genetic variants along 17q, for which several studies have now verified the association with CaP risk^{11–13}. Specifically, 2 SNPs located within 17q12 (allele T of SNP rs4330796) and 17q24.3 (allele G of SNP rs1859962) have been reproducibly shown to be significantly associated with an increase risk. A recent study of patients from Sweden demonstrated that the 17q alleles act in an independent fashion to modestly increase CaP risk (OR 1.28–1.38)¹¹. Moreover, this study found that when combined with SNPs along chromosomal region 8q24, there is a more than a 4-fold (OR=4.47) increased risk for patients who are carriers of at least 4 variants compared to patients with no genetic risk variants. Furthermore, when combined with family history, these genetic variants act in a cumulative manner to increase CaP risk by more than 9-fold (OR=9.46)¹¹. These results have recently been replicated in other patient cohorts^{12–15}.

With the exception of rs4430796 on 17q12 (within the TCF2 gene), the CaP susceptibility variants along 8q24 and 17q lie in relatively gene-poor regions⁸. As such, their mechanism of influencing CaP susceptibility and mode of inheritance is not yet known. In addition, less is known about their relationship with CaP aggressiveness. For example, some studies have demonstrated that variants on 8q24, alone or in combination, are associated with a younger age at diagnosis and high-grade disease^{2, 4, 5, 16, 17}. However, other research groups have reported conflicting results^{11, 18, 19}. The purpose of the present study was to further examine the association of 17q alleles with detailed clinical and pathology features in CaP patients treated with radical prostatectomy and to evaluate the best-fit genetic logistic regression model (i.e. dominant, recessive, additive) that best describes their effects.

MATERIALS AND METHODS

Our case-control study included 1549 Caucasian men. Of these, 759 consecutive men were treated for CaP at Northwestern Memorial Hospital between 2002 to 2007, including 536 men who were previously described in a preliminary analysis⁸. A single surgeon (WJC) performed the radical prostatectomy for 90% of the cases, and the remainder were treated by other physicians in the Northwestern University Specialized Program of Research Excellence (SPORE) group. Serum PSA levels, digital rectal examination (DRE) findings, demographic information, and biopsy findings were collected, when available. Tumors were graded and staged using established criteria. PSA velocity was calculated by regression analysis using PSA measurements from the year prior to diagnosis²⁰. Patients who had more than one year of follow-up were included for analysis of biochemical recurrence, defined as a post-operative PSA >0.2 ng/ml.

As a comparison group, we report on 790 controls with no history of CaP. Of these men 247 were drawn from a control population that has been previously described⁸. An additional 543 healthy volunteers were recruited as part of a CaP screening program conducted in April 2007. To qualify as a control, all men had a PSA < 2.5 ng/ml and normal DRE. The study received institutional review board approval, and informed consent was provided by each participant.

DNA samples were isolated from whole blood, and genotypes were available for all 759 men in the study population and all 790 controls. SNP genotyping for all samples was

carried out at deCODE genetics in Reykjavik, Iceland, using the Centaurus (Nanogen) platform⁸. In particular, we assayed for the presence of the T allele of SNP rs4430796 on 17q12 and the G allele of the SNP rs1859962 on 17q24, since these have been found to be associated with CaP susceptibility^{8, 11}.

We used Fisher's Exact Test to compare the allele frequencies between cases and controls. For each of the two CaP susceptibility loci within 17q, genotype information was compared using Akaike's Information Criteria (AICs) and P-values to choose the best fit genetic logistic regression model (i.e. dominant, recessive, additive) as previously described¹¹. In addition, the Fisher's Exact and Kruskal-Wallis tests were used to compare clinical and pathology features between carriers (defined using either an additive or recessive model) and non-carriers of the 17q genetic variants. All statistical analysis was performed using SAS 9.2 (Statistical Applications System, Cary, NC).

RESULTS

In the overall population, the T allele of SNP rs4430796 along 17q12 was present at a frequency of 0.58 in CaP patients and 0.51 in controls (OR 1.32, 95% C.I. 1.14–1.52, $p=0.0001$). Similarly, the G allele of SNP rs1859962 was present at a frequency of 0.53 in patients with CaP and 0.49 in controls (OR 1.15, 95% C.I. 1.0–1.32, $p=0.057$). Thus, men with CaP had a higher frequency of the 17q sequence variants compared with healthy volunteer controls, consistent with our previously reported results in a subset of the population⁸.

It has previously been suggested that both of the 17q sequence variants follow a recessive inheritance pattern when best-fitting genetic modeling is applied¹¹. However, using logistic regression models, we determined that in our study population, an additive model was the best-fitting genetic model for both risk variants (Table 1).

Of the 759 CaP patients, the vast majority (96%) were carriers (heterozygous or homozygous) for at least one 17q risk allele. Specifically, 630 (83%) were carriers of the T allele of SNP rs4430796 on 17q12, 586 (77%) were carriers of the G allele of rs1859962 on 17q24 (Table 1), and 487 (64%) were carriers of both alleles. In contrast, only 75%, 75%, and 56% of control patients were carriers of the 17q12 variant, 17q24 variant and both alleles, respectively. Among CaP cases, 240 (32%) were homozygous for the T allele of SNP rs4430796 on 17q12, 211 (28%) were homozygous for the G allele of rs1859962 on 17q24, and 63 (8%) were homozygous for both alleles. Finally, 204 (26%) were homozygous for 17q12, 186 (24%) were homozygous for 17q24, and 48 (6%) were homozygous for both.

Next, we examined the clinical characteristics of the 759 CaP patients included in this study. The average age was 59.9 ± 7.4 years, with a mean pre-operative PSA of 6.0 ± 4.2 ng/ml, and a median PSAV of 1.4 ng/ml/yr. More than 30% reported a first-degree relative with CaP. In addition, 70.7% had clinical stage T1c disease. Pathologic analysis of the radical prostatectomy specimen revealed that 79.6% of patients had organ-confined disease, 18.6% had positive surgical margins, 4.7% had seminal vesicle invasion, and 0.8% had lymph node metastases.

Since both variants follow an additive best-fit genetic model, we compared the clinical and pathologic features between carriers and non-carriers of the 17q12 and 17q24 genetic variants using this approach (Table 2). Overall, there were few differences in the frequency of adverse features between carriers and non-carriers of either 17q genetic variant. However, there was a marginal trend for carriers of the 17q12 variants to have higher clinical stage, pathologic stage and biopsy Gleason grade (Table 2a/b). Carriers of the T allele of SNP

rs4430796 of 17q12 were significantly more likely to have a prostatectomy Gleason score ≥ 7 (Table 2b). Similarly, there was a higher percentage of 17q12 homozygote carriers with a biopsy Gleason score $\geq 4+3=7$ (14.8% versus 10.7%) and pathological Gleason score $\geq 4+3=7$ (17.4% versus 13.9%) compared to non-carriers of this variant. Similar trends were not observed for carriers of the G allele of SNP rs1859962 on 17q24 using the additive genetic model (Table 2). In addition, there was no clear association between carrier status and the frequency of short-term (>1 year) biochemical recurrence for either 17q sequence variant (Table 2b). Finally, carriers of both 17q12 and 17q24 variants had similar rates of organ-confined disease, positive surgical margins, and extracapsular tumor extension (data not shown).

Due to the apparent discordance between our results and prior studies with regard to the best-fit genetic model at 17q12, we also determined the clinical and pathology outcomes using a recessive model (i.e. limited to homozygotes) for both the 17q12 and 17q24 risk variants (Table 3). As with the additive genetic models, there were few differences between carriers and non-carriers of the 17q variants with regard to most clinical and pathology tumor features. However, the recessive model demonstrated that carriers of the 17q12 variants were more likely to have palpable disease compared to non-carriers (Table 3a). Finally, there were no obvious differences in clinical or pathologic outcomes in patients who were homozygous carriers of both 17q variants (compared to carriers of ≤ 1 variant) using a recessive model (data not shown). However, men who were homozygous for both alleles demonstrated an increased frequency of both clinical and pathologic high-grade disease (39% and 53%, respectively) compared to carriers of ≤ 1 variant (53% and 49%, respectively).

DISCUSSION

While we have previously demonstrated that the 17q genetic variants are over-represented in patients with CaP⁸, the present study confirms this frequency in a larger population of CaP patients and healthy volunteer controls. In addition, this study specifically examines the differences in clinical and pathology outcomes between carriers and non-carriers of the 17q CaP risk variants. Finally, another important objective of our study was to compare different best-fit genetic models for the risk variants at 17q12 and 17q24. In contrast to prior reports suggesting a recessive or dominant best-fit model^{11,12}, our results suggest that these variants instead act in an additive fashion in our Caucasian population of men treated with radical prostatectomy. Moreover, these data demonstrate that the type of genetic model used in the analysis can alter the apparent association of these risk alleles with surgical outcomes, perhaps explaining some of the differences between studies reported in the literature.

Using an additive genetic model we found that carriers of 17q12 variants were significantly more likely to have high-grade disease. In addition, this genetic model demonstrated marginally significant trends toward a higher clinical stage. Despite the possibility of a spurious association, this association was confirmed with age-adjusted multivariate analysis (data not shown). Nevertheless, the prognostic effects of 17q12 and 17q24 did not appear to be cumulative with one another, since carriers of both risk variants had a similar frequency of adverse pathology features (Table 3).

As mentioned above, it is noteworthy that the best-fitting genetic model highly influenced the interpretation of clinical and pathology outcomes. A previous report in Swedish men suggested that both 17q variants follow a recessive model¹¹; whereas, an additive genetic model had the best fit for both variants in our population. This apparent discrepancy may relate to a variety of factors including, but not limited to, sample size, adjustment for

geographic region, and/or genetic differences between the populations. Additional studies in larger numbers of patients will be required to further examine these models and associations.

It is intriguing that 30% of our study population reported having a first-degree relative with CaP, a slightly higher frequency than in prior reports²¹. A possible explanation is that other genetic factors may directly or indirectly influence the 17q variants and contribute to CaP susceptibility. Alternative possibilities include patient recall bias, referral bias, and selection bias (i.e. patients with a family history may be more willing to participate in a genetic study).

Several limitations of our study deserve mention. First, we limited our study to Caucasian men of European descent. Since prior studies have shown that the frequency of these CaP genetic susceptibility variants differs among ethnic groups, separate studies are needed to test these results in other ethnic groups. In addition, all of the CaP patients in our study underwent radical prostatectomy, which may have introduced a selection bias. A surgical cohort of relatively healthy men does not reflect the full spectrum of CaP patients, and patients who are candidates for surgery also may have systematic genetic differences. Therefore, future studies are warranted in patients with more advanced disease undergoing primary radiation and/or hormonal therapy. Finally, it has previously been suggested that genetic variants contained within other genomic regions, such as 2p15 and Xp11, also may be associated with aggressive pathology features^{1, 6, 9}. Our results suggest that the 17q variants contribute only modestly to the presence of adverse pathological features such as tumor grade and stage. Nevertheless, further research is needed to evaluate the contribution from sequence variants on other chromosomes.

Despite these limitations, our results provide support for a possible association between the 17q12 variants with higher clinical grade and stage using an additive best-fit model. Similar trends were not found for the 17q24 variants. Therefore, it is plausible that only the 17q12 variant is associated with both CaP risk and aggressiveness; alternatively, the 17q24 variant may only contribute to disease aggressiveness in combination with variants on other chromosomes that were not examined in this study. Clearly, many important questions remain unanswered, including a more detailed analysis of the interactions between 17q sequence variants with CaP risk variants elsewhere in the genome.

CONCLUSIONS

In a larger population, we confirmed that the 17q sequence variants are present in a significantly higher proportion of prostate cancer patients compared with healthy controls. The odds ratio was similar to those in other studies¹¹, indicating that both of the 17q variants have an independent and modest effect on CaP risk. While the 17q12 variant may be associated with specific adverse features, including higher Gleason score, the association with pathology features was influenced by the best-fit genetic model used. Additional studies are warranted to further examine the relationship between these CaP risk variants and disease aggressiveness.

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Table 1

Best fit genomic logistic regression model of genotype vs. case-control status in 1,549 men according to p value and Akaike's information criteria

Chromosomal region/SNP/Alternative Alleles/Variant Allele		Genotype Comparisons	OR (95% CI)	p Value
17q12/rs4430796/T, C/T				
	Model			
	Additive	0, 1 or 2 Variants*	1.32 (1.15–1.53)	0.0001
	Recessive	CC, TC	1.00	--
	Recessive	TT	1.33 (1.07–1.66)	0.012
	Dominant	CC	1.00	--
	Dominant	TC or TT	1.61 (1.26–2.07)	0.0002
17q24/rs1859962/G, T/G				
	Model			
	Additive	0, 1 or 2 Variants*	1.15 (1.00–1.32)	0.054
	Recessive	TT or GT	1.00	
	Recessive	GG	1.25 (1.00–1.57)	0.056
	Dominant	TT	1.00	
	Dominant	GT or GG	1.16 (0.92–1.46)	0.224

* Carrier status 0—homozygous WT, 1—heterozygous and 2—homozygous genetic variant.

Table 2

Clinical and pathological features in carriers and noncarriers of 17q CaP sequence variants in additive best fit genetic model

	17q12				17q24			
	Homozygous WT (C,C)	Heterozygous (T,C)	Homozygous (T,T)	p Value *	Homozygous WT (T,T)	Heterozygous (G,T)	Homozygous (G,G)	p Value *
Median age (range)	58 (39–73)	60 (37–87)	59 (41–75)	0.43	60 (41–73)	58 (39–87)	59 (37–77)	0.17
Median ng/ml preop PSA (range)	5.1 (0.6–30.0)	5.0 (0.3–30.0)	5.0 (0.5–48.0)	0.93	5.3 (0.5–25)	4.9 (0.3–39.4)	5.1 (0.8–48.0)	0.99
Median ng/ml/yr PSA velocity (range)	1.4 (–15.3–14.5)	1.6 (–251.4–37.3)	1.2 (–45.0–19.4)	0.19	1.5 (–45.0–20.0)	1.3 (–251.4–37.3)	1.4 (–8.1–19.4)	0.76
No. family history 1 st -degree relative (%)	38 (33)	104 (31)	55 (27)	0.36	47 (31)	100 (31)	50 (8)	0.84
No. Clinical stage ≤T1C (%)	92 (73)	272 (73)	151 (65)	0.10	122 (73)	251 (70)	142 (70)	0.68
No. biopsy Gleason grade ≥7 (%)	30 (25)	128 (35)	73 (32)	0.10	44 (27)	108 (30)	61 (30)	0.68
No. pathological Gleason grade ≥7 (%)	49 (40)	192 (53)	110 (49)	0.04	87 (53)	176 (50)	88 (46)	0.40
No. organ confined ≤pT2 (%)	105 (83)	287 (78)	184 (81)	0.35	130 (78)	287 (80)	159 (80)	0.78
No. extracapsular extension (%)	19 (15)	76 (21)	42 (19)	0.40	33 (20)	68 (19)	36 (18)	0.92
No. positive surgical margins (%)	23 (18)	67 (18)	45 (20)	0.89	30 (18)	63 (18)	42 (21)	0.62
No. seminal vesicle invasion (%)	7 (6)	19 (5)	8 (3)	0.54	9 (5)	15 (4)	10 (5)	0.76
No. pos lymph nodes (%)	1 (1)	3 (1)	2 (1)	0.99	1 (1)	2 (1)	3 (2)	0.56
No. biochemical recurrence (%)**	5 (6)	11 (5)	10 (9)	0.38	9 (9)	14 (7)	3 (3)	0.22

* Kruskal-Wallis test for continuous variables, eg age, PSA and PSA velocity, and Fisher's exact test for categorical variables.

** PSA greater than 0.2 ng/ml

Table 3

Clinical and pathological features in carriers and noncarriers of 17q CaP sequence variants in recessive best fit genetic model

	17q12				17q24		
	No. Pts	Carriers (TT)	Noncarriers (CT or CC)	p Value *	Carriers (G,G)	Noncarriers (G,T or T,T)	p Value *
Median age (range)	759	59 (41–75)	59 (37–77)	0.89	59 (37–77)	59 (39–77)	0.75
Median ng/ml preop PSA (range)	727	5.0 (0.5–48.0)	5.0 (0.3–30.0)	0.71	5.1 (0.8–48.0)	5.0 (0.3–39.4)	0.92
Median ng/ml/yr PSA velocity (range)	313	1.2 (–45.0–19.4)	1.6 (–251.4–37.3)	0.07	1.4 (–8.1–19.4)	1.4 (–251.4–37.3)	0.57
No. family history 1 st degree relative (%)	652	55 (27)	142 (32)	0.17	50 (28)	147 (31)	0.57
No. stage ≤T1C (%)	728	151 (65)	364 (73)	0.04	142 (70)	373 (71)	0.79
No. biopsy Gleason score ≥7 (%)	711	73 (32)	158 (33)	0.93	71 (36)	160 (31)	0.21
No. pathological Gleason score ≥7 (%)	707	110 (49)	241 (50)	0.87	88 (46)	263 (51)	0.24
No. organ confined T2 (%)	724	184 (81)	392 (79)	0.62	159 (80)	417 (80)	0.99
No. extracapsular extension (%)	711	42 (19)	95 (20)	0.84	36 (18)	101 (20)	0.75
No. pos surgical margins (%)	725	45 (20)	90 (18)	0.68	42 (21)	93 (18)	0.34
No. seminal vesicle invasion (%)	725	8 (3)	26 (5)	0.35	10 (5)	24 (5)	0.84
No. pos lymph nodes (%)	723	2 (1)	4 (1)	0.99	3 (2)	3 (1)	0.36
No. biological recurrence (%)**	397	10 (9)	16 (6)	0.18	3 (3)	23 (8)	0.16

* Kruskal-Wallis test for continuous variables, eg age, PSA and PSA velocity, and Fisher's exact test for categorical variables.

** PSA greater than 0.2 ng/ml