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Genetic Variants in the *LEPR*, *CRY1*, *RNASEL*, *IL4*, and *ARVCF* Genes Are Prognostic Markers of Prostate Cancer-Specific Mortality

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Abstract

Background—Prostate cancer is the second leading cause of cancer-related deaths in men, accounting for over 30,000 deaths annually. The purpose of this study was to test whether variation in selected candidate genes in biological pathways of interest for prostate cancer progression could help distinguish patients at higher risk for fatal prostate cancer.

Methods—In this hypothesis-driven study, we genotyped 937 single nucleotide polymorphisms (SNPs) in 156 candidate genes in a population-based cohort of 1,309 prostate cancer patients. We identified 22 top-ranking SNPs (P ≤0.01, FDR ≤0.70) associated with prostate cancer-specific mortality (PCSM). A subsequent validation study was completed in an independent population-based cohort of 2,875 prostate cancer patients.

Results—Five SNPs were validated (P ≤0.05) as being significantly associated with PCSM, one each in the *LEPR*, *CRY1*, *RNASEL*, *IL4*, and *ARVCF* genes. Compared to patients with 0–2 of the at-risk genotypes those with 4–5 at-risk genotypes had a 50% (95% CI, 1.2–1.9) higher risk of PCSM and risk increased with the number of at-risk genotypes carried (P_{trend} = 0.001), adjusting for clinicopathological factors known to influence prognosis.

Conclusion—Five genetic markers were validated to be associated with lethal prostate cancer.

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Impact—This is the first population-based study to demonstrate that germline genetic variants provide prognostic information for prostate cancer-specific survival. The clinical utility of this five-SNP panel to stratify patients at higher risk for adverse outcomes should be evaluated.

Keywords

Prostate cancer-specific mortality; survival; genetic variants; single nucleotide polymorphisms; hazard ratio

Introduction

Prostate cancer accounts for over 200,000 cancer diagnoses each year in the U.S. Although many men at diagnosis have localized tumors that will remain indolent and slow-growing, a substantial number have tumors that will become aggressive, leading to over 30,000 prostate cancer-specific deaths each year in the U.S. (1) Disease features such as Gleason score, stage and serum prostate-specific antigen (PSA) may help distinguish patients at higher risk for adverse outcomes, (2–4) however these factors alone do not accurately stratify patients with indolent versus more aggressive tumors. Biomarkers that could predict which men are at higher risk for having life-threatening prostate cancer would substantially improve patient management, targeting aggressive therapy to those most likely to benefit and avoiding over-treatment of low-risk patients.

Genetic background is known to play a role in the development of prostate cancer, (5–7) and genetic variants have been associated with risk of more advanced disease (8) (9) or with biochemical recurrence, (10–12) although these particular SNPs have not been associated with PCSM. (13–17) Some earlier studies have correlated SNP genotypes with PCSM, (12, 18–24) but results have not been validated. Thus, while evidence suggests genetic background influences prostate cancer outcomes, validated genetic markers associated with lethal disease have yet to be characterized.

To search for genetic markers that distinguish high-risk patients for PCSM, we conducted a hypothesis-driven candidate gene study focused on biological pathways (e.g., steroid hormones, DNA repair, inflammation, circadian rhythm, vitamin D) for which there is evidence for a role in modulating prostate cancer progression. Two independent population-based prostate cancer patient cohorts, one from Seattle and one from Sweden, were studied. Top-ranking SNPs associated with fatal disease in the Seattle cohort ($P \leq 0.01$) were subsequently genotyped in the Swedish cohort for validation. The results reported here are the first to validate a panel of five SNPs in five genes that provide prognostic information at diagnosis for risk stratification of patients with prostate cancer.

Materials and Methods

Study Subjects

Seattle Patient Cohort—The Seattle cohort was established from two population-based case-control studies of prostate cancer in King County, Washington. (25, 26) In the first study, cases were diagnosed between January 1, 1993, and December 31, 1996 and were 40–64 years of age at diagnosis. In the second study, cases were diagnosed between January 1, 2002, and December 31, 2005 and were 35–74 years of age at diagnosis. Overall, 2,244 eligible patients were identified and 1,754 (78%) were interviewed. Blood samples were drawn from 1,457 (83%) interviewed patients.

The current study includes 1,309 Caucasian patients with DNA available. These cases had confirmed adenocarcinoma of the prostate and were ascertained from the Seattle-Puget

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Sound SEER cancer registry, which provided information on Gleason score, (27) cancer stage at diagnosis, (28) diagnostic PSA level and primary therapy. (29) Vital status and underlying cause of death were also obtained through the cancer registry, which links quarterly to the Washington State Center for Health Statistics database. Underlying cause of death was coded according to the International Classification of Diseases (30). A total of 60 patients died of prostate cancer over an average follow-up period of 8.5 years (range 0.8 – 15.9 years); vital status for this analysis was determined as of January 2009.

The study was approved by the Institutional Review Board (IRB) of the Fred Hutchinson Cancer Research Center and written informed consent was obtained from all study participants. Genotyping was approved by the IRB of the National Human Genome Research Institute where genotyping was completed for the Seattle cohort.

Swedish Patient Cohort—The validation cohort is comprised of patients enrolled in Cancer of the Prostate in Sweden (CAPS), a population-based study. (31) Cases were recruited from four regions in Sweden through Regional Oncology Centers between July 2001 and October 2003. A total of 3,648 eligible patients were identified, 3,161 (87%) participated and blood samples were obtained from 2,893 (92%). For the current study, 2,875 patients of European descent had DNA available for genotyping. Information on clinicopathological factors was obtained from the National Prostate Cancer Register, (32) including Gleason score, stage, diagnostic PSA level and initial treatment. Follow-up for mortality as of June 2009 was based on record linkage to the Swedish Cause of Death Register. (33) Prostate cancer was confirmed as the underlying cause of death (30) in 501 patients.

Written informed consent was obtained from all study participants. The research ethics committees at the Karolinska Institutet and Umeå University Hospital approved the study.

Genotyping

A total of 937 SNPs primarily from candidate genes in biological pathways of interest for prostate cancer (e.g., steroid hormones, inflammation, growth factors, DNA repair, circadian clock, vitamin D) were genotyped in the Seattle cohort. Most SNPs were selected using the Genome Variation Server (34); a tagSNP approach based on the HapMap CEU population was utilized to select variants with a minor allele frequency (MAF) of ≥5% and an r^2 ≥0.8. Priority was given to selection of nonsynonymous SNPs, followed by tagSNPs and SNPs previously reported to be associated with prostate cancer. For genotyping, the SNPlex Genotyping System (Applied Biosystems, Inc., Foster City, CA) was used with GeneMapper software to assign genotypes. Replicate samples (n = 140) were interspersed throughout all genotyping batches. Genotyping scores, including quality control data, were re-checked by different laboratory personnel to confirm the accuracy of each assay. Ninety-one SNPs were removed due to genotyping failure (n = 58), monomorphism (n = 27), or a low MAF (n = 6). The remaining 846 SNPs (Supplemental Table 1) were used for permutation testing to identify variants associated with PCSM.

Twenty-two SNPs were found to be significantly associated with PCSM in the Seattle cohort. For these SNPs, call rates were >95% and there was >98% agreement between duplicate samples. In addition, all 22 SNPs were in Hardy-Weinberg equilibrium (P >0.05) in 1,266 genotyped Caucasian controls who were age-matched to the Seattle patient cohort.

The 22 top ranking SNPs discovered in the Seattle cohort were then genotyped in the validation cohort. The MassARRAY iPLEX system (Sequenom, Inc., San Diego, CA) was used to genotype samples at Wake Forest University. Duplicate samples (n = 106) and two negative controls that were blinded to the laboratory technician were included in each 96-

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well plate. The overall concordance level for 20 of the 22 SNPs was 99.9% among duplicated samples. Two SNPs (rs228697 and rs1029153) failed genotyping.

Statistical Analyses

SNP Selection by Permutation Testing—Six Cox regression models (three adjusting for age at diagnosis alone and three adjusting for age in addition to stage, Gleason score, diagnostic PSA, and primary treatment) were completed under dominant, recessive and log-additive (linear trend) genetic models. One-thousand permutation datasets were generated by randomly permuting all 846 SNPs together across subjects while keeping the clinical variables fixed, i.e., the clinical variables were retained with each subject and not permuted, and the same six Cox models were run for each permuted dataset to obtain the distribution of P-values under the null hypothesis of no SNP effect. False Discovery Rates (FDR, *q* value) (35) were calculated based on the distribution of permutation P-values and the observed P-values. This approach is the same as that of Morris and coworkers. (36) Using an *a priori* determined threshold of $P \leq 0.01$ from the original data to select the top ranked SNPs, a total of 22 SNPs associated with PCSM were selected for validation. For these top ranking 22 SNPs, the FDR ranged from 0.26 to 0.70, which we deemed acceptable due to the affordable cost of genotyping in the validation cohort and the desire to not miss potentially informative SNPs for validation.

Cox Models—The hazard ratio (HR), 95% confidence interval (CI) and P-value were obtained for each of the 22 top ranked SNPs (Seattle cohort) under the best-fitting genetic model for each SNP. Cox models using the same underlying best-fitting genetic model from the Seattle cohort, but allowing for three sets of covariates (i.e., 1) age at diagnosis; 2) age at diagnosis, Gleason score, stage, and diagnostic PSA level; and 3) age at diagnosis, Gleason score, stage, diagnostic PSA level and initial treatment), were completed for each of the 20 SNPs genotyped in the Swedish cohort; a SNP was judged to be validated if the P-value from one of the three models was ≤0.05 (one-sided test) and the effect on mortality risk was in the same direction as in the Seattle dataset. HRs for the cumulative number of at-risk genotypes were calculated by Cox models adjusted for age alone and for age plus the four clinicopathological factors. The grouping by number of at-risk genotypes was done to ensure that each group had an expected number of at least five fatal events based on the Seattle cohort. The same grouping of at-risk genotypes (i.e., 0–2, 3, 4, or 5) was used to generate Kaplan-Meier (K–M) curves. A backward stepwise Cox model (adjusted for age and the four clinicopathological factors) was used to rank validated SNPs by level of statistical significance. SNP by SNP interactions were also examined, and an interaction was considered significant if the P-value associated with the HR was <0.001 (Bonferroni adjustment, $P \leq 0.05$).

Results

Characteristics of the two patient cohorts are shown in Table 1. Patients in the Seattle cohort were younger at diagnosis than those in the Swedish cohort (mean age at diagnosis 59.9 versus 65.8 years, respectively, $P < 0.0001$). A higher proportion of patients from Sweden (17.4%) had died of prostate cancer relative to those from Seattle (4.6%) during a median follow-up time of 6.5 years in each cohort. This is consistent with the higher prostate cancer mortality rate in Sweden relative to the U.S. (37) The Swedish population also had a greater proportion of cases with advanced clinicopathological features and who were treated with androgen deprivation therapy.

Permutation testing on 846 SNPs revealed 22 variants that were significantly ($P \leq 0.01$) associated with PCSM in the Seattle cohort (Table 2). Genotyping data validated SNP

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rs1137100 minor allele G as being associated with a decrease in PCSM (HR = 0.82; 95% CI, 0.67–1.00; P =0.027) in the Swedish cohort under the same dominant genetic model adjusted for the same covariates as in the Seattle dataset. Also under the same dominant genetic model as used in the analysis of the Seattle dataset, but allowing for different covariates, four additional SNPs were validated as being significantly associated with PCSM in the Swedish cohort: rs627839 (P =0.024), rs2070874 (P =0.011), rs10778534 (P =0.022), and rs5993891 (P =0.024).

Hazard ratios were then calculated according to cumulative number of at-risk genotypes. As shown in Table 3 for the Swedish cohort, compared to men with 0–2 at-risk SNP genotypes, those with four (HR = 1.51; 95% CI, 1.16–1.97) or five (HR = 1.46; 95% CI, 0.97–2.19) at-risk genotypes had approximately a 50% higher risk of dying from prostate cancer, after adjustment for age and clinicopathological factors. In these analyses, the HRs increased directly with the cumulative number of at-risk genotypes (P_{trend} =0.0005, adjusting for age only, and =0.001 adjusting also for clinicopathological factors). The proportion of all patients carrying four (28%) or five (6%) at-risk alleles was similar in both cohorts.

K–M curves were constructed according to the number of at-risk genotypes in each cohort (Figure 1). As shown, compared to patients with 0–2 at-risk genotypes, those with all five at-risk SNP genotypes had the lowest prostate cancer-specific survival in both the Seattle (P <0.001) and the Swedish (P =0.004) cohorts.

Stepwise backward selection Cox models were completed to evaluate the relative ranking of the five SNP genotypes in relation to PCSM. Based on models adjusted for age at diagnosis and the four clinicopathological variables, the most significant SNP in the Seattle dataset was rs1137100 (P =0.001) in the *LEPR* gene and in the Swedish dataset was rs10778534 (P =0.045) in the *CRY1* gene.

Lastly, we tested the five genetic variants for SNP by SNP interactions. No evidence for significant interaction between these markers was found (all P-values >0.001).

Discussion

Prostate cancer is a heterogeneous disease and current clinical and pathological features are not reliably accurate for predicting individual patient outcomes. (38, 39) The ability to distinguish patients at elevated risk for having aggressive, life-threatening prostate cancer at the time of diagnosis could improve care for the subset of cases most likely to benefit from aggressive therapy and help avoid over-treatment of patients whose tumors are likely to remain indolent. Better biomarkers that can stratify patients according to tumor aggressiveness are urgently needed. Thus, we undertook a hypothesis-testing candidate gene approach to identify and validate genetic variants as prognostic markers for fatal prostate cancer.

The current study was developed based on the notion that the genetic background upon which cancer develops likely modulates tumor growth rate and propensity to metastasize as well as treatment response. This idea is consistent with results from animal models that demonstrate that genetic background influences cancer progression and metastatic potential. (40, 41) Further support comes from a recent study of squamous cell skin cancer in humans that showed somatic events in tumors can depend on an individual's germline genotype. (42)

We and others (43) have hypothesized that inherited predisposition influences prostate cancer progression. Variants in several candidate genes, including *MIC-1*, (18) *SEP15*, (21) *VDR*, *CYP27B1*,and *CYP24A1*, (22) *TLR-9*, (19) *Megalin*, (20) *CYP17*, (23) and *FASN*, (24) and two risk-loci (19q13 and 11q13) (12) have previously been associated with PCSM in

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individual studies, although results have not been validated in independent cohorts. More recently, a GWAS of 196 patients with either metastasis or PCSM found no genome-wide significant results, but one intergenic SNP was replicated (P =0.05) in a highly selected case series. (44) In the present study we investigated a subset of these same candidate gene variants, though none was among our top ranked 22 SNPs.

A nonsynonymous coding SNP (rs1137100) in exon 4 of the *leptin receptor* (*LEPR*) gene was validated as the strongest marker associated with PCSM in our study. LEPR is a cytokine receptor that is highly expressed in normal and malignant prostate tissue. (45) The binding of leptin to its receptor, LEPR, leads to several downstream effects that may affect prostate carcinogenesis, including stimulation of tissue growth, (46) inflammation, (47) angiogenesis, (48) and bone mass regulation. (49) The latter effect makes *LEPR* an interesting candidate for disease progression, (50) since the primary metastatic site for prostate cancer is the bone and bony metastases are predictive of fatal prostate cancer. (51–53)

The other SNPs significantly associated with survival in our study include rs627839, which tags the *RNASEL* gene within the hereditary prostate cancer 1 (HPC1) locus. (54) A role in prostate cancer has been suggested through the protein's ability to increase apoptosis and inhibit inflammation, cell proliferation and adhesion. (55, 56) Of the five genes highlighted here, this is the only one previously evaluated in a study of prostate cancer that found no mortality association. (57) Variant rs2070874 is in the promoter region of *Interleukin 4* (*IL4*), which plays a role in cancer via activation of the *Stat6* transcription factor. (58) Studies have shown that IL4 inhibits tumor growth (59–62) and angiogenesis, (63) and prevents invasion and migration of colon cancer cells. (64) Of note, rs2070874 is in perfect LD with rs2243250, a promoter variant for which the minor allele confers diminished IL4 expression. (65) SNP rs10778354 tags the *Cryptochrome 1* (*CRY1*) gene in the circadian rhythm pathway. (66–68) Circadian clock genes regulate androgen levels, (69) which are known to affect prostate cancer progression, (70) and may also function as tumor suppressors through regulation of cell proliferation, apoptosis and response to DNA damage. (71) Finally, rs5993891 is located in the *ARVCF* gene, a member of the p120catenin family of proteins. Increased expression of ARVCF has been shown to disrupt cell adhesion, (72) which may facilitate cancer progression. This SNP also tags the *COMT* gene, which encodes a protein that neutralizes the genotoxic effects of catechol estrogens. (73, 74)

The five validated SNPs highlighted above represent the first evidence for this panel of genetic variants being associated with prostate cancer mortality. Two variants (rs228697 in *PER3* and rs1029153 in *CXCL12*) associated with PCSM in the Seattle cohort were not evaluated in the Swedish cohort due to genotyping failure. Thus, additional investigation of these variants is warranted. Strengths of this project include the population-based patient cohorts, the discovery-validation study design, the large number of patients and outcomes in the validation cohort, and the hypothesis-driven approach focused on genes in biological pathways of interest. One potential concern relates to the sample size in the discovery cohort, which may have missed additional SNP associations due to limited power. The smaller size of the Seattle cohort and regression to the mean likely explain the reduced HRs associated with the five SNP genotypes observed in the Swedish cohort relative to the Seattle cohort. Another potential issue is the difference in clinicopathological factors between the two cohorts. To accommodate these dissimilar features, adjustment covariates were allowed to vary in the Cox models, although this does potentially lead to multiplicity and false positives. It would be important to confirm our findings in a U.S. cohort with similar clinical features to those of the Seattle cohort so that covariate models could be fixed for validation. The focus on fatal events reduces potential bias related to different screening practices between the two cohorts that likely account for the differing clinical

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characteristics. Interestingly, the proportion of patients carrying 4 or 5 of the at-risk genotypes was similar in the two cohorts. Because Gleason score and stage are strong predictors of PCSM, adjustment for these factors in multivariate models is important even though it may diminish the magnitude of the SNP-PCSM associations.

In conclusion, our study provides initial validation for five germline genetic variants that are associated with lethal prostate cancer outcomes. Three of these polymorphisms (rs1137100, rs2070874, rs10778534) were significantly associated with PCSM in multivariate models that included the traditional clinical factors (i.e., Gleason score, stage) used to predict outcomes, suggesting that these variants contribute independent data beyond the standard prognostic variables. Two other SNPs (rs627839, rs5993891) were validated to be associated with PCSM in models that adjusted for age at diagnosis alone. There was also preliminary evidence for a dose-response effect according to the number of at-risk genotypes carried. A validation study of this five-SNP panel for stratification of patients at the time of diagnosis into those at higher risk for adverse outcomes is urgently needed. Understanding the individual prostate cancer patient's risk for progression to lethal disease will allow more informed counseling of patients regarding therapy options, follow-up plans, and approaches for secondary prevention. Such high-risk patients should benefit most from early aggressive therapy and be ideal candidates for novel adjuvant treatment trials aimed at improving patient survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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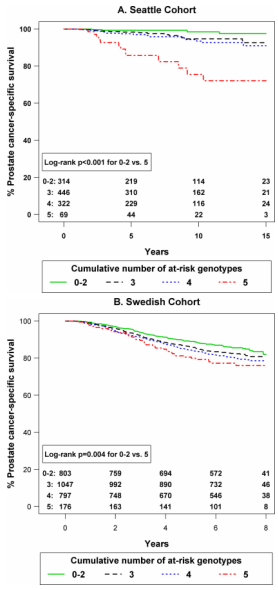

Figure 1.
Kaplan-Meier curves for prostate cancer-specific survival by number of at-risk genotypes for a 5-SNP panel in the Seattle cohort (panel A) and the Swedish cohort (panel B).

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Table 1

Clinicopathological Characteristics of Two Population-based Prostate Cancer Patient Cohorts

	Seattle Cohort (N=1,309)		Swedish Cohort (N=2,875)	
	N	%	N	%
Age at diagnosis, years				
Mean	59.9		65.8	
Median	60.0		64.9	
Range	35.0 – 74.0		44.6 – 80.4	
Follow-up time, years				
Mean	8.5		6.0	
Median	6.5		6.5	
Range	0.8 – 15.9		0.3 – 8.6	
Prostate cancer-specific death				
No[1]	1,249	95.4	2,374	82.6
Yes	60	4.6	501	17.4
Age at death, years				
Mean	63.9		71.2	
Median	65.2		71.2	
Range	44.9–78.3		48.5–85.7	
Stage				
Local	1,023	78.2	1,885	65.6
Regional	254	19.4	651	22.6
Distant	32	2.4	266	9.3
Missing	0	0.0	73	2.5
Gleason score				
2 – 4	67	5.1	106	3.7
5 – 6	680	51.9	1,269	44.1
7	432	33.0	782	27.2
8 – 10	126	9.6	467	16.2
Missing	4	0.3	251	8.7
Diagnostic PSA level, ng/mL				
< 4	178	13.6	148	5.1
4 – 9.9	722	55.2	993	34.5
10 – 19.9	191	14.6	651	22.6
≥ 20	118	9.0	1,003	34.9
Missing	100	7.6	80	2.8
Primary therapy				
Radical prostatectomy	770	58.8	713	24.8
Radiation therapy	359	27.4	682	23.7
Androgen deprivation	61	4.7	927	32.2

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	Seattle Cohort (N=1,309)		Swedish Cohort (N=2,875)	
	N	**%**	**N**	**%**
None	115	8.8	488	17.0
Other	4	0.3	22	0.8
Missing	0	0.0	43	1.5

[1] Includes men who died of other causes and were censored at time of death (Seattle, n=102; Sweden, n=258)

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Table 2

Hazard ratios (HR) for prostate cancer-specific mortality associated with a panel of 22 single nucleotide polymorphisms (SNPs) in candidate genes in a discovery cohort (Seattle) and a validation cohort (Sweden)

				Seattle Cohort					Swedish Cohort					
SNP	**Chr.**	**Gene**	**Alleles[1]**	**MAF[2]**	**HR**	**95% CI**	**P-value (q value)**	**Model[3]**	**MAF[2]**	**HR**	**95% CI**	**P-value[4]**	**Model[3]**	**P-value[5]**
rs1137100	**1p31**	***LEPR***	**A/G**	**0.27**	**0.29**	**0.14–0.60**	**0.0001 (0.26)**	**Dom: ACP**	**0.29**	**0.82**	**0.67–1.00**	**0.027**	**Dom: ACP**	**0.027**
rs228697[†]	1p36	*PER3*	C/G	0.11	0.25	0.10–0.60	0.0002 (0.26)	Dom: ACP						
rs635261	1q25	*RNASEL*	G/C	0.36	0.22	0.07–0.65	0.0007 (0.56)	Rec: ACP	0.35	0.98	0.74–1.29	0.44	Rec: A	0.48
rs627839	**1q25**	***RNASEL***	**G/T**	**0.47**	**3.98**	**1.64–9.65**	**0.0004 (0.26)**	**Dom: ACP**	**0.47**	**1.22**	**1.00–1.50**	**0.024**	**Dom: A**	0.22
rs4583514	2p21	*MSH2*	G/A	0.38	2.49	1.21–5.10	0.01 (0.70)	Dom: ACP	0.43	0.98	0.81–1.18	NS	Dom: A	NS
rs4608577	2p21	*MSH2*	T/G	0.17	2.04	1.36–3.07	0.002 (0.57)	Tre: A	0.21	0.93	0.80–1.09	NS	Tre: A	NS
rs523349	2p23	*SRD5A2*	C/G	0.29	0.49	0.28–0.86	0.01 (0.66)	Dom: A	0.32	1.15	0.94–1.40	NS	Dom: ACP[6]	NS
rs12467911	2p23	*SRD5A2*	C/T	0.28	0.45	0.24–0.81	0.005 (0.57)	Dom: A	0.32	1.16	0.95–1.41	NS	Dom: ACP[6]	NS
rs11710277	3p21	*SEMA3F*	A/G	0.09	3.71	1.75–7.90	0.001 (0.53)	Dom: ACP	0.08	0.86	0.66–1.11	NS	Dom: A	NS
rs11205	5q23	*HSD17B4*	A/G	0.39	0.21	0.06–0.70	0.001 (0.61)	Rec: ACP	0.44	1.08	0.84–1.39	NS	Rec: ACP[6]	NS
rs2070874	**5q31**	***IL4***	**C/T**	**0.16**	**2.16**	**1.27–3.67**	**0.005 (0.57)**	**Dom: A**	**0.19**	**1.27**	**1.04–1.56**	**0.011**	**Dom: ACP[6]**	**0.047**
rs1799964	6p21	*TNF/LTA*	T/C	0.21	0.39	0.20–0.77	0.003 (0.57)	Dom: A	0.20	0.91	0.74–1.13	0.20	Dom: ACP	0.44
rs4645959	8q24	*C-MYC*	A/G	0.04	0	0.00-inf.	0.003 (0.57)	Tre: ACP	0.02	1.23	0.84–1.78	NS	Tre: A	NS
rs1029153 [†]	10q11	*CXCL12*	T/C	0.31	0.22	0.07–0.75	0.005 (0.57)	Tre: A						
rs2839685	10q11	*CXCL12*	C/T	0.15	28.2	7.21–110.2	0.0003 (0.43)	Rec: ACP	0.10	1.31	0.49–3.53	0.30	Rec: ACP[6]	0.34
rs2308327	10q26	*MGMT*	A/G	0.13	0.32	0.13–0.78	0.004 (0.57)	Tre: A	0.13	0.92	0.76–1.12	0.20	Tre: A	0.20
rs10778534	**12q23**	***CRY1***	**T/C**	**0.36**	**2.21**	**1.19–4.12**	**0.008 (0.57)**	**Dom: A**	**0.35**	**1.23**	**1.00–1.51**	**0.022**	**Dom: ACP**	**0.036**
rs2494750	14q32	*AKT1*	C/G	0.07	0.22	0.07–0.70	0.001 (0.50)	Tre: ACP	0.06	0.93	0.70–1.24	0.31	Tre: ACP	0.31
rs1799814	15q24	*CYP1A1*	C/A	0.05	0.13	0.03–0.57	0.0003 (0.26)	Tre: ACP	0.03	1.47	0.86–1.28	NS	Tre: ACP[6]	NS
rs25487	19q13	*XRCC1*	G/A	0.36	0.49	0.31–0.77	0.003 (0.57)	Tre: A	0.35	0.95	0.83–1.08	0.20	Tre: A	0.40
rs915927	19q13	*XRCC1*	A/G	0.43	2.54	1.24–5.18	0.005 (0.57)	Dom: A	0.44	0.88	0.71–1.08	NS	Dom: ACP	NS
rs5993891	**22q11**	***ARVCF***	**C/T**	**0.05**	**0.21**	**0.07–0.61**	**0.0004 (0.26)**	**Dom: ACP**	**0.05**	**0.72**	**0.52–1.01**	**0.024**	**Dom: A**	0.21

[†]These SNPs were not evaluated in the Swedish cohort due to genotyping failure.

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[1] Major/minor allele

[2] MAF: minor allele frequency, calculated from cases that did not die of prostate cancer.

[3] Genetic model of best fit (Dom=dominant, Rec=recessive, Tre=trend) adjusted for age (A) alone, age + clinicopathological (ACP) factors (Gleason score, stage, diagnostic PSA level and primary treatment).

[4] NS= not significant as the HR in the validation (Swedish) dataset is in the opposite direction as in the discovery (Seattle) dataset.

[5] P-value for the Swedish dataset using the same best fitting genetic model and the same covariates as for the Seattle dataset.

[6] Adjusted for age + clinicopathological factors as in footnote 3 above, excluding primary treatment.

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Table 3

Hazard ratios (HR) for prostate cancer-specific mortality associated with the cumulative number of at-risk genotypes for a panel of five validated single nucleotide polymorphisms (SNPs)

	Seattle Cohort					Swedish Cohort				
Number of at-risk genotypes[1]	**Number at-risk / Number of fatal events**	**HR**[2]	**95% CI**	**HR**[3]	**95% CI**	**Number at-risk / Number of fatal events**	**HR**[2]	**95% CI**	**HR**[3]	**95% CI**
0 – 2	314 / 4	1.00		1.00		803 / 113	1.00		1.00	
3	446 / 16	2.82	0.94–8.45	8.14	2.44–27.12	1047 / 181	1.24	0.98–1.57	1.05	0.81–1.37
4	322 / 16	3.92	1.31–11.74	9.08	2.73–30.15	797 / 154	1.44	1.13–1.83	1.51	1.16–1.97
5	69 / 13	15.80	5.14–48.52	15.12	4.44–51.56	176 / 39	1.69	1.17–2.43	1.46	0.97–2.19

[1] Genotypes for SNPs rs1137100, rs627839, rs2070874, rs10778534, and rs5993891; patients missing data for any of the five SNP genotypes were excluded from the analysis (Seattle n=158; Sweden n=52).

[2] Hazard ratio adjusted for age at diagnosis; p-value for trend = 0.0005 in the Swedish cohort.

[3] Hazard ratio adjusted for age at diagnosis, stage, Gleason score, diagnostic PSA, and primary treatment; p-value for trend = 0.001 in the Swedish cohort.