HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2022 July 01; 31(7): 1466–1472.

doi:10.1158/1055-9965.EPI-22-0053.

SNPs at *SMG7* associated with time from biochemical recurrence to prostate cancer death

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Abstract

Background: A previous genome-wide association study identified several loci with genetic variants associated with prostate cancer survival time in two cohorts from Sweden. Whether these variants have an effect in other populations or if their effect is homogenous across the course of disease is unknown.

Methods: These variants were genotyped in a cohort of 1298 patients. Samples were linked with age, PSA level, Gleason score, cancer stage at surgery, and times from surgery to biochemical recurrence to death from prostate cancer. SNPs rs2702185 and rs73055188 were tested for association with prostate-cancer-specific survival time using a multivariate Cox proportional hazard model. SNP rs2702185 was further tested for association with time to biochemical recurrence and time from biochemical recurrence to death with a multi-state model.

Results—SNP rs2702185 at SMG7 was associated with prostate-cancer- specific survival time, specifically the time from biochemical recurrence to prostate cancer death (HR=2.5, 95% CI=1.4–4.5, p=0.0014). Nine variants were in linkage disequilibrium (LD) with rs2702185; one, rs10737246, was found to be most likely to be functional based on LD patterns and overlap with open chromatin. Patterns of open chromatin and correlation with gene expression suggest that this SNP may affect expression of *SMG7* in T cells.

Conclusion: The SNP rs2702185 at the SMG7 locus is associated with time from biochemical recurrence to prostate cancer death, and its LD partner rs10737246 is predicted to be functional.

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The authors declare no potential conflicts of interest

Impact: These results suggest that future association studies of prostate cancer survival should consider various intervals over the course of disease.

Keywords

Prostate cancer; SNPs; SMG7; biochemical recurrence; survival

Introduction

Prostate cancer is the second leading cause of cancer death among men in the United States, though most men diagnosed with prostate cancer will not die from it (1). This apparent paradox is due to the relatively indolent nature of many prostate cancers. Left untreated, most prostate tumors will grow slowly and not be a clinical threat to a man's health. However, for a subset of tumors, progression to metastatic disease, cytotoxic and antiandrogen treatment, and death occur. This has led to a contentious debate on the value of screening for prostate cancer. Although it has been widely accepted that Prostate-Specific Antigen (PSA) screening does reduce prostate cancer mortality, it remains an open question whether current screening modalities result in more harm than good due to the adverse effects of treatment compared with the number of fatal cancers prevented (2–4).

Over the past decade, one approach to improve identification of men at increased risk for prostate cancer has been germline genomic studies. These studies rest on the observation that prostate cancer is highly heritable (5,6). By one measure, such studies have been highly successful; a recent study notes over 269 independent variants that influence the risk of prostate cancer (7). When these variants are combined into a polygenic risk score, men in the highest 10% of risk are 5 times more likely to be diagnosed with prostate cancer than men at average risk(7). However, these variants generally are not associated with prostate cancer survival after diagnosis of disease (8,9). Therefore, incorporation of these variants into screening algorithms could actually exacerbate overdiagnosis.

The extent to which inherited genetic variation influences prostate cancer outcome in men who are diagnosed with disease is unclear. Prostate cancer outcome, like prostate cancer risk, does show familial aggregation suggesting a heritable component (10,11). Recently, we conducted a genome-wide association study of prostate cancer survival and identified several loci for which there was evidence that genetic variation influences prostate cancer survival time (12). One locus, tagged by the SNP rs73055188 at the *AOX1* gene reached a strict threshold for genome-wide significance; a second locus tagged by the SNP rs2702185 at the *SMG7* gene also was strongly associated with survival time.

This previous study was limited by its exclusive examination of individuals from Sweden. Furthermore, it is not clear whether these SNPs influence survival across the entire course of the disease or only at a particular stage. To examine these questions, we looked at the association of these SNPs with prostate cancer survival in a well-annotated, hospital-based cohort of prostate cancer cases (8,9,13,14). We demonstrate that rs2702185 is associated with prostate cancer survival specifically by altering the time from biochemical recurrence to death.

Methods

Patient cohort

Our cohort consists of 1298 individuals who underwent radical prostatectomy at Memorial Sloan Kettering Cancer Center (MSKCC) from January 1990 through January 2006, and from whom de-identified DNA samples are available (8,9,13,14). This study was approved by the MSKCC IRB in accordance with the U.S. Common Rule. Consistent with the patient population at MSKCC, this cohort is primarily of European ancestry. Over half of the men self-identify as Ashkenazi Jewish (AJ), which we define as reporting all four grandparents as being Jewish and from eastern Europe. These data were linked with abstracted clinical records which record, among other variables, age, PSA level, Gleason score and cancer stage at surgery as well as time from surgery to endpoints including biochemical recurrence and death from prostate cancer.

SNP genotyping

DNA previously extracted from blood was used in these analyses (13). To genotype rs2702185 and rs73055188, we used pre-designed TaqMan assays (15) (Thermo Fisher Scientific Inc, MA, USA). A master mix dilution was prepared and 3 μL aliquoted to a 384 well plate using multichannel pipette. Two μL of high molecular DNA diluted to 3ng/μL was added to the plate, spun down, and subjected to thermocycling for 40 cycles on an ABI GeneAmp PCR System 9600. The fluorescent signal was quantified and alleles assigned using the ABI Prism 7900HT instrument and SDS software. Allele frequencies and Hardy-Weinberg equilibrium quality checks were calculated.

Association with PCa survival

The two SNPs rs2702185 and rs73055188 were tested for their association with PCa-specific survival using a Cox proportional hazard model (16) using the R package *survival* (17). Survival time was measured from the date of PCa surgery until the date of PCa-specific death or last follow-up date (mean of 10 years follow-up). Data on death from other causes was not available in this cohort based at a cancer care hospital. Genotypes were coded under an additive model. A log-additive effect (log hazard ratio [HR] per additional minor allele) was estimated. The interactive effects between each SNP and study population (AJ and non-AJ) were considered to capture population-specific effects. Stratified analysis for AJ and non-AJ populations was also performed to evaluate the sensitivity of the estimated parameters. Covariates under adjustment include age, PSA level, Gleason score categories (<7, 7 and 8–10), and World Health Organization stage categories (1–2, 3–4) at surgery. Associations with $p < 0.05$ in the Wald test and HR in the same direction as in discovery cohort were considered significant for validation. Kaplan-Meier curves for the validated associations were plotted and its p-value from log rank test was reported.

Decomposing the effects of PCa survival associated SNP(s) on two stages of PCa progression

To test if the SNP rs2702185 influences different stages of prostate cancer progression in the non-AJ population, we divided disease progression into two distinct time intervals:

from surgery to biochemical recurrence, and from biochemical recurrence to prostate cancer specific death (Figure 1). Biochemical recurrence was defined as PSA of ≥0.2 ng/mL after radical prostatectomy and a value of "nadir + 2" after other therapy (14). This model assumes that patients who died of prostate cancer previously experienced biochemical recurrence. We tested for SNP association with these intervals using a multi-state model under an additive model. We considered three stages including surgery (stage 1), biochemical recurrence (stage 2) and death from disease (stage 3). We defined the transition matrix such that diagnosed patients could only transit to death of disease by passing through biochemical recurrence. Age, PSA level, Gleason score and stage at surgery were adjusted as covariates.

Linkage disequilibrium (LD) analysis

To examine linkage disequilibrium in these populations, we combined data from the 1000 Genomes Project (18) with that from the Ashkenazi Genome Consortium (TAGC) (19). We used vcftools (20) to compute linkage disequilibrium between rs2702185 and all SNPs within one megabase of it. For the 1000 Genomes data, we focused on individuals of northwestern European ancestry (GBR and CEU); we used the complete TAGC data.

Functional Effect and eQTL Analyses

To examine the functional effects, we explored the predicted probabilities of being promoters and enhancers in prostate tissue of 9 SNPs in LD with rs2702185. The predicted functional probabilities were obtained from FUN-LDA (21), a Latent Dirichlet Allocation (LDA) based model that predicts functional effects of non-coding genetic variants by integrating diverse epigenetic annotations for specific cell types and tissues from large scale genomics projects.

To investigate the chromatin accessibility of these SNPS, we used data from the ENCODE project (http://www.encodeproject.org), including the SCREEN browser at http://screen.encodeproject.org (22). To look at chromatin accessibility in the TCGA data, we used the UCSC Xena browser (http://xenabrowser.net/) (23).

To examine eQTLs, we used data from the eQTL Catalogue (24), downloaded on October 9, 2020. For gene expression datasets generated on the Illumina microarray platform, we considered each probe for a given gene as a separate test in cases where more than one probe maps to the same HGNC gene id.

Data Availability Statement

The data generated in this study are not publicly available due to containing Protected Health Information (PHI) but are available upon reasonable request from the corresponding author.

Results

Demographics of PCa cases in the MSKCC cohort

We included 1298 men with incident diagnosis of PCa from MSKCC in our study (Table 1). A total of 162 (12.5%) died from PCa and 632 (48.6%) had biochemical recurrence. The median age at PCa surgery was 68 [IQR 62–72] and 63 [IQR 58–70] years old for AJ and non-AJ men, respectively.

SNPs associated PCa Survival in AJ and non-AJ populations

In univariate analysis, SNP rs2702185 was significantly associated with PCa- specific survival (log rank test p-value = 0.0013) in the non-AJ population (Figure 2A) but not in the AJ population (log rank test p-value = 0.58). The population-level heterogeneity for this association was significant after adjusting for age, PSA, Gleason score and stage at surgery by modeling the interactive effects between rs2702185 and population (AJ vs. non-AJ) in all samples (interactive effects: p=0.010, per-allele HR = 2.696, 95% CI: 1.271–5.715). In this covariate-adjusted model rs2702185 remained significantly associated with PCa-specific survival (p =0.001, per-allele HR = 2.518, 95% CI: 1.468–4.321) in the non-AJ population only; the test for association in the AJ population was clearly not significant (p =0.799, per-allele HR = 0.934, 95% CI: 0.553–1.577) (Table 2). In this model, while age at surgery, PSA and advanced clinical stages were no longer associated with PCa-specific survival after surgery (p>0.05), Gleason score remained highly significant for PCa-specific survival (p=0.0015 for Gleason score 7 vs. <7 and p=1.6E-10 for Gleason score 8–10 vs. <7) (Table S1). The second SNP rs730155188 did not show significant results with PCa- specific survival in both the AJ and non-AJ populations of our cohort. In a covariate-adjusted interaction model, rs730155188 showed an increasing trend of HR (p =0.432, per-allele HR = 1.275, 95% CI: 0.695–2.340) in the non-AJ population, suggesting the likely existence of small effect that was not significant due to small sample sizes. In the AJ population, there was no trend of association (per-allele HR=1.030) with PCa- specific survival. The same patterns were observed for these two SNPs in covariate-adjusted stratified analysis of AJ and non-AJ populations (Table S2).

The SNP rs2702185 associates with cancer progression stages

As rs2702185 was identified to be associated with PCa survival in the non-AJ population in our analysis, we took a closer look at its effects on cancer progression by considering two time periods (Table 3; Figure 2B and C). Interestingly, rs2702185 was not associated with time from surgery to biochemical recurrence in the covariate-adjusted multi-state model (p =0.491, per-allele HR = 1.112, 95% CI: 0.822–1.503; Kaplan-Meier curve in Figure 2B), but significantly associated with time from biochemical recurrence to PCa- specific survival with similar HR as for PCa- specific survival (p =0.0014, per-allele HR = 2.537, 95% CI: 1.435– 4.485; Kaplan-Meier curve in Figure 2C) in the non-AJ population. Details on the subset of individuals with biochemical recurrence are provided in Table S3. This suggests that the effect of rs2702185 does not physiologically manifest itself until later stages of disease. It is worth noting that all covariates were significantly associated with time from surgery to biochemical recurrence (p<0.05), but only Gleason score was also associated with time from biochemical recurrence to death (p=0.001 for Gleason score 8–10 vs. <7).

Linkage disequilibrium analysis and functional annotation suggests a causal SNP at the rs2702185 locus

We next wished to identify candidate causal variants at this locus. As we observed an interaction between the effect of rs2702185 and Ashkenazi ancestry, we examined linkage disequilibrium (LD) in both non-Ashkenazi European and Ashkenazi populations. Using reference data from the 1000 Genomes Consortium, in individuals of northwestern European ancestry, we identified 9 variants that were in LD with rs2702185 ($r2 > 0.2$; Table 4). In contrast, in data from Ashkenazi individuals from the Ashkenazi Genome Consortium (TAGC), LD is lower for six of the variants and one variant found in the 1000 Genomes data is not present in the TAGC data.

To identify candidate functional SNPs among these 9, we investigated the predicted functional probabilities of being in promoter and enhancer regions in prostate tissue from FUN-LDA, a prediction tool built upon large scale functional genomics databases. We observed predicted function for 8 of them, and the highest functional probability is for rs10737246 (87% chance of being in a promoter; Table 4). Consistent with the FUN-LDA result, this SNP is in a candidate cis regulatory element (EH38E1403945) as annotated by the ENCODE project (22).

We next investigated in which cell type(s) this regulatory element may be active. Across all cell types in the ENCODE data, the epigenetic marks observed are annotated as being most consistent with distal enhancer-like signature. Among the ENCODE samples with DNase-Seq data indicating regions of open chromatin, this region was only found to have evidence of DNase hypersensitivity (open chromatin) in bronchial and esophageal epithelial cells. For those cell types without DNase-Seq data, there was no evidence for H3K27Ac peaks which is correlated with enhancer activity. In contrast, several cell types showed evidence for H3K4me3 marks, indicative of promoter activity. Two of the four top cell types with this mark were derived from T-cells. We additionally asked if rs10737246 overlaps regions of open chromatin in samples from The Cancer Genome Atlas (TCGA) (12); we find that it does (Figure S1).

We had previously found that rs2702185 was not associated with expression of *SMG7* in prostate tissue but was weakly associated with *NCF2* and *ARPC5* instead (12). As the functional genomic evidence suggests that rs10737246 may lie in both a distal enhancer in epithelial cells and a promoter element in T cells, we wished to investigate the association of both rs2702185 and rs10737246 with gene expression across a broader range of cell types. To do so, we used data from the eQTL Catalogue, a compendium of *cis*-eQTL results from numerous studies (24). Across all 112 studies in the catalog, there were 2086 tests for association between either rs2702185 or rs10737246 and expression of a nearby gene; for each tissue-gene pair both SNPs were tested. At a Bonferonni significance level of $p<1.2e-05$, 16 of these tissue-gene pairs were significant in at least one gene (Table S4). All but one of these hits were with *SMG7* in cells of the immune system, consistent with the epigenetic evidence and supporting the hypothesis that rs10737246 functions in immune cells rather than prostate epithelium.

Discussion

We performed a validation analysis for two genetic variants that had been previously identified to be associated with PCa-specific mortality (12). We replicated the association of rs2702185 with PCa-specific survival in a cohort of non-Ashkenazi individuals of European ancestry in the U.S. The result for the second SNP, rs73055188, trended in a consistent direction with previous reports but did not reach a level of statistical significance. Intriguingly, when we separately examined the effect of these SNPs on the intervals from surgery to biochemical recurrence, and from biochemical recurrence to death, we found effect heterogeneity; SNP rs2702185 specifically associated with the interval from biochemical recurrence to death. This suggests that a genetic epidemiological approach can be used to identify variants that are active in influencing different stages of prostate cancer progression. Neither SNP appears to be associated with prostate cancer survival in individuals of AJ ancestry. This population heterogeneity may explain why larger international consortia were unable to find SNPs associated with prostate cancer survival while our initial study focused in Sweden did (25). We note that germline *BRCA2* mutations are observed in 2.4% of AJ prostate cancer cases, and are associated with worse outcome(14), compared to less than 1% in prostate cancer cases in general (26,27). In contrast, at least one copy of the minor allele of rs2702185 is found in 19% of AJ and 14% of non-AJ individuals in this study. Thus, we find it unlikely that differences in germline *BRCA2* mutation status explains this difference.

Several other important differences may contribute to the different effects of the SNPs on survival observed in the present study and our previous report (12). For instance, this current study was hospital-based while the prior studies in Sweden were population-based. Furthermore, at the time the studies were undertaken in Sweden PSA screening was not widely used, while the present study focuses on a hospital-based cohort in a setting where PSA screening was common. The overall length of follow-up time was larger in our prior study (12). Finally, we note that due to the “winner’s curse” we would expect to observe attenuated effect sizes in this replication study (28).

It is worth noting that assembly of detailed clinical data is a key limiting factor in these kinds of studies of SNPs associated with cancer survival. In our earlier population-based studies, we utilized a national cancer registry combined with a national death index (12). This allowed us to have a complete view of the specified time points (diagnosis and death from disease), but no details on the intermediate course of disease. In contrast, here we used a hospital-based cohort. To extract detailed information on the course of disease, two urology fellows reviewed each individual medical record. Such an approach is not scalable, and restricts our ability to examine additional clinical variables that were not abstracted initially. With the advent of large biobanks linked to electronic medical records (29), it may be possible to design algorithms to extract some data on the course of prostate cancer, though these databases are often limited to fields like ICD-10 codes, laboratory values, and prescribed medicines. For instance, rising PSA or prescription of anti-androgen or chemotherapeutic agents is likely easy to identify in EMR. Details on Gleason grade or metastatic site are not included in these data. Databases created especially for following patients with prostate cancer prospectively may be especially useful for such studies (30).

We identified a candidate causal variant, rs10737246, which is located in the first intron of *SMG7*. We found functional genomic evidence that this variant lies in a regulatory region. Illustrative of the complexity of interpreting functional genomic data, there is evidence to support both its role as an enhancer in epithelial tissue and as a promoter-like element in T cells. Expression QTL analysis of blood supports the hypothesis that rs10737246 alters gene expression of *SMG7* in immune cells, while we could not find evidence for a cis-eQTL effect on nearby genes in prostate. This raises the intriguing possibility that SNPs associated with prostate cancer survival could exert their effect via the microenvironment rather than the tumor cell itself.

Our results suggest that lower levels of *SMG7* are associated with shorter survival times in prostate cancer. *SMG7* is known to play a role in nonsense-mediated decay (NMD), the process by which mRNA molecules containing premature termination codons (PTCs) are degraded before they can be translated. Specifically, it is thought that *SMG7* links the recognition of a PTC to the mRNA degradation machinery (31). Decreased NMD activity has been linked to a tumor immune response (32). However, such a mechanism of action presupposes action in the cancer cells themselves and, since a tumor immune response is thought to be beneficial, would suggest that decreased expression of *SMG7* should be associated with longer survival times. A role for *SMG7* in immune cells, as suggested by our data, is less clear. SNPs at *SMG7* have been associated with risk of systemic lupus erythematosus (SLE), in which the risk allele is associated with lower expression of *SMG7* in peripheral blood mononuclear cells (33). Decreased NMD could lead to the accumulation of proteins with premature stop codons in immune cells, thereby altering the immune response to the tumor.

This study has several limitations. Though it expanded beyond individuals from Scandanavia (12), it still only examined people of European ancestry. Given the heterogeneity we observe, it remains an open question as to whether these SNPs have an influence on survival in non-European populations. Patients treated at tertiary care centers may not be representative of the general population. We only abstracted a subset of the clinical data that can be found in the medical record and therefore cannot say if these SNPs associate with specific metastatic sites or show different effects depending on adjuvant radiation therapy. Resource availability prevented us from performing a genome-wide scan of these individuals and asking if variants at additional loci are associated with time from biochemical recurrence to mortality. Finally, with longer follow-up time, this study may have greater power to identify additional associations. For future study, we propose to consider larger studies, such as through integration of multiple cohorts, employ alternative strategies to switch focus from SNPs to targeted genes to boost study power, and consider experiments for validation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by R01 CA224948 (R. J. Klein, Z. H. Gümüş, and X. Song) and Cancer Center Support Grant P30 CA196521 (X. Song and M. Ru). This work was supported in part through the computational resources and staff expertise provided by Scientific Computing at the Icahn School of Medicine at Mount Sinai. Research reported in this paper was supported by the Office of Research Infrastructure of the National Institutes of Health under award number S10OD026880 (R. J. Klein). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial Support:

R01 CA224948 to R. J. Klein, Cancer Center Support Grant P30 CA196521, and equipment grant S10OD026880.

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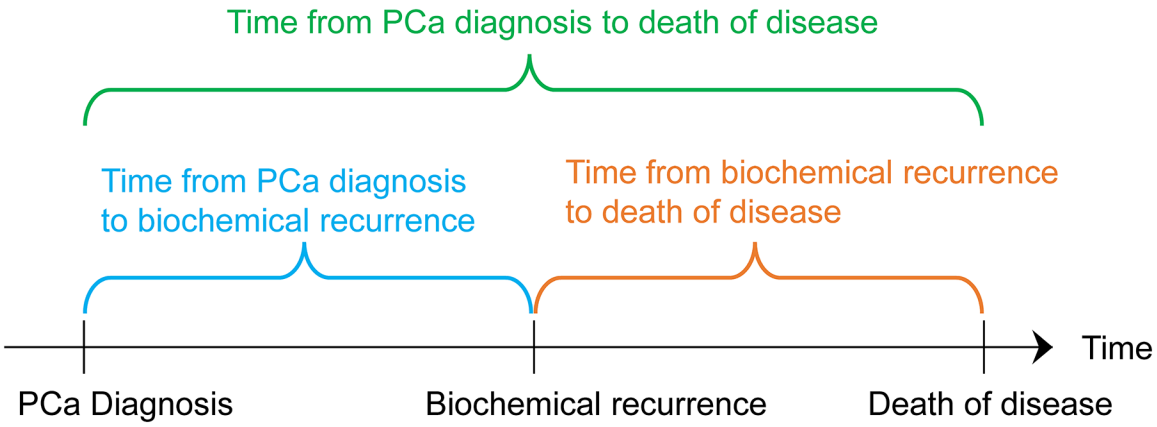

Figure 1.

Stages of PCa progression. Our conceptualization of the stages of prostate cancer progression, with biochemical recurrence in between primary treatment (surgery) and death from disease, is shown.

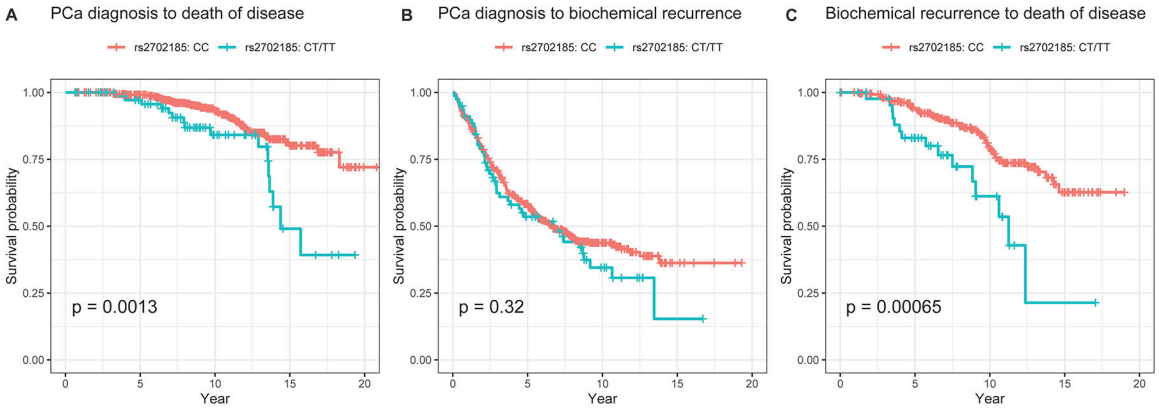

Figure 2.

The Kaplan-Meier curves for three time-to-event outcomes by rs2702185 in non-AJ populations. (A) The Kaplan-Meier curve for time from PCa surgery to death of the disease by rs2702185 in non-AJ populations. (B) The Kaplan-Meier curve for time from PCa surgery to biochemical recurrence by rs2702185 in non-AJ populations. (C) The Kaplan-Meier curve for time from biochemical recurrence to death of the disease by rs2702185 in non-AJ populations. The log rank p-values testing the similarity of the two rs2702185 groups are presented in the figure.

Table 1.

Cohort characteristics

Characteristic	AJ	NON-AJ
No.	723	575
Age at Surgery - Median [IQR]	68 [62, 73]	63 [58, 70]
PSA - Median [IQR]	6.9 [4.6, 11]	7.6 [5.27, 14.2]
Gleason Score Category - no. (%)		
0–6	279 (37.9)	213 (37.0)
7	278 (40.1)	243 (42.3)
8–10	166 (22.0)	119 (20.7)
Clinical Stage - no. (%)		
Non-Advanced (c1–c2)	568 (78.6)	476 (82.8)
Advanced (c3–c4)	155 (21.4)	99 (17.2)
Dead of Disease - no. (%)		
No	627 (86.7)	509 (88.5)
Yes	96 (13.3)	66 (11.5)
Biochemical Recurrence - no. (%)		
No	400 (55.3)	266 (46.3)
Yes	323 (44.7)	309 (53.7)
rs2702185 - no. (%)		
C C	568 (78.4)	494 (85.9)
C T	128 (17.7)	75 (13.0)
T T	1 (0.1)	3 (0.5)
Missing	26 (3.6)	3 (0.5)
rs73055188 - no. (%)		
G G	577 (79.8)	489 (85.0)
A G	109 (15.1)	57 (10.0)
A A	6 (0.8)	4 (0.7)
Missing	31 (4.3)	25 (4.3)

Table 2.

Association of the two SNPs with survival time among AJ and non-AJ individuals in the study

SNP	Population	HR	P	HR LCL	HR UCL
rs2702185	non-AJ	2.519	0.001	1.468	4.321
	AJ	0.934	0.799	0.553	1.577
rs730155188	non-AJ	1.275	0.432	0.695	2.340
	AJ	1.030	0.906	0.633	1.677

Table 3.

Association of rs2702185 with survival across different intervals of disease progression.

	Surgery to Biochemical Recurrence					Biochemical Recurrence to Death of Disease			
	HR	**P**	**HR LCL**	**HR UCL**		**HR**	**P**	**HR LCL**	**HR UCL**
Age at Surgery	0.949	1.96E-13	0.935	0.962		1.008	6.39E-01	0.974	1.043
PSA	1.008	1.05E-03	1.003	1.013		0.991	1.56E-01	0.979	1.003
Stage 3–4 (Ref: Stage 1–2)	1.424	1.25E-02	1.079	1.879		1.196	5.06E-01	0.706	2.028
Gleason Score 7 (Ref: Gleason Score <7)	3.242	8.02E-14	2.381	4.414		1.571	2.76E-01	0.697	3.541
Gleason Score 8–10 (Ref: Gleason Score <7)	4.012	4.24E-15	2.836	5.676		3.891	1.05E-03	1.727	8.769
rs2702185	1.112	4.91E-01	0.822	1.503		2.537	1.36E-03	1.435	4.485

Table 4.

SNPs that are highly correlated (r2 > 0.2) with rs2702185 in northwestern Europeans along with their functional annotations.

SNP	Position	non-AJ r2	AJ r^2	Functional Region in FUN-LDA	Promoter Prob	(Weak) Enhancer Prob
rs7517641	183406643	0.68	0.50	183406626 – 183406650	0.000	0.268
rs6678117	183410168	0.30	0.46	183410151 – 183410175	0.000	0.175
rs10737246	183443785	0.75	0.50	183443776 – 183443800	0.874	0.000
rs4652803	183446620	0.75	N.D.	183446601 – 183446625	0.492	0.047
rs2782412	183501661	0.28	0.50	183501651 – 183501675	0.000	0.268
rs17434335	183505044	0.75	0.50	183505026 – 183505050	0.004	0.076
rs34823167	183534681	0.61	0.50	183534676 – 183534700	0.001	0.166
rs80008821	183563520	0.75	0.37	183563501 – 183563525	0.001	0.216

* Positions are on chromosome 1, build 37.