Research Article

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Single and Multivariate Associations of *MSR1, ELAC2*, and *RNASEL* with Prostate Cancer in an Ethnic Diverse Cohort of Men

Joke Beuten[1,2], Jonathan A.L. Gelfond[3], Jennifer L. Franke[2], Stacey Shook[2], Teresa L. Johnson-Pais[1], Ian M. Thompson[4], and Robin J. Leach[1,2,4]

Abstract

Three genes, namely, *ELAC2* (*HPC2* locus) on chromosome 17p11, 2′-5′-oligoisoadenlyate-synthetase-dependent ribonuclease L (*RNASEL, HPC1* locus), and macrophage scavenger receptor 1 (*MSR1*) within a region of linkage on chromosome 8p, have been identified as hereditary tumor suppressor genes in prostate cancer. We genotyped 41 tagged single nucleotide polymorphisms (SNPs) covering the three genes in a case-control cohort, which included 1,436 Caucasians, 648 Hispanics, and 270 African Americans. SNPs within *MSR1, ELAC2*, and *RNASEL* were significantly associated with risk of prostate cancer albeit with differences among the three ethnic groups ($P = 0.043\text{-}1.0 \times 10^{-5}$). In Caucasians, variants within *MSR1* and *ELAC2* are most likely to confer prostate cancer risk, and rs11545302 (*ELAC2*) showed a main effect independent of other significant SNPs ($P = 2.03 \times 10^{-5}$). A major haplotype *G-A-C-G-C-G* combining five SNPs within *MSR1* was further shown to increase prostate cancer risk significantly in this study group. Variants in *RNASEL* had the strongest effects on prostate cancer risk estimates in Hispanics and also showed an interaction effect of family history. In African Americans, single SNPs within *MSR1* were significantly associated with prostate cancer risk. A major risk haplotype *C-G-G-C-G* of five SNPs within *ELAC2* was found in this group. Combining high-risk genotypes of *MSR1* and *ELAC2* in Caucasians and of *RNASEL* and *MSR1* in Hispanics showed synergistic effects and suggest that an interaction between both genes in each ethnicity is likely to confer prostate cancer risk. Our findings corroborate the involvement of *ELAC2, MSR1*, and *RNASEL* in the etiology of prostate cancer even in individuals without a family history. *Cancer Epidemiol Biomarkers Prev; 19(2); 588–99. ©2010 AACR.*

Introduction

Prostate cancer is the most common non–skin cancer and the second leading cause of cancer death in men in the United States (1). The underlying etiology of prostate cancer remains poorly understood, with both genetic predisposition and environmental factors likely to play a role. Substantial evidence for a genetic component in the susceptibility to prostate cancer has been provided from a study on a large cohort of twins, for which the proportion of prostate cancer risk accounted for by inheritable factors was estimated to be 42% (2). Moreover, a recent study showed that both good and poor survival in prostate cancer aggregate in families, providing evidence on heritability in the prognosis of prostate cancer (3). Despite this strong evidence for a genetic component in prostate cancer, little progress has been made to identify a major gene or genes (4).

The majority of prostate cancer cases most likely involve more common, low- to moderate-penetrance alleles in genes that are components of pathways that influence prostate function, rather than mutations in high-penetrance susceptibility genes (5, 6). There is increased impetus for better understanding of the molecular processes involved in prostate carcinogenesis with the ultimate goal of discovering new biomarkers, which may be beneficial in the detection, prevention, and/or treatment of this disease.

As with breast and colon cancer, familial clustering of prostate cancer has been reported frequently (7-10). Familial prostate cancer represents families in which there are two first-degree or one first-degree and two or more second-degree relatives with prostate cancer. Familial prostate cancer is estimated to account for 10% to 20% of all cases of prostate cancer (5, 6). To date, several genome linkage analyses for prostate cancer predisposition loci have been reported (5, 6, 11), and three strong candidate genes that are involved in pathways critical to DNA damage response (*ELAC2*), apoptosis [2′-5′-oligoisoadenlyate-synthetase–dependent RNase L (*RNASEL*)], and innate immunity [macrophage scavenger receptor 1 (*MSR1*) and (*RNASEL*)] were identified in linkage-critical regions (12).

Authors' Affiliations: Departments of [1]Pediatrics, [2]Cellular and Structural Biology, [3]Epidemiology and Biostatistics, and [4]Urology, The University of Texas Health Science Center, San Antonio, Texas

Corresponding Author: Robin J. Leach, Department of Cellular and Structural Biology, University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78229-3900. Phone: 210-567-6947; Fax: 210-567-6781. E-mail: leach@uthscsa.edu

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The *ELAC2* gene (hereditary prostate cancer 2 locus, *HPC2*) at 17p11 encodes a tRNA 3′ processing endoribonuclease and was the first putative tumor suppressor gene identified for prostate cancer based on linkage analysis (13). An association between prostate cancer and two common missense variants, a serine to leucine change at amino acid 217 (Ser217Leu) and an alanine to threonine change at amino acid 541 (Ala541Thr), neither of which has been shown to alter the enzymatic activities of *ELAC2* (14), has been reported in cases from families with hereditary prostate cancer (13). A meta-analysis by Camp and Tavtigian (2002) and a study by Noonan-Wheeler et al. (2006) and Stanford et al. (2003) of both variants suggested that the *Thr541* allele, either alone or in combination with the *Leu217* allele, confers risk for prostate cancer, in particular within sporadic cancer cases (15-17). However, subsequent studies could not unambiguously confirm a possible role of *ELAC2* in the susceptibility to both sporadic and hereditary prostate cancer (6, 18).

The *RNASEL* gene, within the hereditary prostate cancer 1 (*HPC1*) locus on 1q25, mediates antiviral and proapoptotic activities of the INF-inducible 2-5A system, and is likely to host responses to infections, which may play a role in susceptibility to prostate cancer (19). Previous studies have indicated that the nonsense mutation Glu265X and the initiation codon mutation Met1Ile in the *RNASEL* gene segregate in prostate cancer families that were linked to the *HPC1* locus (20). A truncating mutation (E265X) and an initiation-codon mutation (M1I) segregating with the disease were found in two *HPC1*-linked families. Functional studies showed that both mutations were associated with a reduction in *RNASEL* activity (20). The two most commonly studied variants within *RNASEL* are the nonsynonymous variants *Arg462Gln* and *Asp541Glu*, with the first showing a reduction in enzymatic activity (21). Both variants have been found to be significantly associated with prostate cancer risk albeit with between-study variability in outcome (21-23). On the other hand, several reports show a lack of association for both single nucleotide polymorphisms (SNPs) and prostate cancer, and thus the question remains as to the role of this gene in prostate cancer susceptibility.

Macrophage scavenger receptors (MSR) are trimeric membrane glycoproteins that mediate the binding, internalization, and processing of a wide range of negatively charged macromolecules, including a variety of bacteria (24). The macrophage scavenger receptor 1 (*MSR1*) gene, located at 8p22, has been reported as a strong candidate for prostate cancer susceptibility. Besides the positive linkage findings in hereditary prostate cancer (25), the p22 band of chromosome 8 is also found to be frequently deleted in prostate tumors (26-29). Mutations in *MSR1* have been shown to be associated with prostate cancer risk in both hereditary and sporadic cases in European and African American men (30). Association studies of variants within *MSR1* with prostate cancer risk show both positive and negative results (31).

In summary, numerous studies provide strong support, both functional and epidemiologic, that *ELAC2*, *MSR1*, and/or *RNASEL* confer risk for prostate cancer, yet other studies have suggested that their role may be small. Understanding the role of these three putative prostate cancer susceptibility genes needs more thorough evaluation and replication. In most studies only a small proportion of the estimated number of genetic variants was analyzed, and the contributions of variants in regulatory, noncoding regions of genes, rather than in exons, were often omitted. Moreover, except for our previous study on the association of two SNPs within *RNASEL* (23), Hispanics have not been extensively analyzed, and no association results for *ELAC2* or *MSR1* in Hispanics are currently available. We therefore carried out an association analysis with haplotype-tagged SNPs covering the whole genes in a sample consisting of three ethnic/racial groups. We determined the effects of single SNPs and also considered possible interactions. This is the first study to explore these three genes extensively.

Materials and Methods

Subjects

Study subjects included men in the San Antonio Center for Biomarkers of Risk of Prostate Cancer (SABOR) cohort. SABOR is funded by the National Cancer Institute and has been prospectively enrolling healthy male volunteers from 2001. On each annual visit, a digital rectal examination was done and serum prostate specific antigen level was determined. From this cohort, 226 incident cases (131 non-Hispanic Caucasians, referred to as Caucasians in the text; 59 Hispanic Caucasians, referred to as Hispanics; and 36 African Americans) were available. We also included 646 cases with a known history of prostate cancer that are enrolled within the same time period in a parallel study of prevalent prostate cancer using the same recruiting strategies. Institutional Review Board approval was obtained, as was informed consent from subjects in both studies. Cases had biopsy-confirmed prostate cancer and controls consisted of male volunteers ≥45 y old who had normal digital rectal examinations and prostate specific antigen levels <2.5 ng/mL on all study visits. Race/ethnicity was self-reported on a questionnaire completed at the time of enrollment. A total of 1,436 Caucasians (596 cases, 840 controls), 648 Hispanics (194 cases, 454 controls), and 270 African Americans (82 cases, 188 controls) were included in this analysis. The clinical characteristics of subjects are summarized in Table 1. Study age among controls was the age at last follow-up, and age among cases was the age at prostate cancer diagnosis; controls were younger than prostate cancer cases, with mean age (SD) of 61.3 (9.2) y and 65.5 (8.5) y, respectively ($P < 0.0001$). Because of this difference and the fact that prostate cancer risk increases with age, all the odds ratios (OR) were adjusted for age. First-degree relatives include father, full brother(s) and

Table 1. Clinical data of the study group

Subgroup	Cases (n = 872)	Controls (n = 1,482)	
	No. (%)	No. (%)	
Ethnic background			
Caucasian	596 (68.4)	840 (56.7)	
Hispanic	194 (22.2)	454 (30.6)	
African American	82 (9.4)	188 (12.7)	
Age, in y			
46-50	35 (4.0)	199 (13.4)	
51-60	212 (24.3)	536 (36.1)	
61-70	378 (43.4)	485 (32.7)	
>70	247 (28.3)	262 (17.8)	
Mean ± SD	65.5 ± 8.5	61.3 ± 9.2	$P < 0.0001$
Family history*	95	398	
1st-degree relative	74	300	
Brother	37	79	
Father	52	247	
2nd-degree relative	97	151	
Age onset sporadic	66.3 ± 8.4		$P < 0.0001$
Age onset familial	63.9 ± 8.4		
Disease aggressiveness (Gleason)			
Total <7	332		
Sporadic <7	215		
Familial <7	117		
Total ≥7	247		
Sporadic ≥7	163		
Familial ≥7	84		
Prostate specific antigen (ng/mL)			
≤4.0	180	1482	
4.1-10.0	36	0	
10.1-20.0	3	0	
>20.0	4	0	
Mean ± SD	3.16 ± 4.72	0.86 ± 0.44	$P < 0.0001$

*Family history data are from the SABOR cohort only.

child, and for second-degree relative we considered both maternal and paternal grandfathers and uncles.

SNP Selection and Genotyping

DNA was isolated from whole blood cells using a QIAamp DNA Blood Maxi Kit (Qiagen). Forty-one SNPs spanning the three genes were selected using Haploview. We first selected SNPs from available databases, National Center for Biotechnology Information[5] and SNPper,[6] using the following criteria: (*a*) within each gene, SNPs with a minor allele frequency (MAF) >0.05 that leads to an amino acid substitution and/or are in other coding regions of the gene and thus potentially functionally important were selected, and (*b*) SNPs for which an association with prostate cancer has previously been shown as reported in the literature were chosen. After this initial selection, we identified tagging SNPs within each gene using Haploview with the following criteria: (*a*) a MAF >0.05 to gain more statistical power; (*b*) an r^2 threshold of 0.8 and a log of odds threshold for multimarker testing of 3.0; (*c*) a minimum distance between tags of 60 basepairs; (*d*) we included our preselected SNPs (see above), (*e*) for each gene the search for SNPs extended to a 10 kilobase region surrounding the gene, and (*f*) we used the 2- and 3-marker haplotype tagging option.[7] The selection was based on the information on the European population as provided by HapMap.[8] The SNPs are described in Table 2. Genotyping of 39 SNPs was done with the Goldengate assay of the VeraCode technology using the BeadXpress Reader System according to the manufacturer's protocol (Illumina). Two SNPs within *RNASEL* (rs627928/*Asp541Glu* and rs486907/*Arg462Gln*) were genotyped as previously described (23). To ensure reliability of the results, duplicate samples were included in the analysis as quality controls.

Statistics

Haploview version 4 beta 15 was used to check for Hardy-Weinberg equilibrium for each SNP and to measure linkage disequilibrium (LD) between the SNPs in the controls and cases of each race/ethnicity (32).[9]

The allele frequency for each SNP was determined in each ethnic group, and the frequencies among the case-control groups were compared using the χ^2 test. Association analyses were stratified by ethnicity and done using R statistical software version 2.9.1. The OR and its 95% confidence interval (95% CI) were estimated by unconditional logistic regression as a measure of the associations between genotypes and prostate cancer risk. We tested for additive, dominant, and recessive associations. The model with the strongest association was chosen for presentation (i.e., model with smallest P value with ≥5 individuals). To correct for multiple testing, we used the method of Storey and Tibshirani (2003) based on the concept of false discovery rate (33). This estimation of the false discovery rate showed that for $P < 0.05$, the probability that the association is expected to be a true positive in our sample group is >70% (i.e., the false discovery rate is <30%). To estimate the independent effect of a significant SNP while adjusting for other SNPs, we used a generalized linear model function from the R statistical package so that all SNPs are entered into a single multivariable logistic regression model. SNPs in this model were taken to have additive effects.

Relative risk (RR) ratios for family history, including first- (father and full brother) and second-degree (grandfather and uncle) relatives affected with cancer, were

[5] http://www.ncbi.nlm.nih.gov/projects/SNP/
[6] http://snpper.chip.org/
[7] http://www.broad.mit.edu/mpg/haploview/
[8] http://www.hapmap.org
[9] http://www.broad.mit.edu/mpg/haploview/

calculated in the samples from the SABOR cohort only using Fisher's exact test. To test whether family history (first degree and second degree) modulated the effects of genotypes on prostate cancer risk, a likelihood ratio test on the interaction term between family history and genotype was done. The magnitude of any effect modification was described using parameters obtained in logistic regression stratified by family history.

Table 2. Genes, SNP selection, their location, minor allele frequencies in cases and controls of each ethnic/race group

Gene	SNP	Position	Function SNP	Minor Allele	Caucasians			Hispanics			African Americans		
					MAF case	MAF control	*P**	MAF case	MAF control	*P**	MAF case	MAF control	*P**
RNASEL	rs17568993	chr1:180804117		A	0.126	0.135	0.503	0.08	0.061	0.226	0.073	0.117	0.129
	rs12757998	chr1:180805101		A	0.284	0.309	0.149	0.198	0.198	0.999	0.177	0.139	0.270
	rs635261	chr1:180805664		C	0.383	0.37	0.484	0.402	0.406	0.901	0.287	0.262	0.569
	rs10911099	chr1:180806772		G	0.115	0.116	0.934	0.085	0.062	0.154	0.049	0.028	0.232
	rs1048260	chr1:180809474	3′UTR	G	0.296	0.287	0.628	0.304	0.295	0.752	0.213	0.194	0.621
	rs11072	chr1:180809954	3′UTR	G	0.302	0.297	0.768	0.31	0.304	0.827	0.216	0.201	0.692
	rs1048254	chr1:180810289	3′UTR	C	0.298	0.293	0.756	0.265	0.266	0.987	0.213	0.207	0.865
	rs533259	chr1:180815642		A	0.069	0.064	0.619	0.028	0.043	0.211	0.213	0.238	0.548
	rs627928	chr1:180817960	Glu541Asp	G	0.543	0.553	0.678	0.513	0.467	0.244	0.329	0.314	0.767
	rs516134	chr1:180820316		G	0.03	0.032	0.703	0.008	0.018	0.174	0.152	0.198	0.223
	rs486907	chr1:180821180	Gln462Arg	A	0.351	0.337	0.528	0.313	0.244	0.052	0.236	0.119	**0.004**
	rs3738579	chr1:180822659	5′UTR	G	0.343	0.338	0.759	0.265	0.216	0.061	0.134	0.133	0.965
	rs682585	chr1:180826133		A	0.382	0.39	0.673	0.446	0.486	0.196	0.146	0.108	0.220
MSR1	rs918	chr8:16011449	3′UTR	A	0.055	0.057	0.792	0.098	0.107	0.637	0.189	0.148	0.247
	rs1904577	chr8:16016055		G	0.126	0.128	0.843	0.273	0.302	0.315	0.396	0.444	0.310
	rs11780669	chr8:16018641		G	0.083	0.095	0.247	0.039	0.028	0.325	0.012	0.028	0.273
	rs12114368	chr8:16025334		A	0.035	0.036	0.832	0.169	0.208	0.117	0.08	0.071	0.713
	rs12681382	chr8:16029033		G	0.029	0.031	0.714	0.102	0.129	0.178	0.018	0.019	0.986
	rs2127565	chr8:16030930		G	0.119	0.131	0.355	0.29	0.312	0.445	0.644	0.614	0.528
	rs4333601	chr8:16042345	3′UTR	C	0.234	0.239	0.745	0.418	0.443	0.412	0.433	0.54	**0.025**
	rs12718376	chr8:16042516	3′UTR	A	0.107	0.153	**0.002**	0.301	0.235	0.092	0.46	0.524	0.430
	rs17484273	chr8:16044606		A	0.315	0.335	0.255	0.284	0.299	0.584	0.207	0.207	0.989
	rs17484315	chr8:16055103		C	0.043	0.047	0.606	0.008	0.009	0.843	0.012	0	**0.046**
	rs3747531	chr8:16057019	Ala275Pro	G	0.047	0.058	0.216	0.142	0.179	0.104	0.073	0.075	0.957
	rs351572	chr8:16065839		G	0.438	0.404	0.067	0.265	0.239	0.327	0.341	0.256	**0.049**
	rs754331	chr8:16067989		A	0.465	0.484	0.310	0.363	0.361	0.926	0.256	0.247	0.825
	rs13251251	chr8:16073863		A	0.064	0.06	0.655	0.031	0.031	0.977	0	0.006	0.313
	rs614794	chr8:16085228		G	0.12	0.119	0.894	0.365	0.398	0.277	0.366	0.358	0.865†
	rs3789015	chr8:16087084		G	0.039	0.045	0.461	0.137	0.177	0.079	0.079	0.08	0.970
	rs6530946	chr8:16099299		G	0.14	0.158	0.335	0.392	0.442	0.132	0.594	0	0
ELAC2	rs2072262	chr17:12833668		G	0.129	0.116	0.315	0.104	0.111	0.694	0.134	0.167	0.349
	rs2072261	chr17:12833814		A	0.237	0.239	0.871	0.227	0.25	0.381	0.119	0.108	0.724
	rs2523	chr17:12836540	3′UTR	G	0.349	0.345	0.805	0.381	0.402	0.497	0.476	0.515	0.406
	rs1044564	chr17:12836709	3′UTR	G	0.35	0.348	0.917	0.381	0.401	0.514	0.481	0.534	0.275
	rs17552022	chr17:12839020	Thr631Thr	G	0.122	0.091	**0.018**	0.077	0.059	0.291	0.013	0.01	0.826
	rs11545302	chr17:12840688	Thr520Thr	G	0.268	0.189	**9.1×10^{-6}**	0.259	0.263	0.888	0.2	0.068	**2.0×10^{-4}**
	rs11658321	chr17:12855209		A	0.35	0.341	0.604	0.41	0.408	0.957	0.665	0.698	0.459
	rs2051974	chr17:12862370		A	0.233	0.242	0.601	0.22	0.198	0.382	0.427	0.466	0.411
	rs8077923	chr17:12864712		C	0.14	0.158	0.194	0.179	0.18	0.964	0.201	0.176	0.496
	rs7218504	chr17:12868379		C	0.309	0.315	0.737	0.302	0.27	0.253	0.39	0.41	0.676
	rs12943765	chr17:12868955		G	0.059	0.048	0.201	0.062	0.039	0.087	0.055	0.049	0.795

NOTE: Significant *P* values are in bold.

*Assumes Hardy-Weinberg equilibrium.

†SNP not in Hardy-Weinberg equilibrium ($P < 0.01$).

The cumulative effect of combined genotypes on prostate cancer risk was estimated by counting the number of genotypes associated with prostate cancer, on the basis of the best-fitting genetic inheritance from single-SNP analysis. ORs and their 95% CIs were calculated for men carrying any combination of one, two, or more alleles associated with prostate cancer as compared with men carrying none of the risk genotypes using unconditional logistic regression analysis. We also fit models that estimated the cumulative effect of family history on prostate cancer risk in addition to the risk alleles determined above in an unconditional logistic regression. We selected SNPs that were not in LD with each other ($D' < 0.8$). If several SNPs presented higher LD values, we choose a SNP in a coding region above an intronic SNP, and also selected the most significant SNP.

Logistic regression was used to calculate the ORs of the haplotypes, using the method implemented in the haplo.ccs package (34) where the OR of each major haplotype was computed relative to a reference group consisting of all other haplotypes, including rare haplotypes. Only major haplotypes (estimated frequency >5%) are considered in this report. Three genetic models (additive, dominant, and recessive) were tested. For all statistical analyses, age was used as covariate. Individuals with missing data for a particular analysis were removed from the analysis. Because of the small sample sizes for prostate cancer men with first- or second-degree relatives, we restricted the analysis in this report to the family history data, which include both subgroups. All statistical tests were two-sided and significance was set at $P < 0.05$.

Results

All SNPs were in Hardy-Weiberg equilibrium ($P > 0.01$) in the controls of each ethnic/racial group, except for SNP rs614794, which showed a deviation from Hardy-Weiberg equilibrium in African American controls. This SNP was omitted for further statistical analysis in this study group. Table 2 shows the MAF of the SNPs estimated in all three ethnicities. Significant case/control differences of allele frequencies at a level <0.05 were observed for three and five polymorphisms in Caucasians and African Americans, respectively.

Five SNPs (three in *MSR1* and two in *ELAC2*) were significantly associated with prostate cancer risk in Caucasians (P values 0.043-0.0001). The strongest association, considering both the level of significance and the magnitude of OR, was seen for rs12718376 in *MSR1* and rs11545302 in *ELAC2* (OR, 0.32; 95% CI, 0.12-0.90; $P = 0.031$, and OR, 2.19; 95% CI, 1.25-3.82; $P = 0.006$, respectively; Table 3). SNP rs12718376 is located within the 3′ untranslated region of *MSR1* and the two SNPs in *ELAC2*, rs17552022 and rs11545302, are located within exonic regions of the gene but do not result in amino acid changes. In Hispanics three SNPs within *RNASEL* and one SNP within *MSR1* were found to be significantly associated with prostate cancer risk (P values 0.03-0.003). In addition to the two previously reported nonsynonymous SNPs, rs627928 (*Asp541Glu*) and rs486907 (*Arg462Gln*; ref. 23), rs682585 was also found to be significant in this ethnic group. In African Americans, rs4333601 and rs351572, both located within *MSR1*, showed a significant association with prostate cancer (P values 0.039-0.024). Significance for SNP rs351572 (*MSR1*) was found in both Caucasians and African Americans. All SNPs that were significantly associated with prostate cancer remained significant after adjusting for multiple comparisons. After conditioning on other significant SNPs not in LD with each other, rs11545302 (*ELAC2*) showed a main effect independent of other significant SNPs in Caucasians ($P = 2.03 \times 10^{-5}$), whereas no significant independent associations were found for Hispanics or African Americans.

Of the 226 incident cases, 95 (42%) had a positive family history. A positive family history of prostate cancer, including both first- and second-degree relatives, showed a significant increase in relative risk (RR, 1.79; 95% CI, 1.40-2.27; $P < 0.0001$). For a man suffering from prostate cancer with a first-degree relative affected with prostate cancer the RR is 1.84 (95% CI, 1.41-2.37; $P < 0.0001$), which is slightly higher compared with the risk of having a second-degree relative affected with prostate cancer (RR, 1.71; 95% CI, 1.20-2.38; $P = 0.005$). When more than one first-degree relative is affected with prostate cancer, the risk increases 2-fold (RR, 1.99; 95% CI, 1.13-3.40; $P = 0.03$). We have to mention that these results are based on a small number of samples within the cohort and thus need to be interpreted with caution (Table 1). Logistic regression including both age and family history as covariates, however, did not change the risk estimates for cancer as compared with an age-only adjusted analysis. Adding family history as interaction term in the logistic regression showed that several SNPs within *RNASEL* had a significant interaction effect in Hispanics (Table 4). A stratified analysis by family history further indicated that significant associations were only found in the group with family history, which corroborates the findings of the interaction model. In addition, an increase in effect size was observed for all SNPs except rs627928. No major effects with family history were found in the Caucasians or African Americans.

Age-adjusted multivariate logistic regression of combinations of risk alleles for SNPs not in LD with each other compared with no risk alleles as reference, showed a cumulative effect for SNPs rs351572 and rs11545302 in Caucasians (OR, 2.31; 95% CI, 1.64-3.26; $P_{trend} = 1.73 \times 10^{-6}$). In Hispanics, the combination of three risk alleles for SNPs rs486907, rs682585, and rs12114368 showed a significant association with prostate cancer ($P_{trend} = 0.015$) and a 3.31-fold increase in risk (95% CI, 1.26-8.71; Table 5). No cumulative effect of both significant SNPs in African Americans was observed. For the analysis, we selected significant SNPs not in LD with each other and chose the most significant and/or functional SNP. Of note, however, is that for Caucasians, the three-SNP combination, including

Table 3. Significant results from individual SNP effects on prostate cancer in Caucasians, Hispanics, and African Americans after correction for multiple testing

Gene	SNP	Genotype	Controls (*n*)	Cases (*n*)	OR* (95% CI)	*P*
			Caucasians			
MSR1	rs12718376	GG	484	329	1.00	
		AA	18	5	0.32 (0.12-0.90)	**0.031**
		AG	170	78	0.68 (0.50-0.92)	**0.014**
		AA/AG vs GG	188	83	0.64 (0.48-0.86)	**0.004**
MSR1	rs17484273	GG	371	263	1.00	
		AA	95	44	0.66 (0.45-0.98)	**0.041**
		AG	372	285	1.06 (0.85-1.33)	0.590
		AA vs AG/GG	95	44	0.64 (0.44-0.94)	**0.022**
MSR1	rs351572	AA	306	175	1.00	
		GG	145	102	1.26 (0.91-1.73)	0.159
		AG	388	315	1.40 (1.10-1.78)	**0.007**
		GG/AG vs AA	533	417	1.36 (1.08-1.71)	**0.009**
ELAC2	rs17552022	AA	443	427	1.00	
		GG	5	9	1.92 (0.63-5.83)	0.251
		AG	87	117	1.38 (1.01-1.88)	**0.043**
		GG/AG vs AA	92	126	1.41 (1.04-1.91)	**0.027**
ELAC2	rs11545302†	AA	356	311	1.00	
		GG	21	41	2.19 (1.25-3.82)	**0.006**
		AG	161	229	1.67 (1.29-2.16)	**1.0×10^{-4}**
		GG/AG vs AA	182	270	1.73 (1.36-2.22)	**1.0×10^{-5}**
			Hispanics			
RNASEL	rs627928	TT	59	41	1.00	
		GG	48	45	1.49 (0.83-2.69)	0.186
		GT	120	70	0.80 (0.48-1.33)	0.390
		GG vs GT/TT	48	45	1.72 (1.05-2.81)	**0.030**
RNASEL	rs486907	GG	126	75	1.00	
		AA	7	17	4.18 (1.61-10.85)	**0.003**
		AG	91	64	1.16 (0.75-1.81)	0.508
		AA vs AG/GG	7	17	3.92 (1.54-9.96)	**0.004**
RNASEL	rs682585	GG	96	64	1.00	
		AA	85	43	0.72 (0.43-1.20)	0.207
		AG	210	87	0.52 (0.34-0.80)	**0.003**
		AA/AG vs GG	295	130	0.58 0.38-0.86	**0.007**
MSR1	rs12114368	GG	246	139	1.00	
		AA	20	12	0.97 (0.44-2.14)	0.940
		AG	121	41	0.58 (0.38-0.90)	**0.015**
		AA/AG vs GG	141	53	0.64 (0.43-0.95)	**0.029**
			African Americans			
MSR1	rs4333601	CC	46	14	1.00	
		AA	33	25	2.57 (1.13-5.83)	**0.024**
		AC	83	43	1.74 (0.84-3.58)	0.134
		A # vs C #	162	82	1.59 (1.06-2.39)	**0.024**
MSR1	rs351572	AA	89	33	1.00	
		GG	10	7	2.32 (0.78-6.84)	0.128
		AG	63	42	1.84 (1.03-3.28)	**0.039**
		GG/AG vs AA	73	49	1.90 (1.09-3.32)	**0.025**

NOTE: Significant *P* values are in bold.

*Age adjusted.

†Main effect independent from other significant SNPs.

Table 4. Risk estimates of variants in *RNASEL* for cancer by interaction effects of family history (left) and family history stratification (right) in Hispanics

SNP	Genotype	Interaction model			Genotype	Stratified: no family history			Stratified: family history		
		Controls/ Cases (*n*)	OR (95% CI)	*P*		Controls/ Cases (*n*)	OR (95% CI)	*P*	Controls/Cases (*n*)	OR (95% CI)	*P*
rs12757998	GG	258/126	Ref			213/88	Ref		45/38	Ref	
	AG	114/59	1.41 (0.88-2.25)	0.149		77/47	1.41 (0.88-2.25)	0.148	37/12	0.33 (0.14-0.77)	**0.011**
	AA/AG vs GG	135/68	1.30 (0.83-2.04)	0.246		93/52	1.30 (0.83-2.03)	0.246	42/16	0.41 (0.19-0.88)	**0.023**
	AG*GxE	37/12	0.24 (0.09-0.62)	**0.008**							
	AA/AG vs GG *GxE	135/68	0.32 (0.13-0.76)	**0.010**							
rs635261	GG	140/69	Ref			107/55	Ref		33/14	Ref	
	CC	66/31	0.77 (0.41-1.45)	0.421		61/21	0.77 (0.41-1.44)	0.416	5/10	6.22 (1.67-23.2)	**0.006**
	CC vs CG/GG	66/31	0.83 (0.47-1.48)	0.534		61/21	0.83 (0.47-1.47)	0.527	5/10	4.58 (1.40-15.0)	**0.012**
	CC*GxE	5/10	7.81 (1.86-32.9)	**0.016**							
	CC vs CG/GG *GxE	66/31	5.39 (1.46-19.9)	**0.009**							
rs1048260	CC	191/94	Ref			148/75	Ref		43/19	Ref	
	CG	172/82	0.77 (0.49-1.20)	0.251		134/54	0.77 (0.49-1.20)	0.252	38/28	2.07 (0.94-4.54)	0.069
	GG/CG vs CC	202/100	0.76 (0.50-1.17)	0.210		158/65	0.76 (0.50-1.17)	0.212	44/35	2.18 (1.03-4.63)	**0.042**
	CG*GxE	38/28	2.65 (1.09-6.46)	**0.049**							
	GG/CG vs CC *GxE	202/100	2.82 (1.20-6.62)	**0.016**							
rs11072	AA	183/90	Ref			142/72	Ref		41/18	Ref	
	AG	173/85	0.82 (0.53-1.29)	0.394		135/56	0.82 (0.53-1.29)	0.393	38/29	2.03 (0.92-4.46)	0.078
	GG/AG vs AA	204/102	0.79 (0.51-1.21)	0.273		160/66	0.79 (0.51-1.21)	0.275	44/36	2.13 (1.00-4.54)	**0.049**
	AG*GxE	38/29	2.43 (0.99-5.94)	0.059							
	GG/AG vs AA *GxE	204/102	2.66 (1.13-6.28)	**0.024**							
rs1048254	AA	208/103	Ref			159/82	Ref		49/21	Ref	
	AC	161/79	0.80 (0.51-1.25)	0.326		126/51	0.80 (0.51-1.25)	0.325	35/28	1.93 (0.90-4.11)	0.090
	CC/AC vs AA	185/91	0.76 (0.50-1.17)	0.215		147/58	0.76 (0.50-1.17)	0.215	38/33	2.14 (1.03-4.46)	**0.042**
	AC*GxE	35/28	2.40 (1.00-5.76)	**0.022**							
	CC/AC vs AA *GxE	185/91	2.80 (1.20-6.52)	**0.016**							
rs627928*	TT	59/41	Ref		GG	40/28	Ref		19/16	Ref	
	GT	120/69	1.05 (0.57-1.96)	0.866	GT	90/58	0.83 (0.45-1.53)	0.559	30/11	0.40 (0.15-1.08)	0.071
	GG vs GT/TT	48/45	1.21 (0.68-2.15)	0.519	TT vs GT/GG	40/25	0.90 (0.50-1.62)	0.715	8/17	4.40 (1.63-11.9)	**0.003**
	GT*GxE	30/11	0.37 (0.12-1.20)	0.013							
	GG vs GT/TT *GxE	48/45	3.85 (1.23-12.0)	**0.018**							

NOTE: Significant *P* values are in bold.
Abbreviation: GxE, Interaction gene-environment.
*SNP significant in single-SNP analysis.

Table 5. Cumulative effects of risk variants

Markers	Number of risk genotypes	Controls	Cases	OR (95% CI)*	*P*
Caucasians					
rs351572, rs11545302	0	136	99	Ref	-
	1	275	272	1.36 (0.99-1.86)	0.055
	2	127	208	2.27 (1.61-3.21)	3.29×10^{-6}
	Trend			2.31 (1.64-3.26)	**1.73×10^{-6}**
Add family history	Trend			2.47 (1.75-3.49)	**2.88×10^{-7}**
Hispanics					
rs486907, rs682585,rs12114368	0	39	25	Ref	-
	1	90	89	1.71 (0.93-3.16)	0.085
	2	32	31	1.75 (0.84-3.67)	0.137
	3	2	10	8.5 (1.63-44.26)	0.011
	Trend			3.31 (1.26-8.71)	**0.015**
Add family history	Trend			3.15 (1.38-7.20)	**0.007**

NOTE: Significant *P* values are in bold.
*Age adjusted.

rs12718376, rs351572, and rs11545302 with rs12718376 and rs351572 being in LD, showed an even stronger cumulative effect with a >4-fold increase in OR (OR, 4.05; 95% CI, 2.09-7.87; $P = 3.66 \times 20^{-5}$; data not shown). After adding the presence of family history and checking for risk estimates of prostate cancer in men carrying a combination of multiple risk alleles and also having a family history, the OR slightly increased in Caucasians (from 2.31 to 2.47) and slightly decreased in Hispanics (from 3.31 to 3.15; Table 5).

Haplotype analysis of SNPs not in LD within each of the three genes showed a major haplotype (39%) *G-A-C-G-C-G* for the SNPs rs918-rs1904577-rs2127565-rs12718376-rs3747531-rs351572 within *MSR1* that significantly increased the risk for prostate cancer in Caucasians under the dominant model (OR, 1.58; 95% CI, 1.23-2.04; $P = 4.02 \times 10^{-4}$; Table 5). In African Americans, the major haplotype *C-G-G-C-G* (6%) for SNPs rs2072262-rs2523-rs11545302-rs8077923-rs7218504 within *ELAC2* is significantly associated with disease risk with an OR of 3.65 (95% CI, 1.38-9.68; $P = 0.009$) under the additive model (Table 6).

Discussion

Substantial evidence exists indicating that the etiology of prostate cancer involves the interplay among genetic, environmental, and dietary factors. Whereas several of the risk factors are merely the result of individual choices and thus modifiable (e.g., diet, exposure to UV radiation, tobacco use), some major risk factors for prostate cancer are determined and unchangeable, including age, ethnicity, and family history. Finding which and to what extent such factors confer increased risk of prostate cancer has been a burden and major challenge for researchers over the last several years.

We studied three candidate susceptibility genes, *ELAC2* on chromosome 17p11/*HPC2* region, *RNASEL* within the *HPC1* region, and *MSR1* within a region of linkage on chromosome 8p, that have been previously suggested to play a role in hereditary prostate cancer. Forty-one tagged SNPs covering each of the three genes were genotyped in a case-control cohort consisting of 1,436 Caucasians (596 cases, 840 controls), 648 Hispanics (194 cases, 454 controls), and 270 African Americans (82 cases, 188 controls). Single-SNP analysis showed that SNPs within *MSR1* were significantly associated in all three ethnicities ($P = 0.04$-0.004), with rs351572 being in common between Caucasians and African Americans. None of the significant SNPs within *MSR1* found in this study have been reported previously. Of interest is that SNP rs433601, significant in African Americans and located in the 3′untranslated region of the gene, has an allele-specific alteration of an exon splicer enhancer binding site according to PupaSuite. Moreover, a major *G-A-C-G-C-G* haplotype for the SNP combination rs918-rs1904577-rs2127565-rs12718376-rs3747531-rs351572 showed a significant increase in prostate cancer risk in Caucasians. The nonsynonymous SNP rs3747531, included in this haplotype, results in an alanine to proline change, which, according to Polyphen, has a damaging effect.[10] However, no evidence has been shown for possible phenotypic effects of the allelic variation for this SNP. The majority of previous studies did not find associations of variants within *MSR1* and prostate cancer (35-37), although Hsing et al. (2007) reported on significant associations between *MSR1* variants and prostate cancer in Chinese (38). The lack of positive association findings

[10] http://genetics.bwh.harvard.edu/pph/

for *MSR1* variants could be explained by the fact that only a few SNPs were investigated per study, in particular coding SNPs, underestimating the importance of noncoding intronic SNPs. Alternatively, (geographic) differences in population structures, and/or insufficient power to detect single SNP associations for some studies due to small sample sizes could explain between-study differences in association results. This study shows that, in addition to coding SNPs, noncoding intronic SNPs within *MSR1* play a role in determining susceptibility to prostate cancer and are part of high-risk haplotypes. Moreover, a potential role of *MSR1* in the susceptibility to prostate cancer is suggested in the three ethnicities studied, albeit with subgroup differences in significance of SNPs likely due to population-specific allele frequencies and LD structure. Studies in animals have shown that mutations in *MSR1* increase the likelihood of bacterial infections. Therefore, our findings support a previous hypothesis that infection and prostate cancer could be linked (39).

This study also found two synonymous SNPS (rs11545302/*Thr520Thr* in exon 17 and rs17552022/*Thr631Thr* in exon 20) within *ELAC2* that showed significant risk effects on prostate cancer in Caucasians. SNP rs11545302 further showed an independent effect from other significant SNPs in this group ($P = 0.0001$). Although two recent genome-wide association studies have found several regions to be implicated in prostate cancer risk in Europeans, no significance was found for rs11545302 (40, 41). Both studies used the HumanHap300 and HumanHap240 panels from Illumina for the analysis which does not contain rs11545302. Nonetheless, previous studies report negative findings for association of single SNPs within *ELAC2* in Caucasians, which is in contrast with our findings (18, 42). On the other hand, positive associations were also found in Japanese men (43, 44) and African Americans (45), with the latter consistent with our results. Although not significant for the single-SNP analysis, a major *C-G-G-C-G* haplotype for SNPs rs2072262-rs2523-rs11545302-rs8077923-rs7218504 showed a significant increase in risk for prostate cancer in African Americans. This risk haplotype contains a SNP (rs2523) that is located within a microRNA binding site (miR-648) at the 3′ untranslated region of the *ELAC2* gene (information retrieved from PupaSuite). Currently there are no reports that describe possible functions of this microRNA. Moreover, the function of *ELAC2* is unknown but the gene is believed to play a role in cell cycle progression. Consequently, it remains to be determined to what extent variants within *ELAC2* confer increased risk of prostate cancer.

Three SNPs within *RNASEL* showed a significant association with prostate cancer risk in Hispanics. These findings conform with our previous results showing a significant increase in prostate cancer risk for two nonsynonymous SNPs, rs627928 (*Asp541Glu*) and rs486907 (*Arg462Gln*; ref. 23). The allelic variant at position 462 (*Arg462Gln*), which reduces *RNASEL* enzymatic activity 3-fold, is associated with an increase in risk of prostate cancer as found in Hispanics in this study and other previous studies (23, 39). Our findings further showed a significant association between rs682585, located just upstream of *RNASEL*, and prostate cancer risk in Hispanics. An association between prostate

Table 6. Association of common haplotypes with prostate cancer risk in Caucasian and African American men

SNP combination	Freq	No. of haplotypes		OR* (95% CI)	*P*
Caucasians†		Cases	Controls		
MSR1: rs918-rs1904577-rs2127565-rs12718376-rs3747531-rs351572					
G-A-C-G-C-G	39%	259	392	**1.58 (1.23-2.04)**	**4.02×10^{-4}**
G-A-C-G-C-A	31%	208	346	1.10 (0.86-1.40)	0.443
G-A-C-A-C-A	8%	44	118	0.63 (0.44-0.90)	0.010
African Americans‡					
ELAC2: rs2072262-rs2523-rs11545302-rs8077923-rs7218504					
C-A-A-A-C	30%	35	58	0.76 (0.48-1.20)	0.235
C-G-A-A-G	24%	29	51	0.64 (0.38-1.07)	0.090
C-A-A-A-G	17%	28	30	1.23 (0.73-2.08)	0.435
C-G-G-C-G	6%	15	6	**3.65 (1.38-9.68)**	**0.009**
G-G-A-A-G	5%	6	13	0.59 (0.21-1.65)	0.314

NOTE: Significant results after Bonferroni correction are in bold ($P < 0.017$ and $P < 0.01$ in Caucasians and African Americans, respectively).
Only common haplotypes (>5%) are shown.
*OR is age adjusted.
†Dominant model.
‡Additive model.

cancer and rs682585 has not been reported previously. A viral etiology for prostate cancer has been suggested from recent findings, including the observation that a novel retrovirus, the xenotropic murine leukemia-related virus, was frequently found in prostate tissue of men with the *Arg462Gln* allelic variant (39, 46, 47). It was further shown that *RNASEL*-deficient cells and animals are more susceptible to viral infections (48). Therefore, *RNASEL* was suggested to be implicated in the suppression of xenotropic murine leukemia-related virus infections of the prostate.

A positive family history is a well-established and important epidemiologic risk factor for prostate cancer, and our findings corroborate a previous meta-analysis on the increased family-history associated risk for prostate cancer. A risk ratio of 1.8 for first-degree relatives found in our sample was higher than the RR of 1.53 found by Roemeling et al. (2006) but lower than reported in the meta-analysis by Noe et al. (2008; RR range between 2.2 and 2.5; refs. 49, 50). This could be explained by the smaller number of participants in our study as compared with the meta-analysis and/or because we did not stratify the analysis by ethnicity. However, previous reports showed that the increased risk of prostate cancer in family members is similar among Caucasians, Hispanics, and African-Americans within the United States (51-53). On the other hand, the RR, being 1.7 for second-degree relatives, is similar to the meta-analysis by Noe et al. (2008; RR between 1.68 and 1.88; ref. 50). In general, the relative risk of prostate cancer increases markedly with increasing number of affected relatives suggesting a genetic component of prostate cancer. Incorporation of family history into our model did not dramatically change the results in Caucasians and African Americans. In Hispanics, however, several SNPs within *RNASEL* showed an interaction effect of family history.

Combining the two high-risk genotypes of *MSR1* and *ELAC2* in Caucasians and the three high-risk genotypes of *RNASEL* and *MSR1* in Hispanics showed synergistic effects, and individuals with multiple-risk genotypes are at higher risk as compared with individuals with a single high-risk genotype. From these findings one could assume that an interaction between both genes in each ethnicity is likely to confer prostate cancer risk. Although a biological explanation awaits further experimental studies, the function of these genes in cellular defense against inflammation and oxidative stress is supportive of a possible interaction between these genes, which also corroborates previous suggestions that infection and prostate cancer could be linked.

A possible limitation of the study is that 13.4% of our control group was between 45 and 50 years old compared with 4% of our cases in this age range. This is a limitation because the average age of men diagnosed with prostate cancer is over the age of 60 years, and according to the American Cancer Society two thirds of prostate cancers are found in men over the age of 65. In our heavily screened population, however, we noted that 50% of the cancers had a diagnosis before the age of 65 years. Furthermore, for the analyses in this study we adjusted statistically for age difference. In addition, the presence of potential cases in the control group will merely result in an underestimation of the effect of significant associations. Another limitation of our study is that selection of the tagged SNPs was based on HapMap data of the European population. Due to the ethnic-specific LD patterns, these SNPs selected may not fully represent all tagged variants in Hispanics and/or African Americans. Furthermore, the power of this study is limited by the sample size (2,354 in total, with 1,435 Caucasians, 648 Hispanics, and 270 African Americans), the MAF, the baseline incidence of disease (~6%), and the unknown OR of a genetic risk factor. Assuming a type I error of 0.05, an OR of 1.5, and a MAF of 20%, we estimated the power of the study with the method of Slager and Schaid to be 99%, 75%, and 38% in Caucasians, Hispanics, and African Americans, respectively. Even with these weaknesses, however, our findings indicate that variants within *ELAC2*, *RNASEL*, and *MSR1* play a significant role in the susceptibility to prostate cancer risk. We did not report on the risk effects of the investigated SNPs on Gleason grade (Gleason score $\geq$7 versus <7) or prognosis (defined as Gleason score of $\geq$7 or stage T_{3b} or higher) due to the small number of cases with information on the trait of interest. However, a case only logistic regression analysis showed that in Caucasians variants in *RNASEL* and *ELAC2* could be involved in Gleason grade and prognosis, respectively. A trend towards significance for SNPs within *MSR1* was seen for Gleason grade and within both *RNASEL* and *MSR1* for prognosis in Hispanics. There results have to be considered with caution due to the number of cases. The sample size of the African Americans was too small for data analysis.

In summary, this is the first association study to cover the three susceptibility genes for prostate cancer with haplotype-tagged SNPs. Our results show that variants in *ELAC2*, *RNASEL*, and *MSR1* play a role in the development of prostate cancer albeit with ethnic-specific differences in risk estimates. Our findings suggest that interactions among these genes likely confer prostate cancer risk consistent with a polygenic model for cancer susceptibility. Moreover, a function of these genes in cellular response to inflammation corroborates the hypothesis of a link between infection and etiology of prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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