Association of RNASEL Variants with Prostate Cancer Risk in Hispanic Caucasians and African Americans

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Abstract

Purpose: The *RNASEL* gene at 1q25 has been identified as a hereditary prostate cancer susceptibility gene, but to date, no study has investigated the role of RNASEL variants in Hispanic Caucasian men with prostate cancer.

Experimental Design: Two RNASEL common variants, located at amino acids 462 and 541, were genotyped in non-Hispanic Caucasian, Hispanic Caucasian, and African American prostate cancer cases and controls.

Results: The RNASEL 462 AA genotype was found to increase prostate cancer risk over 4-fold in Hispanic Caucasians [odds ratio (OR), 4.43; 95% confidence interval (95% CI), 1.68-11.68; $P = 0.003$] and over 10-fold in African Americans (OR, 10.41; 95% CI, 2.62-41.40; $P = 0.001$) when compared with the GG genotype. Analysis of the RNASEL 541 variant showed that Hispanic Caucasian patients with the GG genotype had a statistically significant increase in their risk for developing prostate cancer when compared with the TT and GT genotypes (OR, 1.91; 95% CI, 1.16-3.14; $P = 0.01$). A common G-T haplotype for the combination of the RNASEL 462 and 541 variants was found to occur more frequently in controls compared with cases in African Americans ($P = 0.04$) but not in non-Hispanic Caucasians or Hispanic Caucasians.

Conclusions: This is the first study that investigates the association of prostate cancer risk with RNASEL variants in Hispanic men. Our data support the role of RNASEL as a predisposition gene for prostate cancer and showed a significant association between the RNASEL 462 variant and prostate cancer risk in African Americans and Hispanic Caucasians.

Over 218,000 men in the United States are estimated to be diagnosed with prostate cancer (MIM 176807) in 2007 alone and approximately 27,000 men will die from it (1). Although prostate cancer is the most common non-skin cancer and the second leading cause of cancer death in men in the United States, little is known about inherited factors that influence its genetic predisposition. Many factors are known to contribute to the risk of prostate cancer, including diet, race and ethnicity, age, sexual history, and family history (2–6).

Currently, elevated serum levels of prostate-specific antigen and/or an abnormal digital rectal exam are the main methods for diagnosing this disease (7). However, 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 (8). Only limited association studies on candidate genes and/or linkage analyses for susceptibility loci have consistently produced positive findings. In 1996, the first prostate cancer susceptibility locus, the *hereditary prostate cancer* (*HPC*) *1* locus (*HPC1*; MIM 601518), was mapped to chromosomal region 1q24-q25 by linkage analysis (9) and since this initial report, several prostate cancer susceptibility loci have been identified (10–18). Because the majority of these regions have not been consistently confirmed in independent populations, evidence has emerged that prostate cancer is a genetically complex and heterogeneous disorder, with multiple genetic and environmental factors contributing to the disease.

There is substantial evidence for a genetic component in the vulnerability to prostate cancer. A cohort study of twins reported by Lichtenstein et al. (19) indicated that the proportion of prostate cancer risk accounted for by heritable factors is estimated to be 42%. Prostate cancer is classified as hereditary (HPC) or sporadic and it is assumed that HPC might be caused by rare, highly penetrant alleles at single gene forms of the disease (20). Alternatively, the sporadic prostate cancer cases may involve some of the same genes and pathways that determine HPC incidence, but they most likely involve more common, low- to moderate-penetrant alleles in genes that are components of pathways that influence prostate function (21–23).

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An important gene involved in innate immunity and apoptosis is the gene encoding 2′-5′-oligoadenylate (2-5A)–dependent RNASEL (*RNASEL*; MIM 180435). *RNASEL*, located at 1q25, regulates cell proliferation and apoptosis through the IFN-regulated 2-5A pathway (24) that mediates antiviral and antiproliferative activities (25–27) and has been suggested to be a candidate tumor suppressor gene. Previous studies indicated that germ-line mutations in the *RNASEL* gene segregate in prostate cancer families that show linkage to the HPC1 region (28). The investigators also found a truncating mutation (E265X) and an initiation-codon mutation (M1I) segregating with the disease in two HPC1-linked families. Functional studies show that both mutations were associated with a reduction in RNASEL activity (28). Furthermore, loss of the wild-type *RNASEL* allele was found in tumor tissue from an affected patient in a family with the E265X mutation, accompanied by absent protein expression. This E265X mutation was also associated with HPC in Finnish patients (29). Follow-up studies revealed a frameshift mutation, 471delAAAG, as a founder allele in Ashkenazi Jews (30).

There are numerous nucleotide variants identified in the *RNASEL* gene, with seven of them resulting in protein sequence changes (29). Six variants cause missense alterations and one rare variant creates a nonsense mutation. The two most commonly found variants in the U.S. non-Hispanic Caucasian population are the nonsynonymous variants: $Arg^{462}Gln$ (G→A) and $Asp^{541}Glu$ (T→G). The $Arg^{462}Gln$ variant reduces the ability of the cell to cause apoptosis in response to activation by 2-5 (A) and also has three times less enzymatic activity than normal (31), whereas the $Asp^{541}Glu$ variant has no known effect on RNASEL protein function (32). There continues to be much debate over whether these common variants increase the risk of prostate cancer. The $Arg^{462}Gln$ AA genotype has been associated with both increased prostate cancer in U.S. Caucasian sample groups (31, 32) and decreased prostate cancer risk in Caucasian and Japanese sample groups (33, 34). Previous studies using the $Asp^{541}Glu$ variant within RNASEL indicated that the GG and TT genotypes were associated with an increased risk for prostate cancer in Japanese (34) and European-American samples, respectively (17). On the other hand, a significant negative association of the TT genotype with prostate cancer in Swedish Caucasian samples was reported by Wiklund et al. (35).

In summary, several studies provide strong support, both functional and epidemiologic, that RNASEL plays a role in HPC, yet other studies have suggested that its role may be small. To date, no association study has been done using Hispanic Caucasian prostate cancer cases. Furthermore, no significant association has been reported in African American prostate cancer cases thus far. In this study, we analyzed an extended group of samples from three different racial/ethnic groups to determine whether a significant association exists between the allelic variants RNASEL 462 and/or RNASEL 541 and prostate cancer in non-Hispanic Caucasians, Hispanic Caucasians, and/or African Americans.

Materials and Methods

Study participants. The San Antonio Center for Biomarkers of Risk of Prostate Cancer cohort was used for the study. The San Antonio Center for Biomarkers of Risk of Prostate Cancer is funded by the National Cancer Institute and has been prospectively enrolling healthy male volunteers for over 6 years. Digital rectal exams were done and serum prostate-specific antigen levels were determined at every annual visit. Cases were individuals with a known history of prostate cancer enrolled in a parallel study of prevalent prostate cancer or individuals enrolled in the San Antonio Center for Biomarkers of Risk of Prostate Cancer Study who were diagnosed with prostate cancer. Cases had biopsy-confirmed prostate cancer and controls consisted of male volunteers of at least 45 years old who had normal digital rectal exams and prostate-specific antigen levels of <2.5 ng/mL on at least two and up to six study visits. Race/ethnicity was self-reported. Table 1 shows the characteristics of the study samples. For this study, we used 933 non-Hispanic Caucasians (430 cases and 503 controls), 392 Hispanic Caucasians (150 cases and 242 controls), and 214 African Americans (68 cases and 146 controls). This study received Institutional Review Board approval from the University of Texas Health Science Center at San Antonio. Informed consent was obtained from all subjects.

DNA isolation and genotyping. DNA was isolated from participants' whole blood cells using a QIAamp DNA Blood Maxi kit (Qiagen) and was used for genotyping. The Taqman allelic discrimination assay (Applied Biosystems) was used to genotype the nucleotide variants RNASEL $Arg^{462}Gln$ (rs486907) and $Asp^{541}Glu$ (rs627928). Primers and probes were designed using Primer Express (Applied Biosystems). The primers and probes for $Arg^{462}Gln$ were as follows: forward primer 5′-GGAAGATGTGGAAAATGAGGAAGA-3′, reverse primer 5′-TGCAGATCCTGGTGGGTGTA-3′, and probes 5′-VICCAGGACATTTCGGGCAA-MGB and 5′-FAMCAGGACATTTTGGGCAA-MGB. The primers and probes for $Asp^{541}Glu$ were as follows: forward primer 5′-TCTATGTGGTAAAGAAGGGAAGCA-3′, reverse primer 5′-TTGAACCACCTCTTCATTACTTTGAG-3′, and probes 5′-VICTTTCAGATCCTCAAAT-MGB and 5′-FAMTTTCAGCTCCTCAAAT-MGB. The target sequences were amplified by PCR in 7 μL reaction mix containing

Table 1. Characteristics of subjects for this study

Subgroup	Cases (*n* = 732)	Controls (*n* = 1,546)
	n (%)	*n* (%)
Ethnic background		
Non-Hispanic Caucasian	503 (68.7)	840 (54.3)
Hispanic Caucasian	159 (21.7)	501 (32.4)
African American	70 (9.6)	205 (13.3)
Age (y)		
≤50	21 (2.9)	214 (13.8)
51-60	165 (22.5)	601 (38.9)
61-70	329 (45.0)	485 (31.4)
>70	217 (29.6)	246 (15.9)
PSA (ng/mL)		
≤4.0	138	1,546
4.1-10.0	30	0
10.1-20.0	2	0
>20.0	4	0
Mean (SD)	3.284 (4.21)	0.895 (0.461)
DRE		
Normal	47	1,546
Abnormal	113	0
Family history of PCa		
Negative	531 (72.5)	1,260 (81.5)
Positive	201 (27.5)	286 (18.5)
Gleason score	*n* = 560	
<7	326 (58.2)	
7	153 (27.3)	
>7	81 (14.5)	

Abbreviations: PSA, prostate-specific antigen; DRE, digital rectal exam; PCa, prostate cancer; SD, standard deviation.

Table 2. Allele frequencies for the more common allele by race/ethnicity and case-control status

SNP	NCBI reported CEU	NCBI reported YRI	Non-Hispanic Caucasians			Hispanic Caucasians			African Americans		
			Cases (n = 430)	Controls (n = 503)	P	Cases (n = 150)	Controls (n = 242)	P	Cases (n = 68)	Controls (n = 146)	P
RNASEL 462 G	0.592	0.942	0.649	0.663	0.90	0.687	0.766	**0.01**	0.754	0.874	**0.0005**
RNASEL 541 G	0.625	0.217	0.545	0.560	0.66						
RNASEL 541 T						0.493	0.529	0.33	0.657	0.689	0.52

Abbreviations: NCBI, National Center for Biotechnology Information; CEU, CEPH (Utah residents with ancestry from northern and western Europe); YRI, Yoruba in Ibadan, Nigeria.

10 ng of genomic DNA, 900 nmol/L of each primer, 200 nmol/L of each probe, and 1× Taqman Universal PCR Master Mix (Applied Biosystems). PCRs were incubated at 95°C for 10 min followed by 40 cycles of denaturing at 95°C for 15 s and annealing/extending at 60°C for 1 min. Genotypes were determined using an ABI 7900HT Sequence Detection System (Applied Biosystems) and analyzed with the SDS 2.0 software (Applied Biosystems). To ensure the quality of the genotyping, consistent results were required for eight control samples added to each 384-well reaction plate. We also repeated ~15% of the control samples to check for error rates and found a 100% concordance rate for the genotyping results of RNASEL 462 and one mismatch for marker RNASEL 541. Both markers were in Hardy-Weinberg equilibrium in the control samples ($P > 0.05$).

Statistics. For each single nucleotide polymorphism (SNP), allele frequency was determined for the three ethnic groups individually and the frequencies among the ethnic sample groups were compared using the χ^2 test. The Hardy-Weinberg equilibrium test was done on the control population for both SNPs. To estimate the association between prostate cancer risk and each RNASEL SNP, age-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were determined using logistic regression models. For the purpose of these calculations, study age among controls was the age at last follow-up, whereas age among cases was the age at cancer diagnosis. All analyses were done using SAS statistical software version 9.1 (SAS Institute) and stratified by ethnicity. All statistical tests were two sided and significance was set at $P < 0.05$. Haplotypes and measures of linkage disequilibrium between the two markers were determined using Haploview version 3.2[6] (36) for each race/ethnicity.

Results

Allele frequencies. We determined the allelic frequency for the Arg[462]Gln and Asp[541]Glu SNPs from 1,539 individuals (648 cases and 891 controls) enrolled in the San Antonio Center for Biomarkers of Risk of Prostate Cancer cohort, including 933 non-Hispanic Caucasian men (503 controls and 430 cases), 392 Hispanic Caucasian men (242 controls and 150 cases), and 214 African American men (146 controls and 68 cases; Table 2). Allelic frequencies for the Arg[462]Gln SNP are significantly different among the Hispanic Caucasians and African Americans (P = 0.01 and 0.0005, respectively; Table 2). The G allele was the most common allele found for the Arg[462]Gln SNP across all ethnic/racial groups. Conversely, the G allele of the Asp[541]Glu SNP was more prevalent among the non-Hispanic Caucasian men, whereas the T allele was more common among Hispanic Caucasian men and African American men (Table 2).

[6] http://www.broad.mit.edu/mpg/haploview/

Our control population was, on average, younger than our prostate cancer cases ($P < 0.0001$). Mean age (SD) for the control group was 61.8 (8.9) years, whereas mean age (SD) for our cases was 65.5 (8.3) years (Table 1). Because of this difference across our two groups and the fact that prostate cancer risk increases with age, all the ORs were adjusted for age. The markers were determined to be in Hardy-Weinberg equilibrium in the control population.

Associations of RNASEL 462 and 541 SNPs with prostate cancer risk. Age-adjusted logistic regression analysis stratified by ethnicity showed a statistically significant association between the AA genotype of Arg[462]Gln and prostate cancer risk in Hispanic Caucasian men, with a >4-fold increase in prostate cancer risk (OR, 4.43; 95% CI, 1.68-11.68; P = 0.003) compared with the GG genotype (Table 3). Furthermore, a >10-fold increase in prostate cancer risk was observed for the AA genotype at Arg[462]Gln in the African American samples (OR, 10.41; 95% CI, 2.62-41.40; P = 0.001; Table 3). In the non-Hispanic Caucasian men, however, no significant association for the Arg[462]Gln variant could be found. Assuming a recessive model, age-adjusted ORs for the presence of the AA genotype in the RNASEL 462 SNP, compared with GG and AG genotypes, showed that the observed risk estimate is slightly decreased in both sample groups (OR, 4.03; 95% CI, 1.56-10.42 in Hispanic Caucasian men, P = 0.004; OR, 9.84; 95% CI, 2.51-38.54 in African American men, P = 0.001; Table 3). In the African American men, we also noticed a significant result under the dominant model (AA/AG versus GG genotypes), with a 2-fold increase in risk estimate (OR, 2.07; 95% CI, 1.06-4.05; P = 0.03; Table 3).

Association analysis of the RNASEL 541 SNP with prostate cancer in age-adjusted samples from the three different ethnic groups revealed that under the assumption of a recessive model, Hispanic Caucasian men with a GG genotype showed a slightly higher risk for prostate cancer (OR, 1.91; 95% CI, 1.16-3.14; P = 0.01; Table 4). No significant association was found in the non-Hispanic Caucasian or African American men for this variant.

The effect of the 462 variant on prostate cancer was calculated using the population attributable fraction where population attributable fraction = F (RR - 1) / RR in which F equals the proportion of cases with mutated allele (0.313 for Hispanic Caucasians and 0.246 for African Americans) and RR equals the relative risk (estimated here with the conservative OR of 1.5; ref. 37). This gives a population attributable fraction of 0.10 for Hispanic Caucasians and of 0.08 for African Americans, indicating that the mutated allele of the 462 variant

Table 3. Age-adjusted ORs for RNASEL 462 SNP and prostate cancer risk

	Genotype	Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)	*P*
Non-Hispanic Caucasians		*n* = 430	*n* = 503		
	GG	187 (43.5)	221 (44)	1.0 (Reference)	
	AG	183 (42.5)	225 (45)	0.98 (0.74-1.30)	0.89
	AA	60 (14)	57 (11)	1.30 (0.86-1.98)	0.21
	AA vs AG/GG (Rec A)			1.32 (0.89-1.95)	0.17
	AA/AG vs GG (Dom A)			1.04 (0.80-1.36)	0.75
Hispanic Caucasians		*n* = 150	*n* = 239		
	GG	72 (48)	136 (57)	1.0 (Reference)	
	AG	62 (41)	96 (40)	1.24 (0.79-1.93)	0.35
	AA	16 (11)	7 (3)	**4.43 (1.68-11.68)**	**0.003**
	AA vs AG/GG (Rec A)			**4.03 (1.56-10.42)**	**0.004**
	AA/AG vs GG (Dom A)			1.45 (0.95-2.22)	0.09
African Americans		*n* = 68	*n* = 145		
	GG	45 (66)	111 (77)	1.0 (Reference)	
	AG	13 (19)	31 (21)	1.26 (0.58-2.73)	0.56
	AA	10 (15)	3 (2)	**10.41 (2.62-41.40)**	**0.001**
	AA vs AG/GG (Rec A)			**9.84 (2.51-38.54)**	**0.001**
	AA/AG vs GG (Dom A)			**2.07 (1.06-4.05)**	**0.03**

Abbreviations: Rec, recessive; Dom, dominant.

is implicated in 10% of the Hispanic Caucasian prostate cancer cases and 8% of the African American prostate cancer cases that we studied. The population attributable fraction or effect of the 541 variant on prostate cancer indicates that the mutated allele is implicated in 17% of Hispanic Caucasian prostate cancer cases of our study group.

Haplotype analysis of RNASEL 462 and 541 SNPs with prostate cancer risk. There was high linkage disequilibrium between the two polymorphisms in the three ethnic/racial sample groups with D-prime values >0.90 in both the Hispanic Caucasians and non-Hispanic Caucasians, indicating that both SNPs are in nearly complete linkage disequilibrium in these sample groups. The D-prime value in the African Americans was 0.79. In the non-Hispanic Caucasians, both SNPs are part of a haplotype block as defined by the Haploview program with the option of adopting block definition proposed by Gabriel et al. (38). A common G-T haplotype for the RNASEL 462 and 541 SNP combination was found to occur more frequently in controls compared with cases in African Americans (controls, 0.686; cases, 0.586; $P = 0.04$) but not in non-Hispanic Caucasians (controls, 0.444; cases, 0.448; $P = 0.87$) or in Hispanic Caucasians (control, 0.526; cases, 0.464; $P = 0.08$; Table 5).

Discussion

Linkage analyses of high-risk prostate cancer families provide convincing evidence that the *HPC1* locus is likely to harbor a prostate cancer susceptibility gene (9). *RNASEL* has been proposed as the putative tumor suppressor gene for this region through a positional cloning and candidate gene approach (28). Association analysis of two variants within RNASEL ($Arg^{462}Gln$ and $Asp^{541}Glu$) indicated that the results are controversial, and several of the studies have failed to reveal

Table 4. Age-adjusted ORs for RNASEL 541 SNP and prostate cancer risk

	Genotype	Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)	*P*
Non-Hispanic Caucasians		*n* = 430	*n* = 484		
	TT	100 (23)	91 (19)	1.0 (Reference)	
	GT	190 (44)	254 (52)	0.71 (0.51-1.01)	0.06
	GG	140 (33)	139 (29)	0.95 (0.66-1.38)	0.80
	GG vs GT/TT (Rec G)			1.21 (0.91-1.60)	0.20
	GG/GT vs TT (Dom G)			0.80 (0.58-1.10)	0.17
Hispanic Caucasians		*n* = 150	*n* = 242		
	TT	41 (27)	69 (28)	1.0 (Reference)	
	GT	66 (44)	125 (52)	0.88 (0.53-1.47)	0.63
	GG	43 (29)	48 (20)	1.76 (0.98-3.19)	0.06
	GG vs GT/TT (Rec G)			**1.91 (1.16-3.14)**	**0.01**
	GG/GT vs TT (Dom G)			1.11 (0.69-1.78)	0.67
African Americans		*n* = 68	*n* = 146		
	TT	31 (46)	71 (49)	1.0 (Reference)	
	GT	28 (41)	60 (41)	1.02 (0.54-1.94)	0.94
	GG	9 (13)	15 (10)	1.69 (0.65-4.41)	0.29
	GG vs GT/TT (Rec G)			1.67 (0.67-4.16)	0.27
	GG/GT vs TT (Dom G)			1.14 (0.63-2.07)	0.66

Table 5. Estimated frequencies for common haplotypes

	Non-Hispanic Caucasians			Hispanic Caucasians			African Americans		
	Cases (n = 430)	Controls (n = 503)	P	Cases (n = 150)	Controls (n = 242)	P	Cases (n = 68)	Controls (n = 146)	P
RNASEL 462-541									
G-T	0.448	0.444	0.87	0.464	0.526	0.08	0.586	0.686	**0.04**
A-G	0.344	0.346	0.93	0.284	0.232	0.10	0.168	0.197	0.47
G-G	0.201	0.209	0.69	0.223	0.239	0.60	0.175	0.114	0.08

an association. The $Arg^{462}Gln$ AA genotype has been associated with both increased prostate cancer in U.S. Caucasian sample groups (31, 32) as well as decreased prostate cancer risk in Caucasian and Japanese sample groups (33, 34). These findings were in contrast to other studies concluding that the 462 variant was not associated with prostate cancer disease risk in different sample groups including Caucasians from the United States, Sweden, or Germany and Japanese samples (17, 29, 35, 39). The reported results might be conflicting given potential genetic differences in prostate cancer across ethnic and racial groups (5, 6). Other possible explanations for the observed differences might be the manner in which controls were selected for these studies and/or the lack of power to detect association due to small sample sizes.

Previous studies using the $Asp^{541}Glu$ variant within RNASEL indicated that the GG genotype was associated with an increased risk for prostate cancer in a Japanese study (34). On the other hand, a study in European-American samples resulted in a significant positive association of the TT genotype with prostate cancer (17) and in a significant negative association of the TT genotype with prostate cancer in Swedish Caucasian samples (35). No association for the $Asp^{541}Glu$ variant was found in several other studies (29, 31, 33, 39). Furthermore, no study reported to date has examined/confirmed the role of RNASEL variants in the Hispanic Caucasian or African American population.

To test the hypothesis that RNASEL sequence variants are associated with prostate cancer risk, we did a case-control genotype analysis on two common variants of RNASEL in more than 1,500 men from the South Texas region including 933 non-Hispanic Caucasians, 214 African Americans, and 392 Hispanic Caucasians. We included African Americans and Hispanic Caucasians in the analysis because these ethnic study groups are of particular interest; African Americans have the highest risk and death rate, whereas Hispanics are the fastest growing minority population in the United States. The two RNASEL variants analyzed in this study have not been extensively evaluated in African American populations and have not been studied at all in Hispanic Caucasian populations.

The allelic frequencies for $Arg^{462}Gln$ are significantly different among the Hispanic Caucasians and African Americans. This suggests an ethnic-specific allele distribution and is a likely explanation why substantial differences in the incidence of prostate cancer are observed among populations.

The most significant finding was the association of the $Arg^{462}Gln$ genotype with increased prostate cancer risk in both the Hispanic Caucasian and African American samples. Age-adjusted ORs for Arg/Gln (AG) and Gln/Gln (GG) genotypes, compared with Arg/Arg (AA), showed that the Arg/Arg (AA) genotype increases prostate cancer risk over 4-fold in Hispanic Caucasians and over 10-fold in African Americans, which suggests a recessive model for the RNASEL 462 AA genotype. This is to our knowledge the first report on the significant association of $Arg^{462}Gln$ genotypes with increased prostate cancer risk in Hispanic Caucasian or African American men. Our results support the findings of Casey et al. (31) and Xiang et al. (32) showing that the AA genotype of the Gln462 variant is significantly associated with prostate cancer, although they differ from the findings of Casey et al. (31) in that we found the association in Hispanic Caucasians and African Americans but not in non-Hispanic Caucasians. Our results suggest that the role of the $Arg^{462}Gln$ variant in the development of prostate cancer is different across populations. From our sample group, we conclude that the genetic influence of the $Arg^{462}Gln$ variant within RNASEL on prostate cancer in the non-Hispanic Caucasian samples is relatively small, if there is any effect at all. Because it has been shown that the Gln462 AA genotype has three times less enzymatic activity than the wild-type protein (31), our data support the hypothesis that the less active RNASEL protein could leave viral infections intact, leading to inflammation, which eventually could lead to prostate cancer. Additional functional evidence for this variant's role in prostate cancer development comes from the observation that the $Arg^{462}Gln$ variant reduced the ability of RNASEL to cause apoptosis in response to activation by 2-5A (32) and suppresses antiviral effects of IFN (25–27). Furthermore, a strong association between infection with the xenotropic MuLV-related (XMRV) virus and homozygous mutant (Gln462 AA genotype) cases has been reported by Urisman et al. (40), which implicates that defects in RNASEL activity may lead to persistent viral infection *in vivo*.

Analysis of the RNASEL $Asp^{541}Glu$ variant in the three racial/ethnic groups revealed a statistically significant increase in the risk for developing prostate cancer for the RNASEL 541 Glu/Glu (GG) genotype versus the combined Asp/Asp and Asp/Glu genotypes in the Hispanic Caucasian samples. An association of the GG genotype at RNASEL 541 with a slightly increased prostate cancer risk was also reported by Noonan-Wheeler et al. (17) among Caucasian individuals. However, we observed the finding in the Hispanic Caucasian group, whereas non-Hispanic Caucasians did not show a significant positive association for the GG genotype. Our data suggest that susceptibility to develop prostate cancer at this variant is likely ethnic specific and that the RNASEL $Asp^{541}Glu$ variant does not seem to have a major effect on the development of prostate cancer in our non-Hispanic Caucasian or African-American population, whereas it seems to play a role in the Hispanic Caucasian cancer cases. Alternatively, because the $Asp^{541}Glu$ variant had similar enzymatic activity as wild-type RNASEL (32), the substitution of the amino acid Glu by Asp might not

be of any functional significance and it is therefore possible that the RNASEL 541 variant may be in linkage disequilibrium with a nearby functional polymorphism(s) within the *RNASEL* gene or within another gene nearby such that the actual causal variant(s) resides on diverse haplotypes in different study populations. Therefore, additional studies are needed to confirm and clarify the functional significance of these findings in the vulnerability/etiology of prostate cancer.

A common G-T haplotype for the combination of the RNASEL 462 and 541 variants was found to occur more frequently in controls compared with cases in African Americans but not in non-Hispanic Caucasians or in Hispanic Caucasians. These findings are consistent with the observation of Wiklund et al. (35) who found that in sporadic cancer cases, the frequency of the haplotype significantly associated with prostate cancer risk (containing the G-T alleles for RNASEL 462 and 541, respectively) also occurred at higher frequencies among controls compared with sporadic prostate cancer cases.

In conclusion, we confirm the likely involvement of RNASEL in the etiology of prostate cancer and we further provide the first evidence for an association of the *RNASEL* gene with prostate cancer in Hispanic Caucasian and African American men. The prostate cancer risk differs widely between racial/ethnic groups, indicating that race/ethnicity plays a role in the development of prostate cancer. This is likely because each individual brings with them genetic material that sets each race and ethnicity apart. Furthermore, there may be different exposures to environmental factors between the populations. Involvement of environmental factors combined with genetic background may result in the differences in incidence of prostate cancer observed in these populations.

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