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ORIGINAL ARTICLE

Predictive value in the analysis of RNASEL genotypes in relation to prostate cancer

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BACKGROUND: We would like to compare the different RNASEL genotypes with the stage of the cancer using parameters such as PSA levels, Gleason score and T-stage, and to develop a clinical protocol for the monitoring of the disease for trying a better evolution of the patient.

METHODS: A total of 231 patients with sporadic prostate cancer and 100 of controls were genotyped in RNASEL gene by sequencing the exons 1 and 3. A survey of clinical information was collected by a specialist following the Helsinki protocol. All patients and controls were interviewed by a researcher and signed their informed consent to participation in the study, which was approved by Ethics Committee of the hospital. The genetic information was processed and collected with an ABI PRISM Genetic Analyser 3130 using SeqScape software v.2.6. All the patients were analysed by comparing the genetic and clinical data. χ^2-tests, Monte Carlo, Fisher tests and contigency tables were performed using SPSS v.15.0 and ARLEQUIN v.3.5 software on patient population.

RESULTS: Significant differences were found only between patients and controls in D541E, R461Q and I97L genotypes, the remainder of the variants did not seem relevant to our population in contrast to other populations, such as north-Caucasians, Afro Americans and Ashkenazi Jews. The genotypes associated with the worst prognoses are G/G in D541E, A/A in R462Q and A/G in I97L. The controls were included in our study to determine an approximation of the genotype in our population compared with the patients, but they did not account for the statistical process.

CONCLUSIONS: The genetic profile of patients with this cancer combined with other parameters could be used as a prognosis factor in deciding to give more radical and frequent treatments, depending on personal genotype.

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Keywords: genetic profile; RNASEL; South European population

Introduction

An autosomal dominant cancer syndrome has been discovered that is associated with the development of renal carcinoma in patients with familial von Hippel-Lindau (VHL) disease. VHL has also been shown to be important in sporadic conventional renal cell carcinomas, with a large number of studies reporting potential loss of VHL function as a result of allele loss, mutation, and promoter methylation.[1,2] It has been determined that the presence of VHL gene mutations in tumour tissue from patients with sporadic renal cell carcinoma, could act as a prognostic factor.[3] Similar to renal carcinoma, genes in prostate cancer that are relevant in familial disease are also important in sporadic disease.[4,5] A study in African Americans and Hispanic Caucasians has concluded that RNASEL genetic variants have a role in prostate cancer risk.[6] The main genetic variants described are missense mutations (R462Q and D541E), the stop mutation (E265X)[7] and other variants such as 471delAAAG,[8] G265X, M1I[9] and I97L.[10] These studies describe results in Caucasian (from northern Europe), Jewish, African and American populations. However, information about population of southern Europe is lacking. A difficulty associated with prostate cancer is the existence of different promoting factors, including genetic, epigenetic and environmental influences, which may be responsible for ethnic variations in the post-induction progression of the disease.[11]

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Some patients with levels of PSA not typically predictive of poor prognosis, after treatment, experience progression of the disease.[12] The main purpose of this article is to provide genetic information to serve as a tool, allowing the urologist to monitor each patient individually, depending on his genetic classification regarding the RNASEL gene, to manage a specific population of southern Europe.

Materials and methods

Study population and sample analysis

This study was supported by the Urology Department of the University Hospital Virgen de las Nieves, Granada, Spain. Men enrolled in this study were analysed by a urologist, who also made notations about important parameters for prostate cancer, such as PSA, T-score, Gleason score, and information such as age and place of birth. This project included unrelated adult Caucasian males with recent diagnoses of prostate cancer, and clinical diagnosis of primary adenocarcinoma of the prostate was histopathologically confirmed after abnormal serum PSA findings and lower urinary tract symptoms ($n = 231$). Healthy, unrelated Caucasian men ($n = 100$) from the same geographic area with no history of prostate cancer were enrolled as controls (no PSA levels were detected and clinical evolution over some years was followed to avoid including affected men with prostate cancer as controls). Controls belonged to the same age group as patients; they all were men with health problems like renal lithiasis or andrological problems, so PSA analysis was performed to dismiss a possible prostate cancer. They all have normal PSA values with blood levels below 4 mg ml^{-1}, as well as a normal rectal touch. All these analysis confirmed that selected controls had no prostate cancer. Furthermore, men with family history of prostate cancer were dismissed.

In this study, controls were used in the first stage of a two-phase design (case–control study) to determine which of the seven variants in RNASEL gene (M1I, G59F, I97L, S113S, 471delAAAG, I220V, E262X, E265X, S406F, R462Q, Y530C and D541E) were associated with prostate cancer risk, and having genotype differences between patients and controls. (Further details are included in Table 2.) We have only selected the three variants (D541E, R462Q and I97L), where genetic differences between controls and patients were found. At this point, we conducted a case–case analysis to determine which of the variants associated with prostate cancer risk are also associated with a specific phenotype. This study was conducted from 2007 till the beginning of 2011, and informed consent was obtained from all the patients and controls. Peripheral blood samples were drawn from all participants into tubes containing K3-EDTA. All, patients and controls, were interviewed by a researcher and signed their informed consent to participation in the study, which was approved by Ethics Committee of the hospital. Patient characteristics are summarised in Table 1.

The analyses were performed by LORGEN.GP and the Laboratory of Genetic Identification of Granada. DNA from the samples was extracted from peripheral blood using an organic extraction procedure by phenol/chloroform/isoamyl alcohol and proteinase K. It was purified using Microcon100 (Millipore, Billerica, MA, USA). Quantification of extracted DNA was performed by 0.8% agarose gel. To cover all variations in the RNASEL gene (R462Q, D541E, E265X, 471delAAAG, G265X, M1I and I97L), amplification of exons 1 and 3 was carried out with specific primers designed for these regions (Table 1). The amplification was performed using the AmpliTaq GoldPCR Master Mix (Applied Biosystems, Foster City, CA, USA), which includes all the chemical components, except the primers and template, necessary for PCR, using a GeneAmp System2400 thermal cycler. Sequencing reactions were made only in the samples in which an amplification band was observed in a 2% agarose gel. Sequencing was generated using ABI PRISMBigDye Terminator v.3.1 Cycle Sequencing Ready Reaction Kits (Foster City, CA, USA). The amplicons were analysed using the ABI PRISM 3130 (Applied Biosystems) automated DNA sequencer. Each template was sequenced in both directions. The results of the analysis were edited using the ABI PRISM SeqScape v.2.6 software (Applied Biosystems).

Table 1 Clinical characteristics of patients ($n = 231$)

Variables	*Patients* (n = *231*)	*%*
Age at study		
<69	171	74.03
70–79	49	21.21
>80	11	4.76
T stage		
1	25	8.5
2	92	37.8
3	88	37.5
4	26	16.2
N stage		
N0	187	63.2
N1	44	36.8
M stage		
M0	170	76.3
M1	61	23.7
Gleason score		
2–6	107	46.2
7–8	98	45
9–10	26	8.8
PSA levels, ng ml^{-1}		
<10	49	23.3
10–19.99	51	23
>20	110	46.5
>100	21	7

The range of age at study is clustered in three groups whereas later in the statistical analyses it is done in four ranges ($\leqslant$55, 56–60, 61–65, >65) to have a deeper analyses of the population.

Statistical analysis

For each single nucleotide, R462Q, D541E and I97L, allele frequencies were compared with the χ^2-test using the software package SPSS v.15.0 (Chicago, IL, USA). The Hardy–Weinberg equilibrium test and an analysis of the linkage of the loci of the RNASEL gene were performed with ARLEQUIN v.3.5 software[13] (Bern, Switzerland).

Table 2 Studied mutations in locus HPC1 (1q24-q25) of the RNASEL gene

EXON1-R1 (1–377) *F: TGGTAGCAGGTGGCATTTAC* *R: AAGCCATAAAAATCACACTCA*	*EXON1-R2 (449–848)* *F: AATGTGAATTTGAGGCGAAAG* *R: AGTTCAACAGCAAGCAGC*		*EXON1-R3 (1070–1459)* *F: ATACCGCCCTATGATTGGCA* *R: GCAGATCCTGGTGGGTGTATC*		*EXON 3* *(1567–1772)* *F: CTTCCCTCCCTAACAAGCCT* *R: GCACCACCTTACCCTTCC*	
M1I (3 G>A)	100% Patients G/G	471 delAAAG	100% Patients delAAAG	S406F (1217C>T)	100% Patients C/C	Y530C (A>G)	100% Patients A/A
	100% Controls G/G		100% Controls delAAAG		100% Controls C/C		100% Controls A/A
G59F (175 G>A)	100% Patients G/G	I220V (661 A>G)	100% Patients A/A	R462Q (1384 G>A)	15.62% Patients A/A	D541E (1623 T>G)	32.91% Patients G/G
					50.63% Patients G/A		52.32% Patients T/G
					33.75% Patients G/G		14.77% Patients T/T
	100% Controls G/G		100% Controls A/A		16.67% Controls A/A		36.11% Controls G/G
					56.94% Controls G/A		47.22% Controls T/G
					26.39% Controls G/G		16.67% Controls T/T
I97L (289 A>G)	0.85% Patients A/G	E262X (784 G>T)	100% Patients G/G				
	1.27% Patients A/C						
	96.17% Patients A/A						
	100% Controls A/A		100% Controls G/G				
S113S (339 T>C)	100% Patients T/T	E265X (793 G>T)	100% Patients G/G				
	100% Controls T/T		100% Controls G/G				

Comparisons between each locus and clinical informations such as PSA, age, stage and Gleason score were obtained with contingency tables using the χ^2-test, Monte Carlo and Fisher exact test. In order to gain deeper analyses of the population, age was clustered into four ranges ($\leqslant$55, 56–60, 61–65, $>$65) for statistical analysis, however, some tables within this paper have a cluster of age into three groups for easier interpretation.

Analysis of variance was also performed with the data. All the data were represented using bar charts and other plots generated by SPSS v.15.0.

Results

In the genetic analysis of all regions of the RNASEL gene performed in this study, genetic differences were not found between controls and patients in some mutations (100% of patients and controls have the same genotype), such as in variants M1I, G59F, S113S, 471delAAAG, I220V, E262X, S406F and Y530C, whereas significant differences were obtained in I97L, R462Q and D541E. Therefore, statistical analyses were reduced to the above three mutations.

There are some parameters for which *P*-value covers the rate $\leqslant$0.05, which means the cut-point below where results would be considered statistically significant. These results imply that a significant association exists among variables such as D541E with the stage of the cancer (*P*-value $<$0.0001), PSA (*P*-value = 0. 021) and Gleason score (*P*-value = 0.008); R462Q with age (*P*-value = 0. 047), stage (*P*-value $<$0.0001), Gleason score (*P*-value = 0.001) and PSA (*P*-value = 0. 015); and I97L with PSA (*P*-value = 0.002).

Further details for each single mutation and all the parameters analysed are represented in bar charts generated by SPSS v.15.0. (Figures 1 and 2).

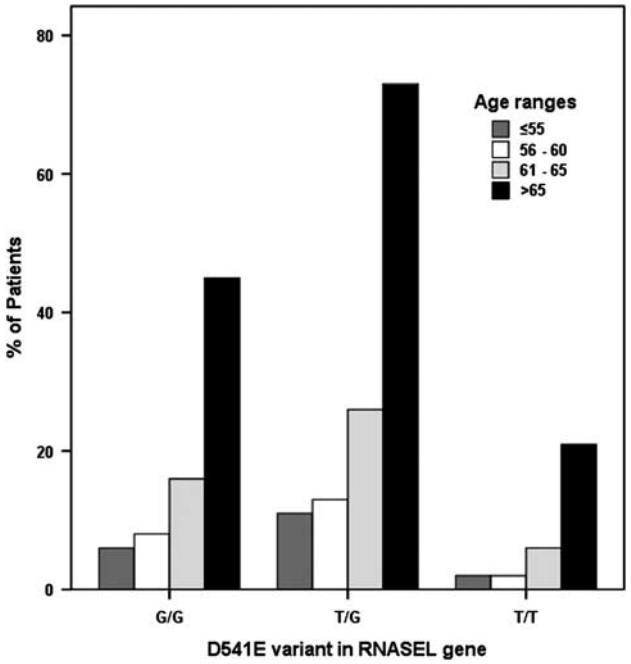

Figure 1 Bar chart representation of D541E variants. Representation of groups according to age generated by SPSS V.15.0.

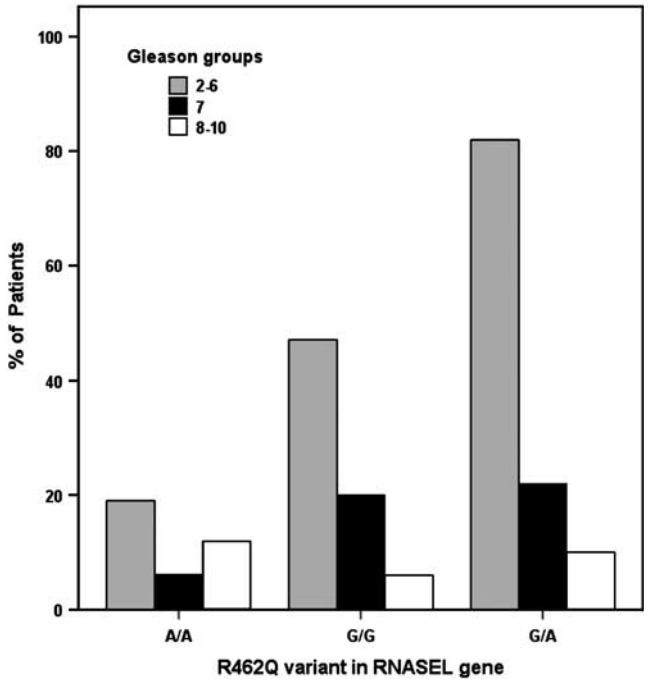

Figure 2 Bar chart representation of R462Q variants. Representation of the variants in R462Q according to the Gleason score.

As can be seen in Figure 1, although D541E and age are not statistically significant (P-value = 0.986), the variant T/G has a higher representation in patients >65 years old (59.3%), whereas T/T has the lowest proportion in this age range. In all, 21% of the patients were in the age range 70–79, in contrast to the control population, which had 12% in this age range. Analysis of the other clinical parameters indicates that T/T has better clinical parameters, such as the absence of individuals in stage 4, statistically significant with a P-value of <0.0001 and no presence of Gleason score in the range of 8–10, statistically significant with a P-value of 0.008 as well as no measurements in the highest ranges of PSA (>1000 ng ml^{-1}), P-value = 0.021. In contrast, the variant G/G has the worst clinical prognosis. This variant includes the highest proportions of stages 3 and 4 (35.1% and 20.3%, respectively contrasting with a proportion of 16.4% and 7.4% in T/G; 9.7% and 0% in T/T variant in stages 3 and 4, respectively), as well as the highest prevalence of Gleason scores 7 and 8–10 (23 and 21.6% contrasting with proportions below 20% in the rest of the variants). Similar results are found in PSA levels, which reach the highest values in this variant, that is, >20 and >1000 ng ml^{-1} with a proportion of 23.3 and 8.7%, in contrast to proportions below 15 and 3% in the other variants. Figure 1 shows that the lowest values of age occur in the variant G/G; thus, the cancer will have an earlier appearance and a worse prognosis in this case. To confirm the results, an analysis of variance was performed in age P-value: 0.898, stage of the cancer (P-value <0.0001), Gleason score (P-value = 0.012) and PSA (P-value <0.0001). As can be seen, similar results were obtained.

In R462Q, the means of lowest age as well as the worst values of the clinical data analysed are located in A/A variant. For example, with regard to cancer stage, higher values for stages 3 and 4 occurred with this variant (around 80% of patients with A/A), and stages 1 and 2 were nearly non-existent (around 20% of patients with A/A). However, stage 2 was highly prevalent with the G/A variant (73%) and this genotype had a higher proportion in patients >65 years old (58%) and in those between 61–65 years-old (25%). Nevertheless, 88% of controls are in the age range of <69 years old and 12% in the range between 70–79 years old.

On analysing the groups of Gleason scores, the A/A variant had the highest proportion of Gleason scores in the range of 8–10 and the lowest proportion of 2–6. However, there were also Gleason scores of 7 and 8–10 with the G/A and G/G variants. According to PSA levels, the A/A variant also had the highest proportion of PSA levels in the range of >20 ng ml^{-1} and >1000 ng ml^{-1} (32.4% and 14.7% in contrast to 13% and 2.8%; 15.9% and 1.4% in variant G/A and in variant G/G, respectively).

In I97L, most variants were A/A; however, some patients had A/G and A/C variants. The A/G variant was initially related to worse clinical values, such as a Gleason score of 7, although there were no statistically significant differences (P-value = 0.064), and PSA levels were between 10.1–20 ng ml^{-1}.

However, we would like to note that although PSA values >50 ng ml^{-1} are predictive of metastatic disease, we have also added values above this range because we have found them in our patient population.

Other statistic analysis such as the Hardy–Weinberg equilibrium test and an analysis of the linkage of the loci in the RNASEL gene were performed using ARLEQUIN v.3.5 software.[13] All of the variants are in Hardy–Weinberg equilibrium, but we would also like to remark that although the genotype distributions are in Hardy–Weinberg equilibrium, they also have slight linkage, which is normal for all the variants located in the same gene. The three variants were evaluated for linkage-disequilibrium (an example, r^2 in the D541E variant is 0.3667). However, every single variant is located in the same gene (RNASEL), so there is linkage heredity.

After analysing all the samples by the χ^2-test, and confirming the data by the analysis of variance test, we have performed multiple comparisons with contingency tables and the adjustment was made by Fisher exact test.

Discussion

Substantial evidence indicates that the aetiology of prostate cancer involves an interaction among genetic, environmental and dietary factors. However, having a positive family history is the strongest epidemiological risk factor for prostate cancer.[5] Among all the genes described as relevant in the developing of prostate cancer, the RNASEL gene has been highlighted as having the greatest effect.[9,14,15] Many variants [15] described in this gene, such as Arg462Gln, have been found to be associated with sporadic prostate cancer risk among Caucasians and African Americans.[16] However, the same variant (R462Q or Arg462Gln) has been found with decreased familial prostate cancer risk in a Japanese population with the Gln/Gln genotype.[17] Similarly,

inconclusive results have been obtained with the other variants, such as a study in a D541E in a northern Indian population that found no association between this variant and the risk of prostate cancer.[18] However, other studies show an association between D541E and prostate cancer risk. A study of a Japanese population[17] and studies of a European–American Caucasian sample[6,19] found a strong positive association with prostate cancer and D541E. The results are diverse and vary among populations and ethnic groups in relation to RNASEL variants and others related to prostate cancer risk as well as in the specific genotypes that confer susceptibility.[20]

In our population of south Spain (European Caucasians), the most relevant variants in the RNASEL gene were D541E, R462Q and I97L. However, other variants, such as E265X, M1I, 471delAAAG, G59F, S113S, I220V, S406F and Y530C have representative roles in the development of prostate cancer in some populations, such as Ashkenazi Jews,[21] Finns[6,22] and African Americans,[10] but there were no differences in our population between patients and controls. For the variants (D541E, R462Q and I97L), which have statistically significant values, the genotypes that had the worst prognoses were G/G in D541E, A/A in R462Q and A/G in I97L, whereas the ones that represented better clinical characteristics were T/T in D541E, G/G in R462Q and A/C in I97L. A similar study in R462Q has been carried out in other populations, such as in Cleveland, Ohio and Detroit, Michigan, where men who are heterozygous with respect to the mutated allele were found to have a 50% greater risk of prostate cancer than non-carriers, and homozygotes had more than double the risk.[16] Our study in R462Q indicated that homozygotes with the A/A genotype had worse clinical characteristics in prostate cancer than individuals with the G/G genotype or with the G/A genotype in the middle. A study of a Finnish population found that variants R462Q and D541E had an important role in prostate cancer.[22] However, concerning in D541E in the Finnish population, the variant that showed a higher correlation with prostate cancer was G/T, whereas in our population it was G/G.

Both genetic and clinical data could confer relevant information about the control of prostate cancer. This work indicates that in each single population genetic data for RNASEL gene have different prognosis values. Meanwhile, different variants of the same region analysed in the RNASEL gene have the same pathological evolution for prostate cancer, depending on the population in which it is analysed. With all this data, we may find genetic differences depending on the population analysed. Moreover, these genetic data could be an important tool in improving the clinical evolution of patients affected by prostate cancer, but knowing that prostate cancer is a polygenic cancer and further studies in other genes will confer accurate information.

Knowing that patients with a specific genotype will develop worse characteristic of this cancer than other patients, will help us to focus on different clinical treatments and attempt to avoid rapid progression of the cancer and a decreased quality of life. As it can be infered by the clinical data, the genetic profile in patients with this cancer could be used as a prognostic factor for decision making regarding more radical and frequent treatment, depending on personal genotype.

Conflict of interest

The authors declare no conflict of interest.

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