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ORIGINAL ARTICLE

Association Between the Interleukin-17 Gene Polymorphism -197G>A and the Risk of Prostate Cancer in a Galician Population

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Abstract

A case-control study was carried out in which the role of the Single Nucleotide Polymorphism rs2275913 in the pathogenesis of prostate cancer was analysed for the first time. This polymorphism is located in −197 position of *IL-17A* gene and implies a A>G change. The sample consists of 433 Galician men, 241 of whom are prostate cancer patients and 192 are healthy men with no tumours. Besides the influence of this marker, directly involved in the inflammatory process, other variables that were described as prostate cancer risk factors were also studied: age, smoking and Body Mass Index (BMI). By the analysis of Odds Ratio (OR) (CI 95%) a protective effect of heterozygous genotype AG was observed in comparison with homozygous genotypes AA and GG. As regards other risk factors, a significant increased risk was observed in smokers homozygous between 10 and 32 pack-years ($p = 0.032$). Age and BMI show interesting patterns, but not significant ones. This study shows a possible link between the rs2275913 and the onset of PCa which could be influenced by age, BMI and above all, smoking.

Keywords Interleukin-17A (IL-17A) · SNP · Prostate cancer (PCa) · Inflammation

Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed in the world, reaching first position among men in Europe and Spain [1]. Its incidence has increased considerably in recent years and it is predicted that it will continue rising in the near future. In Spain 32,641 new cases were diagnosed in 2014 [2]. The mortality rate for PCa in men varies depending on the human population group. In the totality of European countries, a contrast can be observed between Mediterranean regions, which have below average mortality rates, and the rest of the European countries [3]. The mortality rate for PCa in Spain is usually similar to that of other industrialised countries, although the Autonomous Community of Galicia has a higher rate (23 per 100,000 inhabitants) [4, 5].

Inflammation is a coordinated combination of chemical signs and cellular processes designed to repair tissue damage [6]. Different epidemiological studies have shown the existence of a relation between inflammation and the development and progression of PCa [7, 8]. Cytokines are important inflammation mediators, which behave directly or indirectly to regulate inflammatory pathways. They act on target cells by joining to specific receptors, starting a transduction signal and paths for secondary messengers within target cells [9].

Il-17 or IL-17A belongs to a homonymous pro-inflammatory cytokine family which includes six members (IL-17A - F) and five receptors (IL-17RA – RE) [10]. This interleukin is secreted mainly by a specific type of collaborated T cells called Th17, but it can also be produced by other types of T cells such as NKT cells, T CD8+ and T-γζ [11]. Many of the effects regulated by Th17 cells are attributed to this cytokine. However, there are numerous factors which intervene in its induction, stabilisation and activation, as well factors which act on IL-17A (ROR-γt, ROR-α, RUNX1, Foxp3, BATF, SMAD, etc) [11–13]. IL-17A shows synergy when it joins with TNF-α, LT-α and IL-1β. It is an early initiation factor of the inflammation response and plays an equally important role in both adaptive and innate immunity [14]. It starts the migration of endothelial cells and induces the

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fibroblasts to regulate positively pro-angiogenic factors such as VEGF, MIP, prostaglandin and nitric oxide. The genes stimulated by IL-17A codify antimicrobial proteins, activation of neutrophil factors and inductors of acute phase response. It behaves principally on epithelial, endothelial and stromal cells [12].

Inflammation is a natural process and in principle beneficial for the individual, nevertheless, its persistence can stimulate tumour development [13]. In this way, an excess of IL-17A production is associated with abnormal inflammation which can be implicated in pathologies like tumour growth. IL-17A is also related to the tumour process by chronic and acute inflammation [11, 15, 16].

The gene *IL-17A* is located in the promote region of chromosome 6p12 and it is made up of 3 exons and 2 introns [8, 13]. Multiple studies have found that elevated expression of *IL-17A* could be associated with several tumour tissues, including gastric, breast, bladder, colorectal and cervical cancer among others [13, 17–20].

Several polymorphisms have been described in the *IL-17A* gene which could affect its expression and, therefore, its function [13, 21]. Among these polymorphisms, SNP rs2275913 has been studied relative to the development of different types of cancer [22, 23]. The current study aims to investigate, for the first time, the possible link between SNP rs2275913 (−197G>A) and the risk of developing PCa, also taking into account the influence of other variables like age (one of the main risk factors of PCa), BMI or smoking.

Materials and Methods

Study Population and Genotyping

The sample consists of 241 cases, native males from Galicia (Spain) with diagnosed prostate cancer (PCa) and 192 controls, native Galician males without any type of neoplasia. The data of each individual, both case and controls, were obtained through personal interviews which include age, date of diagnosis, PSA, BMI, smoking, family history of prostate cancer, etc. The subjects participating in the study provided a sample of total venous blood, from which the extraction of DNA was performed by the phenol-chloroform-isoamyl method.

Next, we proceeded to genotyping all individuals using Mass Array from Sequenom, by means of the MALDI-TOF (Matrix Assisted Laser Desorption/Ionisation-Time Of Flight) technique, which allows the joint analysis of several dozen polymorphisms. It consists of an amplification process, purification and allelic discrimination by mini-sequencing using the Iplex Gold technique. Then the products are read using a mass spectrophotometer MA4. All of this genotyping process was carried out at the National Genotyping Center (Centro Nacional de Genotipado, CeGen) following the protocol published by Oeth et al. [24].

Statistical Analysis

As a first approximation to the sample genotypic distribution, we checked whether the controls were in Hardy-Weinberg equilibrium for the marker studied, by means of the $\chi 2$ test. The test statistic t_s described by Sokal & Rohlf was calculated [25], with which the differences between the allelic frequencies of cases and controls were evaluated. A logistic regression was used to calculate the risk associated with the genotypes by calculating Odds Ratio (OR) with 95% confidence intervals (CI). Interactions between genes and environment and their effects on the risk of prostate cancer were evaluated through a stratified analysis using age, BMI and smoking (pack-years, PY) as variables. These analyses were made using SPSS (Statistical Package for Social Science, Windows, v.20, SPSS Inc.) and SNPstats [26].

Results

Genotype frequency distributions and allelic frequencies of the Galician population sample, which was analysed for IL-17A rs2275913, are presented in Table 1. These frequencies are similar to those observed in other European populations (f(A) ≈ 0.35–0.49) [27]. Genotype frequency distribution of controls is in agreement with that expected under the Hardy-

Table 1 Genotype and allelic sample distribution

Genotypes	Cases (%)	Controls (%)	Alleles	Cases Freq. ± σ	Controls Freq. ± σ
GG	108 (44.81)	81 (42.19)	G	0.674 ± 0.021	0.669 ± 0.024
AA	24 (9.96)	16 (8.33)	A	0.326 ± 0.021	0.331 ± 0.024
GA	109 (45.23)	95 (49.48)			
HWE. $\chi 2$ (p)					2.657 (0.103)
t_s (p)			0.156 (0.876)		
Het. I. ± sd				0.439 ± 0.025	0.443 ± 0.025

Freq. Allelic frequencies, *HWE.* Hardy-Weinberg equilibrium, *Het. I.* Heterozygosity index, σ standard deviation

Weinberg equilibrium and the t_s ($t_s = 0.156$; $p = 0.451$) does not detect significant differences between cases and controls allelic frequencies.

Association analyses, which were carried out by calculating OR in all of the studied individuals, are shown in Table 2. It was observed that being a carrier of the AG genotype has a protective effect against the risk of developing PCa regarding either homozygote (Table 2), although no statistically significant association was observed in either calculated OR. The overdominant genetic model ($p = 0.379$) provided the most relevant data of this analysis.

Genetic variation impact of rs2275913 on the PCa risk becomes more evident when stratification analyses are addressed (Table 3).

With regard to age, Table 3 shows risk values calculated by applying the overdominant genetic model, paying attention to the risk effect of homozygotes versus the heterozygote (AA+GGvsAG). Among the data obtained, a point of special impact stands out starting at 75 years, in which an OR of 5.77 ($p = 0.079$) is obtained. This result is confirmed by the codominant model with OR equally higher from 75 years ($OR_{AAvsAG} = 5$, $p = 0.190$; $OR_{GGvsAG} = 6$, $p = 0.077$). In addition, significant results with this model were obtained in the range between 65 and 67 years, with OR = 3.17 ($p = 0.045$) for GGvsAG comparation.

Table 4 shows the results of an analysis in which the risk associated to the set of individuals with homozygous genotype, both AA and GG, is compared by age group, taking the younger age group (< 65 years) as the reference. The results obtained for the older age stratum (≥70 years) are statistically significant with an OR of 4.57 (95% CI 1.79–11.69; $p =$ 0,001). The same analysis based on age was carried out with heterozygous genotype individuals, again obtaining a statistically significant result for the older group (≥70 years): OR 2.91 (95% CI 1.17–7.20; $p =$ 0,019).

Table 2 Odds Ratio genetic models

Genetic model	OR (95% CI)	χ2	*p*
Dominant			
GGvsAA+AG	1.11 (0.759–1.632)	0.299	0.584
Recessive			
GG + AGvsAA	0.82 (0.423–1.595)	0.337	0.562
Allelic			
GvsA	1.02 (0.769–1.361)	0.024	0.876
Overdominant			
GG + AAvsAG	1.19 (0.811–1.735)	0.775	0.379
Codominant			
GGvsAA	0.89 (0.443–1.783)	0.110	0.740
GGvsAG	1.16 (0.780–1.731)	0.546	0.460
AAsAG	1.31 (0.656–2.606)	0.582	0.446

OR Odds Ratio; *CI 95%* 95% confidence interval

Table 3 Stratification by age, smoking and BMI

Variables	Cases	Controls	OR (95% CI)*	χ2	*p*
Age (years)					
< 65	106	61	1.30 (0.686–2.448)	0.644	0.422
≥ 65 - <75	121	87	1.31 (0.755–2.284)	0.933	0.334
≥ 75	11	41	5.77 (0.799–41.662)	3.078	0.079
Smoking (pack-years)					
Non-smokers	70	57	1.42 (0.695–2.897)	0.932	0.334
Smokers	165	130	1.10 (0.696–1.748)	0.174	0.676
< 10	28	32	1.48 (0.531–4.141)	0.577	0.448
10–32	62	24	**2.95 (1.088–7.994)**	4.571	**0.032**
> 32	75	74	0.67 (0.349–1.273)	1.519	0.218
BMI					
< 28	107	55	0.56 (0.290–1.091)	2.918	0.088
≥ 28	116	83	1.62 (0.918–2.856)	2.784	0.095

Significant results are bolded ($p < 0.05$)

*OR for the overdominant genetic model GG + AAvsAG

In relation to stratification by BMI, we observed a connection between the genetic variability of *IL-17A* and the risk of developing PCa for values of BMI above 33, with results near to the threshold according to the overdominant model (OR = 3.54, $p =$ 0.055) (Fig. 1). The codominant model corroborates the outcome obtained in analysis with the overdominant model with $OR_{AAvsAG} = 5$ ($p = 0.159$) and $OR_{GGvsAG} = 3.50$ ($p = 0.091$).

Finally, when we did a global analysis using the overdominant model, the group of smokers does not show a relation between the risk of developing PCa and the genotype (OR = 1.10, $p = 0.676$), the same as for non-smokers. However, when we carried out an isolated analysis of individuals with an intermediate-high tobacco intake (10–32 PY), a significant OR was obtained ($OR_{AA + GGvsAG}$ 2.95, $p = 0.032$). Codominant model is consistent with this result, with $OR_{AAvsAG} = 1.82$ ($p = 0.410$) and $OR_{GGvsAG} = 3.79$ ($p = 0.025$).

Discussion

This case-control study investigated the possible relationship between the polymorphism rs2275913 and risk of developing PCa. The data appear to suggest that the heterozygous genotype (AG) gives a certain amount of protection ($OR_{AA + GGvsAG} = 1.19$; $p = 0.379$).

The influence of the genetic variability of *IL-17A* is not reflected in younger ages. It is from the older ages that connection is visible and the effect of age is greater in homozygous individuals. This PCa risk factor for homozygous men over 70 years of age is 457% greater than for individuals under 60. In the same way, for those with heterozygous genotype, being more than 70 implies an increased risk of 291% as compared to those under 60. On the other hand, one can observe a clear

Table 4 Analysis of age within SNP rs2275913

Genotype	Age (years)	Cases	Controls	OR (95% CI)	χ^2 (p)
GG + AA	< 60	24	7	1.00 (ref)	–
	60–69.9	67	36	1.84 (0.72–4.69)	1.67 (0.196)
	≥70	39	52	**4.57 (1.79–11.69)**	**11.06 (0.001)**
AG	< 60	21	10	1.00 (ref)	–
	60–69.9	61	48	1.65 (0.71–3.84)	1.38 (0.240)
	≥70	26	36	**2.91 (1.17–7.20)**	**5.51 (0.019)**

Test for interaction in the trend $p = 0.67$

Significant results are bolded ($p < 0.05$)

increase in the protective effect of the heterozygote against the homozygotes in higher age groups (≥75, OR = 5.77; $p = 0.079$). All of these results, therefore, illustrate that the AG genotype has a protective character in comparison with homozygotes AA and GG, which function as risk genotypes, above all as age increases. In other words, the simultaneous presence of both alleles in the heterozygous genotype produces a protective effect, while the presence of a single allele has a risk effect. There are different cellular factors which could explain this relationship. Cellular ageing is a factor associated with carcinogenesis and age [28]. It could be due to a reduced capacity of DNA repair and the accumulation of genetic damage. The inflammation account on its own is associated with the integrity and functionality of DNA [29] in such a way that the effectiveness of the interleukin is directly involved in the inflammation process, although it is not expressed in younger ages, but rather in a moment in the life of the cells in which a great amount of damage has accumulated due to the advanced age and the reduction in homeostasis.

Values obtained in the BMI analysis point to a protective function of the heterozygous AG genotype in individuals with overweight and obesity, if it is compared with homozygotes AA and GG, especially starting at values over 33 BMI (OR = 3.54; $p = 0.055$) (Fig. 1). The increase of adipose tissue is a risk factor for multiple pathologies, and is, for example, one of the main risk factors for cardiovascular diseases, type II diabetes, etc. [30]. Obesity is associated with chronic inflammation, the increase of inflammatory cytokines production and it influences immunity cells which are added to the production of mediator inflammatory cells [31]. Assuming that both homozygotes of *IL-17A* are partially dysfunctional variables, it makes sense that this dysfunction manifests itself in a significant way when the BMI has increased and with it also increases the requirement of the organism in terms of inflammatory response.

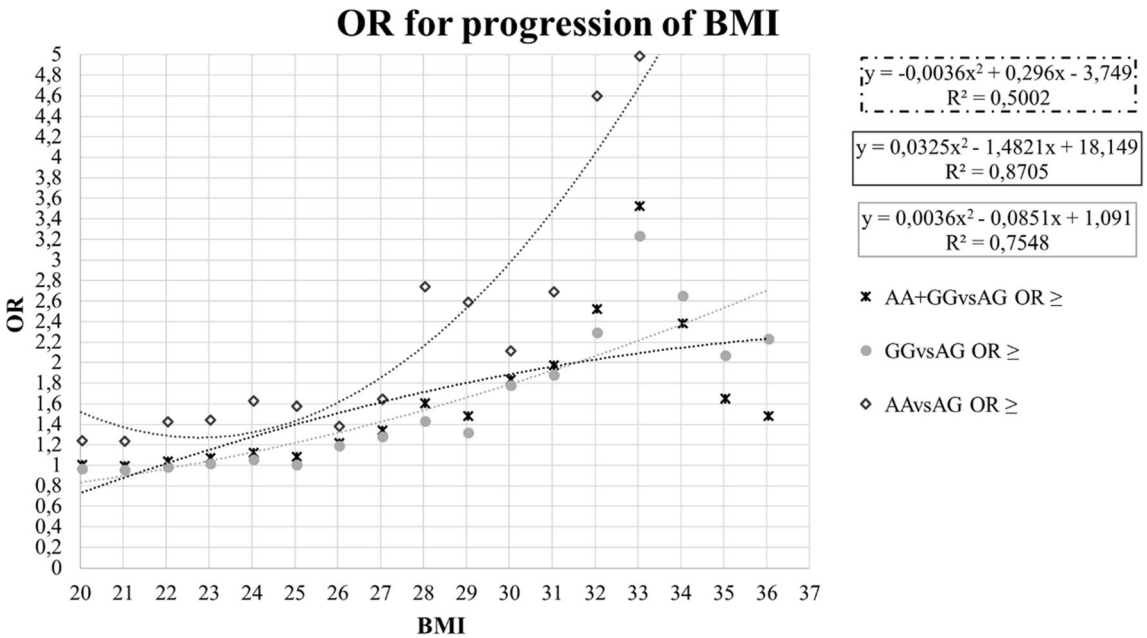

Fig. 1 Relation between OR and increase in BMI. In asterisks overdominant model (AA+GGvsAG), in circles codominant model (GG vs AG), in black diamonds codominant model (AAvsAG)

With regard to smoking, a rise in the negative impact of homozygous genotypes is observed as the number of PY increases. In the sector of the population with moderate tobacco consumption, the AG genotype behaves significantly as a protective genotype in the development of PCa. Both homozygous genotypes, despite having unequal risk values, seem to present a certain dysfunctionality that leads to a greater risk level as the damage produced by tobacco increases. When smoking reaches values over 32 PY, the risk associated with carrying the homozygous genotypes decreases. A possible explanation for this behaviour is that as the harm from smoking increases, not only homozygous classes are unable to carry out their function effectively, but it also affects the heterozygous genotype and its protective effect, lowering the effect of carrying one genotype or another. The results show that with the highest values of smoking, the heterozygous class AG seems unable to respond adequately, with the OR values reaching close to 1 (OR 1.16; $p = 0.743$). In other words, for the highest observed values of tobacco consumption, the protective effect of heterozygous genotype is slowly reduced until its risk is equal to that associated with homozygous genotype.

The scientific literature includes several studies which relate this SNP to the risk of developing different types of cancer. Nevertheless, none of these were conducted with prostate cancer. The results obtained in these studies are very varied. Although the majority of them have described the allele A as the risk factor, in some causes the allele G appears to increase the possibility of developing cancer. In addition, statistically significant OR has not been obtained in all of the cases [13, 14, 18, 20, 21, 32–43].

Inflammation and cytokines involved in its progress (as IL-6, IL-10, IL-17, etc.) play an important role in the development of PCa, as multiple studies show [6, 44–47, etc], so that high levels of pro-inflammatory cytokines are related with the growing of the tumour. Recent studies suggest that IL-17A is an essential proinflammatory cytokine which could cause the secretion of other cytokines and chemokines through different cell types, such as mesenchymal and myeloid cells, in order to retain monocytes and neutrophils in the inflammation microenvironment [48]. Multiple studies have shown that variations of a single nucleotide, such as rs2275913, can affect the functions of these genes and their protein expression, thus influencing cell proliferation and increasing the risk of developing cancer [49–51]. In some of the studies that relate rs2275913 to the development of cancer, it has been suggested that allele A involves a higher concentration of IL-17 in peripheral blood and thus favours the onset of diseases such as tumours. However, not all results obtained support this hypothesis [38, 52–54]. In our study, the fact that the heterozygous genotype has a protective effect implies that not only the A allele has a risk effect on the development of PCa. In this sense, IL-17 interacts with multiple molecules in their immunological activity, so that changes in the expression of a gene could affect cell routes in multiple ways.

In conclusion, this analysis shows a possible associate between the IL-17A rs2275913 and the onset of PCa which could be influenced for age, BMI and above all, smoking. These results, together with the conclusion of previous studies, lays bare the need to carry out more studies. Further research should increase sample size, conduct stratified analyses and take into account the importance of interactions in cellular process, in the same way as interactions between genes and environment.

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Compliance with Ethical Standards

Conflict of Interest No competing interests are declared by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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