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ORIGINAL ARTICLE

CAG REPEAT NUMBER IN THE ANDROGEN RECEPTOR GENE AND PROSTATE CANCER

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ABSTRACT

Prostate cancer (PC) is the second leading cause of cancer deaths in men. The effects of androgens on prostatic tissue are mediated by the androgen receptor (AR) gene. The 5' end of exon 1 of the AR gene includes a polymorphic CAG triplet repeat that numbers between 10 to 36 in the normal population. The length of the CAG repeats is inversely related to the transactivation function of the AR gene. There is controversy over association between short CAG repeat numbers in the AR gene and PC. This retrospective case-control study evaluates the possible effect of short CAG repeats on the AR gene in prostate cancer risk in Macedonian males. A total of 392 male subjects, 134 PC patients, 106 patients with benign prostatic hyperplasia (BPH) and 152 males from the general Macedonian population were enrolled in this study. The CAG repeat length was determined by fluorescent polymerase chain reaction (PCR) amplification of exon1 of the AR gene followed by capillary electrophoresis (CE) on a genetic analyzer. The mean repeat length in PC patients was 21.5 ± 2.65, in controls 22.28 ± 2.86 (p = 0.009) and in BPH patients 22.1 ± 2.52 (p = 0.038). Short CAG repeats (<19) were found in 21.64% of PC patients *vs.* 9.43% in BPH patients (p = 0.0154). We also found an association of low Gleason score (<7) with short CAG repeat (<19) in PC patients (p = 0.0306), and no association between the age at diagnosis of PC and BPH and CAG repeat length. These results suggest that reduced CAG repeat length may be associated with increased prostate cancer risk in Macedonian men.

Keywords: Prostrate cancer (PC); Androgen receptor (AR) gene; CAG repeat; Benign prostatic hyperplasia (BPH)

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INTRODUCTION

Prostate cancer (PC) is the second leading cause of cancer deaths in men and is the most common male-specific cancer in most Western countries [1-5]. An expanding body of epidemiological data suggests several risk factors that predispose to PC development (for example, advanced age, positive family history, African ancestry and potentially ethnicity) [6], but the etiology of PC remains poorly understood. However, involvement of genetic and environmental factors, may also contribute to the ethnic differences in incidence rates [7-9]. The development and progression of prostate tumors are influenced by androgens [10]. The effects of androgens on prostatic tissue are mediated by the androgen receptor (AR) through the AR-androgen complex, stimulating transcription and expression of a

cascade of androgen-responsive genes and genes involved in the cell cycle control [11].

The AR is a ligand-activated nuclear transcription factor encoded by the *AR* gene, which spans more than 90 kb of the genomic DNA on the X chromosome (Xq11-12). The gene consists of eight exons that encode four functional domains of AR for DNA binding, ligand binding and transcriptional regulation [12]. Exon 1 encodes the N-terminal (transactivation) domain that controls its transcriptional activity. The 5' end of this exon 1 includes a CAG polymorphic trinucleotide repeat that codes for a polyglutamine tract in the N-terminal domain [13]. The triplet repeat numbers between 8 and 36 in the normal population [14].

The length of the CAG repeats is inversely related to the transactivation function of the *AR* gene so that shorter CAG repeats increase the transactivation activity [15]. Many studies have focused on establishing an association of CAG repeat with increased risk of developing PC. In these, shorter repeat lengths have been associated with increased risk of PC [14,16-18], but this finding has not been consistent [19-21]. The ethnic variation in the CAG repeat variation in the *AR* gene suggests that this may have a role in the substantial racial difference in PC risk [22-25]. In this study, we have examined the possible effect of short CAG repeats in the *AR* gene on PC risk in Macedonian males.

MATERIALS AND METHODS

Materials. We enrolled 134 PC patients, 106 patients with benign prostatic hyperplasia (BPH) and 152 males from the general Macedonian population for this study. Informed consent was obtained from all and the study was approved by the Ethic Committees of the Macedonian Academy of Sciences and Arts and Faculty of Pharmacy, Skopje, Republic of Macedonia. Prostate cancer patients and those with BPH were recruited from the Department of Urology, Medical Faculty, Skopje, Republic of Macedonia and were referred to the Pharmacogenetic Laboratory, Faculty of Pharmacy, Skopje, Republic of Macedonia. Only those with histopathologically-confirmed diagnoses were included. The mean ages of the PC and BPH patients were 68.19 ± 7.36 and 69.72 ±.55 years, respectively. Males from the general population were selected at the Research Center for Genetic Engineering and Biotechnology "Georgi D. Efremov," Macedonian Academy of Sciences and Arts, Skopje, Republic of Macedonia to produce a control sample that was age-matched to the samples of PC and BPH patients.

Methods. Genomic DNA was extracted from EDTA whole blood following a standard phenol/chloroform method. The CAG repeat number was determined by fluorescent polymerase chain reaction (PCR) amplification of exon 1 of AR gene. Approximately 50–100 ng genomic DNA was subjected to 35 cycles of PCR amplification using fluorescently-labeled forward primer 5'-(HEX) TCC AGA ATC TGT TCC AGA GCG TGC-3' and unlabeled reverse prime r5'-GCT GTG AAG GTT GCT GTT CCT CA-3'. The PCR amplification was performed as follows: 45 seconds at 94°C, 30 seconds at 62°C and 1 min. at 72°C. The size of the PCR product was determined by capillary electrophoresis (CE) on an ABI PRISM™ 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The number of CAG repeats predicted by the Genescan software v.6 (Applied Biosystems) was compared with the actual CAG repeats determined by direct dideoxy terminator cycle sequencing using the BigDye Terminator Sequencing Kit v1.0 (Applied Biosystems) in male DNA samples as described previously [26].

Statistical Analyses. The frequency of the CAG repeat alleles was compared between the studied groups using the $\chi 2$ and Fisher's exact tests. Values were expressed as mean ± standard deviation (SD). Differences in the mean of (CAG)n length between different groups of patients (PC, BPH) *vs.* controls were tested by the independent samples *t*-test using SPSS 14.0 (SPSS Chicago, IL, USA), after checking for normal distribution. The association of different CAG repeat length was tested at different cut-off points: ≤19, ≤20, ≤21, ≤22 and >22. Statistical significance was defined as $p < 0.05$.

RESULTS

The range of CAG repeats among patients with PC and with BPH, and in control subjects was 15-29, 17-30 and 14-30, respectively. The frequency of CAG repeats in PC and BPH patients and control subjects are given in Figure 1.

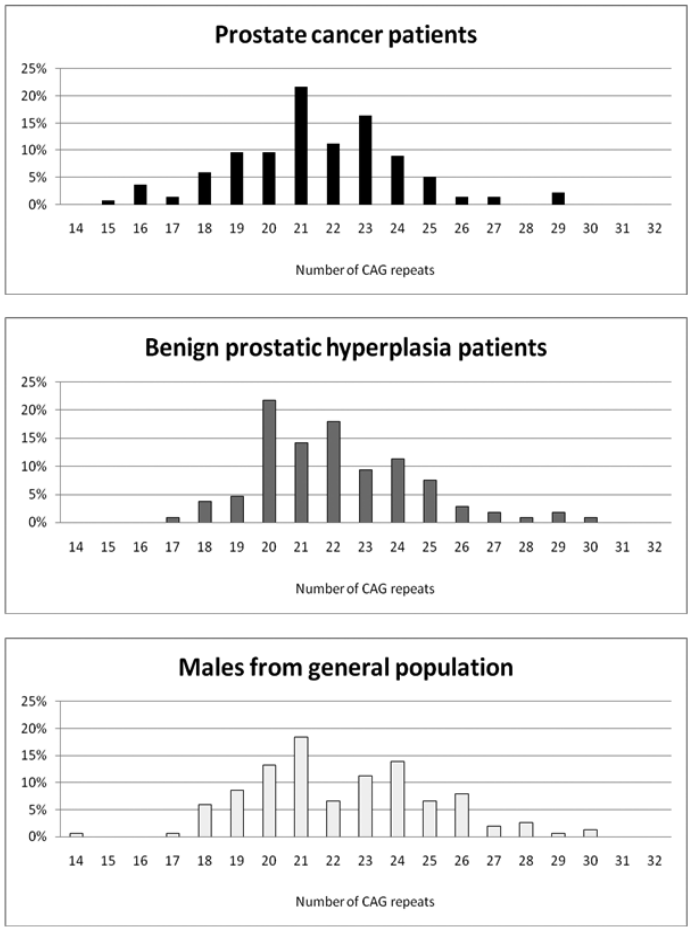

Figure 1. Distribution of CAG repeats in exon 1 of the AR gene in PC patients, BHP patients and males from the general population.

The mean repeat length in the PC patients was 21.5 ± 2.65, in BPH patients 22.1 ± 2.52 ($p = 0.038$) and in the control subjects 22.28 ± 2.86 ($p = 0.009$).

Figure 2 shows the distribution of the short CAG repeats in the studied groups. The association of the CAG repeat lengths at different cut-off points with PC patients is shown in Table 1. We found a significantly higher percentage of short CAG repeats (≤19) in PC patients (21.64%) than in BPH patients (9.43%) ($p = 0.0154$).

Table 2 shows the association of early (≤65 years) and advanced (>65 years) age at diagnosis of PC and BPH patients with different CAG repeat length of the AR gene. We found no association between the repeat length and age at diagnosis of either group. The distribution of PC and BPH diagnosed in these age groups was similar at the different cut-off point of CAG repeat length.

The association of CAG repeats at different cut-off points with a Gleason score was analyzed in 110 PC patients (Table 3). A Gleason score of <7 was found in 35 (31.82%), and a Gleason score of ≥7 in 75 (68.18%). In the PC patients with repeat number of ≤19, we found a significantly higher percentage (34.3%, $p = 0.0306$) of low grade tumors (Gleason score <7) against 16.0% that were high grade PC tumors (Gleason score ≥7). The similar distribution of low and high grade tumors was present at cut-off points of CAG repeats of ≤21 ($p = 0.0624$) and CAG repeats of ≤22 ($p = 0.0868$) but these differences are not statistically significant. Relative to the repeat length of ≤21 and a Gleason score of <7, the odds ratio (OR) for the ≤22 was 2.15, 95% CI (95% confidence interval) (0.887-5.211) and for the CAG repeat length of >22 it was 0.465, 95% CI (0.192-1.128).

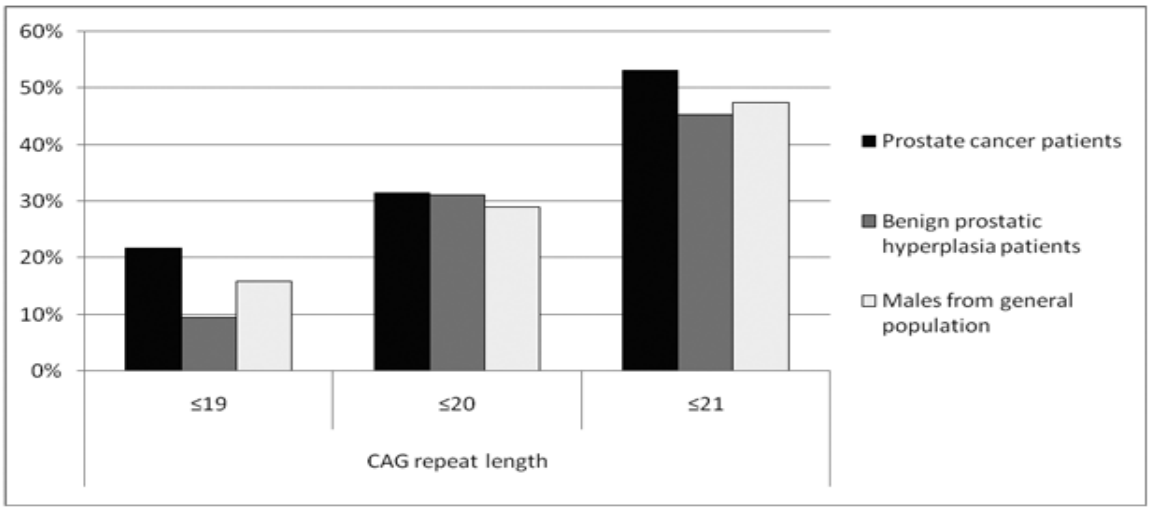

Figure 2. Distribution of short CAG repeats in exon 1 of the AR gene in the three studied groups.

Table 1. Association of CAG repeat lengths at different cut-off points in the studied groups.

	CAG Repeat Lengths					
Studied Groups	≤19	≤20	≤21	≤22	>22	Total
PC patients, *n* (%)	29 (21.6)	42 (31.3)	71 (53.0)	86 (64.2)	48 (35.8)	134
BPH patients, *n* (%)	10 (9.4)	33 (31.1)	48 (45.3)	67 (63.2)	39 (36.8)	106
OR (95% CI)	2.531 (1.173-5.461)	1.010 (0.583-1.750)	1.362 (0.817-2.271)	1.043 (0.614-1.771)	0.959 (0.565-1.628)	
***p* value**	**0.0154**	1.0000	0.2360	0.8764	0.8764	
GP males, *n* (%)	24 (15.8)	44 (29.0)	72 (47.4)	82 (54.0)	70 (46.1)	152
OR (95% CI)	1.473 (0.809-2.682)	1.121 (0.676-1.859)	1.252 (0.876-1.994)	1.529 (0.950-2.461)	0.654 (0.406-1.052)	
***p* value**	0.2037	0.6593	0.3431	0.0794	0.0794	

PC: prostate cancer; BPH: benign prostatic hyperplasia; GP: general population; the BPH *p* value is of statistical significance (0.05).

Table 2. Association of CAG repeat lengths at different cut-off points, by age at diagnosis.

	CAG Repeat Lengths					
Studied Groups	≤19	≤20	≤21	≤22	>22	Total
PC patients, *n* (%)	27 (21.6)	39 (31.7)	67 (54.5)	81 (65.9)	42 (34.2)	123 (100.0)
<65 years	7 (17.5)	10 (25.0)	20 (50.0)	25 (62.5)	15 (37.5)	40 (32.5)
>65 years	20 (24.1)	29 (34.9)	47 (56.6)	56 (57.5)	27 (32.5)	83 (67.5)
OR (95% CI)	0.668 (0.256-1.742)	0.621 (0.266-1.446)	0.766 (0.359-1.632)	0.804 (0.365-1.767)	1.244 (0.566-2.736)	
***p* value**	0.4077	0.2671	0.4894	0.5861	0.5861	
BPH patients, *n* (%)	9 (22.0)	33 (31.7)	48 (54.5)	67 (65.9)	39 (34.2)	106 (100.0)
<65 years	2 (6.3)	9 (28.1)	13 (40.6)	20 (62.5)	12 (37.5)	32 (30.2)
>65 years	7 (9.5)	24 (32.4)	35 (47.3)	47 (63.5)	27 (36.5)	74 (69.8)
OR (95% CI)	0.638 (0.125-3.255)	0.815 (0.328-2.028)	0762 (0.329-1.766)	0.957 (0.406-2.258)	1.044 (0.443-2.463)	
***p* value**	0.5863	0.6602	0.5264	1.0000	1.0000	

PC: prostate cancer; BPH: benign prostatic hyperplasia.

Table 3. Association of CAG repeat lengths at different cut-off points by Gleason score in PC patients.

	CAG Repeat Lengths					
	≤19	≤20	≤21	≤22	>22	Total
PC patients, *n* (%)	24 (21.8)	35 (31.8)	58 (52.7)	69 (62.7)	41 (37.3)	110 (100.0)
Gleason <7	12 (34.3)	14 (40.0)	23 (65.7)	26 (74.3)	9 (25.7)	35 (31.8)
Gleason ≥7	12 (16.0)	21 (28.0)	35 (46.7)	43 (57.3)	32 (42.7)	75 (68.2)
OR (95% CI)	2.739 (1.079-6.955)	1.714 (0.738-3.985)	2.190 (0.953-5.036)	2.150 (0.897-5.211)	0.465 (0.192-1.128)	
***p* value**	**0.0306**	0.2082	0.0624	0.0868	0.0868	

PC: prostate cancer; the bold letters indicate a statistical significance ($p < 0.05$).

DISCUSSION

The hypothesis that variation in transcriptional activity of the AR related to polymorphic CAG repeats [27] influences prostate carcinogenesis [28], has been tested in many studies. The results have not been in full agreement, some finding moderate-to-significant association of short CAG repeats with increased PC risk, others failing to confirm this.

Our results suggest that a shorter CAG repeat length (≤19) is associated with an increased risk of PC. This agrees with previous reports that short CAG repeat lengths in the AR gene predisposes to PC [14,29,30]. However others, studying French-German populations [31] and North American populations [20,32], have reported no such association.

The association between PC and increasing age is very strong [33]. In our study the same proportion of patients with PC and with BPH (about 2/3) was diagnosed at >65 years, and we found no association between short CAG repeat length and age at diagnosis. This supports the importance of age as an independent risk factor for PC and BPH [34].

To test if short CAG repeats may predispose to more aggressive forms of PC [14,35], we performed a case analysis according to Gleason score and found an association between repeat length ≤19 and low grade PC tumors (Gleason score <7). For advanced disease, we observed a suggestive lower risk with fewer CAG repeats, unlike in the Physicians'

Health Study [36], which showed a monotonically increasing risk with decreasing number of CAG repeats for advanced cases. The possible explanation is that androgens may influence the stage and grade of PC independently, and the increased androgenic stimulation in PC patients with lower CAG repeat length and subsequently higher AR activity, may prevent the dedifferentiation of the prostate epithelium in the nascent tumor [37]. This needs to be clarified and further investigated to determine the influence of androgens on differentiation status in cases that are restricted to uniform stage.

We found that CAG repeat length was not significantly different in BPH patients than in controls ($p = 0.9166$) but was significantly different between PC and BPH ($p = 0.038$). This agrees with previous studies and the Prostate Cancer Prevention Trial [38,39]. Our results suggest the possibility that the risk of malignancy is not higher in BPH patients than in controls, and that BPH is an independent entity and is not a precancerous state [40]. We conclude that short CAG repeats ($\leq$19) may be associated with increased PC risk in Macedonian men and that our results provide potential tools to assist in prediction strategies for this important disease.

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