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Androgen Receptor CAG Repeat Length is Not Associated with the Risk of Incident Symptomatic Benign Prostatic Hyperplasia: Results from the Prostate Cancer Prevention Trial

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Abstract

This study examined whether androgen receptor (*AR*) CAG repeat length was associated with the risk of incident benign prostatic hyperplasia (BPH), in a nested case-control study of 416 BPH cases and 527 controls drawn from Prostate Cancer Prevention Trial placebo-arm participants who were free of BPH at baseline. BPH was assessed over 7 years and was defined as receipt of medical or surgical treatment, two scores >14 on the International Prostate Symptom Score (IPSS), or two increases in IPSS ≥ 5 with at least one score ≥ 12 . There were no associations of *AR* CAG repeat length and BPH risk. Compared to men with *AR* repeat length = 19, the covariate-adjusted odds ratios [95% CI] were 1.07 [0.73, 1.57] and 0.90 [0.55, 1.45] for repeat length 20–24 and ≥ 25 , respectively. There was a weak association of *AR* repeat length with baseline serum testosterone (T) (Spearman $r=0.09$, $p<0.02$); however, control for or stratification by T did not change study results. Further, results did not differ when stratified by body mass index, baseline IPSS, or baseline concentration of 3 α -diol glucuronide, and were similar for all BPH definitions. This study suggests that knowledge of *AR* CAG repeat length will have little clinical utility for the prevention of symptomatic BPH.

Keywords

Benign prostatic hyperplasia; androgen receptor CAG repeat length; lower urinary tract symptoms; steroid hormones

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common medical conditions in middle-aged and older males, affecting 40 to 50 percent of men by age 50 and up to 80 percent of men by age 70[1,2]. The pathogenesis of BPH is androgen dependent: it does not occur in men castrated before puberty[3]; high concentrations of 5- α -androstane-3 α , 17 β -diol-glucuronide (3 α -dG), which is an indirect measure of intraprostatic DHT, is associated with increased BPH risk[4]; and treatment with 5 α -reductase inhibitors, which markedly reduce intraprostatic dihydrotestosterone (DHT) concentrations, both treat and prevent BPH [5]. Further, polymorphic variability in the transcriptional activity of the androgen receptor (AR), which is inversely associated with the number of CAG repeats in exon 1[6], may also play a role in the pathogenesis of BPH. Only three large studies have examined AR CAG repeat length and risk of clinically significant BPH; two reported a significant inverse association[7,8] and the other a significant positive association[9]. Other studies have examined a variety of surrogate measures related to BPH and found inconsistent [10], no [11,12] or positive associations [13]. Similar to findings on AR CAG repeat length and prostate cancer risk, the literature is inconsistent.

The relationship of AR CAG repeat length with BPH risk may be complex, due to the interrelationships among AR CAG repeat length and two risk factors for BPH, body mass index (BMI) and serum androgen concentration. For example, high AR CAG repeat length is associated with higher serum testosterone (T)[14,15]. Higher T is also associated with increased fat-free and decreased fat mass, and this relationship may be stronger among men with high AR CAG repeat lengths[16]. It is thus possible that associations of AR CAG repeat length with BPH may be modified by obesity or concentrations of circulating and/or intraprostatic androgens.

Here we give results of a nested case-control study examining the risk of incident, symptomatic BPH in a population of healthy men aged 55 and older who participated in the Prostate Cancer Prevention Trial (PCPT). Data from the PCPT include rigorous assessment of both the symptoms and treatment of BPH along with extensive information on anthropometric, dietary, hormonal and other factors that affect BPH risk. This report examines whether AR CAG repeat length is associated with the risk of incident, symptomatic BPH. We also examine associations of CAG repeat length with BMI and serum concentrations of testosterone and 3 α -dG, and test whether associations of AR CAG repeat length with BPH risk are modified by concentrations of serum androgens and obesity.

METHODS

Data are from the PCPT, a randomized, placebo-controlled trial testing whether finasteride, a 5 α -reductase inhibitor, could reduce the 7-year period prevalence of prostate cancer. Details regarding study design and participant characteristics have been described previously[5]. Briefly, 18,880 men age 55 years and older with a normal digital rectal exam, prostate-specific antigen level of 3 ng/ml or below, no history of prostate cancer or other clinically significant coexisting conditions, and no severe BPH symptoms (International Prostate Symptom Score (IPSS) of 20 or higher), were randomized to receive finasteride (5 mg/day) or placebo.

Participants for this nested case-control study were drawn from the 9,457 men randomized to the placebo arm of the PCPT. Exclusion criteria included men who, at baseline, had medical or surgical treatment for BPH (n=701), a self-reported history of BPH (n=1,904), an IPSS >7 (n=1,820), or reported steroid hormone use (n=61), leaving 4,971 men eligible for this study.

Extensive medical data, including physician diagnosis of and treatment for BPH were collected at the baseline visit, each clinic visit (6- and 12-month), and at every phone contact (3- and 9-month) between clinic visits. At recruitment (3 months prior to randomization), randomization and each 12-month clinic visit, participants completed the 7-item IPSS as a self-administered questionnaire. Clinic staff measured height, weight, waist and hip circumference at randomization, and body mass index (BMI) was calculated as weight (kg) divided by height² (m). Age, race/ethnicity, physical activity (type, frequency, duration, pace, and intensity), alcohol consumption (type, frequency and dose) and history of smoking were collected at baseline using self-administered questionnaires.

Incident BPH was defined either as a report of treatment for or development of significant lower urinary tract symptoms. Treatments included use of α -blockers, finasteride or any surgical intervention (transurethral prostatectomy, balloon dilation or laser prostatectomy). Development of significant symptoms was defined as either (1) two IPSS scores >14 ; or (2) an increase of 5 in IPSS from baseline documented on at least two occasions plus at least one score ≥ 12 . There were a total of 727 incident BPH cases, which were further categorized into clinical BPH (322 cases defined by medical or surgical treatment and 105 cases defined by two IPSS scores of 15 or higher) and symptomatic progressive BPH (300 cases defined by two IPSS scores at least 5 units higher than baseline plus at least one score ≥ 12). Men who reported transient elevations in IPSS or a physician diagnosis of BPH in the absence of symptoms or treatment were not included as cases.

Controls were drawn from the 1,497 men who, during seven years of observation, had no more than two missing IPSS measures, no single IPSS >7 , no surgical or medical treatment for BPH, and no report of a diagnosis of BPH. From this sample, we selected all men aged 70 years and older and all non-Caucasian men, in order to maximize statistical power when examining these subgroups. Remaining controls were randomly selected to yield a total control sample ($n=727$) that was frequency matched to the age distribution (in 5 year age groups) of cases. From this sample of cases and controls, DNA was available only from the 416 cases (57%) and 527 controls (72%) who had consented to a special blood draw for lymphocyte collection instituted late in the trial. DNA was available from more controls because they had to have completed the full 7 years of the trial to be eligible for this study, whereas men with a BPH diagnosis anytime during the trial, regardless of length of study participation, were eligible.

Blood for lymphocyte collection was drawn into a 7 ml EDTA vacutainer tube and shipped overnight to a central storage facility, where it was centrifuged, aliquoted and stored at -70°C until analysis. DNA was extracted on a Qiagen BioRobot M48 Workstation using the MagAttract DNA Blood Midi M48 Kit. The DNA was amplified by the polymerase chain reaction (PCR) using 5ul of the extracted DNA ($\sim 20\text{ng}/\text{ul}$), 20pmol of each primer (ARF1=5'-ACAGCCTGTTGAACTCTTCTGAG-3', ARR1=5'-CCAGCAGGGACAACGTGGATG-3'), 1 $\times$ PCR buffer (Perkin-Elmer), 1.5mM MgCl_2 , and 1 unit of Platinum Taq polymerase (Invitrogen) in a reaction volume of 50ul. After a 5 minute (95°C) denaturation period, the reaction was subjected to 40 cycles of PCR (94°C , 30 secs.; 70°C , 30 secs.; 72°C , 30 secs.) followed by a 7 minute extension on the final cycle. Upon completion of amplification, 10ul of amplified product was electrophoresed on a 2% agarose gel to view quality and quantity of the DNA. Excess oligonucleotide primers were eliminated by column purification (Microcon YM-100, Millipore Corp., Bedford, MA) according to the manufacturer's instructions. Sequencing was performed using the Big Dye terminator v3.1 cycle sequencing reaction kit (Applied Biosystems, Foster City, CA) primed with either ARF2 (5'-GATTCAGCCAAGCTCAAGGATG-3') or ARR2 (5'-CTCTGGGACGCAACCTCTCTC-3'). Sequenced DNA was analyzed on an ABI 3130xl Genetic Analyzer, and CAG repeat length was determined using Sequencing Analysis 5.3.1

(Applied Biosystems) and read independently by two individuals. Any questionable findings were repeated to gain a conclusive result. Detailed descriptions of assays for serum steroids and sex hormone binding globulin (SHBG) assays are given elsewhere[4].

Descriptive statistics were used to characterize the study sample and distribution of *AR* CAG repeat length in cases and controls. Unconditional logistic regression was used to calculate the relative odds ratios (OR) and their 95% confidence intervals associated with CAG repeat length, using categories from previously-published studies (18, 19–24 and 25 and 19, 20–24 and 25) and based on the sample median (21 and 22). Results are given for statistical models adjusted for (1) matching variables alone (age [continuous] and race [white vs. others]); (2) matching variables plus covariates associated with BPH risk in either the published literature or this study (alcohol [drinks/day], physical activity [sedentary, light, moderate, active], body mass index [continuous], smoking [current vs. not], and baseline IPSS [continuous]); and (3) matching variables and covariates plus T, 3 α -dG and SHBG (all continuous). Tests for linear trend across CAG repeat length categories were performed by using an ordinal variable corresponding to rank from lowest to highest category[17]. Linear regression was used to calculate least squared mean BMI, T and 3 α -dG by category of *AR* CAG repeat length, and Spearman correlations were used to examine the rank order associations of CAG repeat length with BMI, T and 3 α -dG.

Additional models examined the joint effects of CAG repeat length with BMI, T and 3 α -dG. Formal interaction tests were based on the interaction term of CAG repeat length (, 20–24, 25) times BMI (<25, 25–<30, 30), T and 3 α -dG (both in tertiles), using ordinal variables corresponding to the rank order of each variable. All p-values were two-sided and considered statistically significant at $p < 0.05$. Statistical analyses were conducted using SAS (version 9.0 Cary, NC).

Results

Participants were mostly white, overweight or obese, and non-smokers. Distributions of age, race/ethnicity, BMI, physical activity, smoking and CAG repeat length were similar in cases and controls (Table 1). Baseline IPSS and serum 3 α -dG were significantly higher and alcoholic beverage consumption and serum T were significantly lower in cases compared to controls.

There were no associations of CAG repeat length with BPH risk (Table 2). Associations were similar when controlled for age and race only (Model 1), controlled in addition for alcohol consumption, physical activity, BMI, smoking and baseline IPSS (Model 2), and controlled in addition for serum T, 3 α -dG and SHBG. Associations were also similar when CAG repeat length was categorized using 18, 19 or 21 (median) as the contrast group.

There was a weak positive association of *AR* CAG with serum T. The Spearman correlation, controlled age, BMI and SHBG, was 0.09 ($p < 0.02$), and adjusted mean T concentrations across *AR* CAG repeat length categories (19, 20–24, 25) were 491, 512 and 533, respectively ($p_{\text{trend}} < 0.05$). This association between *AR* CAG repeats and androgen levels was similar for both free T and the T:SHBG ratio. There were no associations of *AR* CAG repeat length with either BMI or 3 α -dG (data not shown)

Table 3 gives odds ratios for the joint effects of CAG repeat length cross-classified by BMI, T and 3 α -dG on BPH risk. There were no significant differences in associations of CAG repeat length with BPH risk across strata of these variables, nor was there evidence that the positive association of BMI and 3 α -dG and inverse association of T with BPH risk[4,18] differed by *AR* CAG repeat length. Associations of CAG repeat length with BPH also

differed little across strata defined by age (<65 vs. ≥65), baseline IPSS (0–4 vs. 5–7), time from baseline to BPH diagnosis (<4 vs. ≥4 years) and type of BPH endpoint (treatment or two IPSS >14 vs. increase of ≥5 from baseline IPSS) (data not shown).

Discussion

This study found no association of *AR* CAG repeat length with the risk of incident benign prostatic hyperplasia. There was a weak, positive association of *AR* CAG repeat length with serum T; however, there was no evidence that serum T levels either confounded or modified associations of *AR* CAG repeat length BPH risk.

Only three studies have directly examined the association of *AR* CAG repeat length with risk of clinically significant BPH. In one cross-sectional study based on 449 cases and 449 controls, Giovannucci and colleagues reported that the risk of prevalence of BPH, defined as either a physician diagnosis of an enlarged prostate or receipt of surgical treatment, was 97% higher among men with *AR* CAG repeat length ≥19 compared to ≤25[8]. In a second cohort of 310 cases and 1,041 controls, Giovannucci and colleagues reported that the risk of incident BPH, defined as receipt of surgical treatment, was 76% higher in men with *AR* CAG repeat length ≥19 compared to ≤25[7]. An additional cross-sectional study found a positive association between *AR* repeat length and receipt of BPH surgery; however, the study design and statistical methods are not described fully and this result may be attributable to methodological problems[9]. In part, the discrepancy between the results of both Giovannucci studies and the results reported here could be due to substantial differences in definitions of BPH cases and controls. The Giovannucci studies contrasted men with either severe lower urinary tract symptoms (LUTS) or severe LUTS and/or a physician diagnosis to a mix of men with no, mild and moderate LUTS; this study contrasted asymptomatic men who, over 7 years, develop moderate to severe LUTS to those who remain asymptomatic (IPSS <7). It is possible that short *AR* CAG repeat length increases only the risk of developing symptoms sufficiently severe to require surgery; however, when we restricted our cases to men receiving medical or surgical treatment there was no association of *AR* CAG repeat length with BPH risk. It is also possible that the control group in one Giovannucci study[7] was biased to exclude men with low *AR* CAG repeat length, because control men in the BPH study were drawn from control men in a previous study of prostate cancer risk in which short *AR* CAG repeat length was associated with increased prostate cancer risk[19]. Whether such a bias would substantially influence their findings is uncertain.

The only other relevant study on *AR* CAG repeat length and BPH risk is by Roberts and colleagues [10], who reported inconsistent findings for associations of *AR* CAG repeat length with surrogate measures of BPH. In a cohort of 510 men followed for a maximum of 10 years, high *AR* CAG repeat length was significantly but weakly associated with maximum IPSS and IPSS slope (Spearman $r=0.09$ and 0.10 , respectively) and in contrast, *AR* CAG repeat length ≥20 was associated with increased risks of a prostate volume >30g and PSA concentration >1.4 ng/ml. In addition, *AR* CAG repeat length ≥20 was associated with neither a minimally elevated IPSS score (>7) nor reduced urinary flow (<12 ml/second). The interpretation of these conflicting findings is difficult given the non-specific nature of these surrogate measures with clinically significant BPH.

This study confirmed previous findings of a weak, positive association of *AR* CAG repeat length with serum T [14,15,20]. This association may reflect a higher hypothalamic-pituitary-gonadal feedback loop set-point in men with reduced androgen sensitivity [21]. In the PCPT, high T was associated with reduced BPH risk[4]; however, given the very small

difference in serum T across extreme *AR* CAG categories, it is unlikely that the modulation of T by *AR* CAG repeat length is relevant for BPH.

In summary, we found no association of *AR* CAG repeat length and risk of incident, symptomatic BPH in a cohort of healthy, asymptomatic men. The reason for the discrepancy of our findings with those previously reported is unclear. It is possible that *AR* CAG length could modulate response to 5 α -reductase inhibitors used to treat or prevent BPH, because higher *AR* transcription in an environment of low intraprostatic DHT could be physiologically important. Nevertheless, based on the results given here, it is unlikely that knowledge of *AR* CAG length will be of any clinical utility in the prevention of BPH.

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Table 1

Demographic and Lifestyle Characteristics of the Study Population^a

	Benign Prostatic Hyperplasia (BPH)		<i>P</i> ^b
	Cases (N=416)	Controls (N=527)	
	n	(%)	n (%)
Age			
55–60	125	(30.05)	171 (32.45)
60–65	119	(28.61)	160 (30.36)
65–70	106	(25.48)	130 (24.67)
70+	66	(15.87)	66 (12.52)
Race/Ethnicity			
Black	13	(3.13)	16 (3.04)
Hispanic	12	(2.88)	15 (2.85)
Other	3	(0.72)	9 (1.71)
White	388	(93.27)	487 (92.41)
Body Mass Index (kg/m ²)			
Normal (<25)	102	(24.82)	143 (27.29)
Overweight (25–<30)	213	(51.82)	268 (51.15)
Obese (≥ 30)	96	(23.36)	113 (21.56)
Alcohol Consumption			
< 1 drink/month	107	(25.72)	99 (18.82)
1–3 drinks/month	52	(12.50)	50 (9.51)
1–6 drinks/week	136	(32.69)	188 (35.74)
7 – 13 drinks/week	70	(16.83)	98 (18.63)
14 drinks/week	51	(12.26)	91 (17.30)
Physical activity			
Sedentary	67	(16.14)	70 (13.31)
Light activity	179	(43.13)	224 (42.59)
Moderate activity	124	(29.88)	177 (33.65)
Very active	45	(10.84)	55 (10.46)
Smoking			

Benign Prostatic Hyperplasia (BPH)					<i>p^b</i>
Cases (N=416)		Controls (N=527)			
n	(%)	n	(%)		
No (former/never)	386	(92.79)	499	(94.69)	0.23
Yes (current)	30	(7.21)	28	(5.31)	
CAG Repeat Length					
CAG 19	99	(18.79)	74	(17.79)	0.51
CAG 19–24	329	(62.43)	274	(65.87)	
CAG 25	99	(17.79)	68	(16.34)	
Baseline IPSS					
1–3	167	(40.83)	325	(72.38)	<0.01
4–5	128	(31.30)	88	(19.60)	
6–7	114	(27.87)	36	(8.02)	
Mean	SD	Mean	SD	<i>p^c</i>	
Testosterone (ng/dl)	493.4	198.2	524.9	222.5	0.03
3α-diol glucuronide (ng/ml)	7.47	6.29	6.62	4.41	0.02
AR CAG Repeats (n)	22.0	3.0	22.0	3.0	0.97

^aNumbers may not add up to the total number of cases/controls and percentages may not add up to 100 due to missing data.

^bp from chi-square test

^cp from t-test

Table 2
Associations of AR CAG Repeat Length with Risk of Incident Benign Prostatatic Hyperplasia

AR CAG Repeats (n)	n		Model 1 ^a		Model 2 ^b		Model 3 ^c	
	Control	Case	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
19	99	74						
20-24	329	274	1.09	0.77, 1.53	1.07	0.73, 1.57	1.16	0.79, 1.72
25	99	68	0.90	0.58, 1.38	0.90	0.55, 1.45	0.98	0.60, 1.61
20	170	124	1.00		1.00		1.00	
21-24	258	224	1.18	0.88, 1.59	1.21	0.87, 1.68	1.29	0.92, 1.8
25	99	68	0.93	0.63, 1.38	0.96	0.62, 1.47	1.03	0.66, 1.61
21	253	193						
22	274	223	1.06	0.82, 1.37	1.12	0.84, 1.5	1.17	0.87, 1.57

^aControlled for matching variables (age and race)

^bControlled in addition for alcohol, physical activity, body mass index, current smoking, and baseline IPSS

^cControlled in addition for testosterone, 3- α -diol glucuronide and SHBG

Joint Effects of AR CAG Repeat Length and Body Mass Index, Testosterone and 3 α -diol Glucuronide on Risk of Incident Benign Prostatic Hyperplasia

Table 3

Population	AR CAG Repeats (n)	Control (n)	Case (n)	Odds Ratio ^c	95% Confidence Interval	P Inter-Action
Body Mass Index (kg/m²)						
<25	19	25	19		ref	0.70
	20–24	98	72	1.10	0.51,2.35	
	25	23	16	0.83	0.29,2.32	
	19	51	35	1.05	0.45,2.41	
25 – <30	20–24	165	142	1.05	0.41,2.71	
	25	52	36	1.22	0.35,4.22	
	19	23	20	0.89	0.33,2.41	
	20–24	66	60	1.21	0.40,3.69	
30	25	24	16	1.49	0.35,6.26	
Testosterone (ng/dl)						
<402	19	49	36	ref		0.41
	20–24	148	147	1.31	0.68,2.51	
	25	40	38	1.19	0.53,2.70	
	19	48	34	1.12	0.46,2.71	
402 – <558	20–24	171	121	0.74	0.28,1.97	
	25	56	27	0.88	0.26,3.01	
	19	44	28	0.82	0.35,1.90	
	20–24	173	127	0.90	0.36,2.29	
558	25	52	32	0.61	0.19,1.97	
3α-diol glucuronide (ng/dl)						
<4.71	19	49	36	ref		0.71
	20–24	148	147	1.26	0.46,2.61	
	25	40	38	0.70	0.28,1.73	
	19	48	34	1.10	0.46,2.61	
4.71 – 7.29	20–24	171	121	0.84	0.32,2.22	
	25	56	27	2.40	0.70,8.28	

Population	AR CAG Repeats (n)	Control (n)	Case (n)	Odds Ratio ^c	95% Confidence Interval	P Inter-Action
7,29	19	44	28	1.42	0.59,3.43	
	20–24	173	127	0.96	0.36,2.58	
	25	52	32	1.27	0.37,4.36	

^aControlled for matching variables (age and race), alcohol, physical activity, body mass index, current smoking, baseline IPSS, testosterone, 3- α -diol glucoronide and SHBG.