Androgen Receptor Gene Polymorphisms and Increased Risk of Urologic Measures of Benign Prostatic Hyperplasia

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The association between androgen receptor gene polymorphisms and benign prostatic hyperplasia was investigated among 510 men randomly selected from Olmsted County, Minnesota. From 1990 through 2000, lower urinary tract symptom severity was assessed by the American Urological Association Symptom Index (AUASI), and peak urinary flow rate, prostate volume, and serum prostate-specific antigen level were measured. Androgen receptor CAG and GGN genotyping was performed. A CAG repeat length of <21 was associated with an enlarged prostate (hazard ratio (HR) = 1.4, 95% confidence interval (CI): 1.0, 1.9) and a serum prostate-specific antigen level > 1.4 ng/ml (HR = 1.5, 95% CI: 1.1, 2.0). A GGN repeat length of <16 was associated with an AUASI > 7 (HR = 1.6, 95% CI: 1.1, 2.3) and a serum prostate-specific antigen level > 1.4 ng/ml (HR = 1.5, 95% CI: 1.0, 2.3). Having <21 CAG repeats and <16 GGN repeats compared with having neither was associated with an enlarged prostate (HR = 2.5, 95% CI: 1.5, 4.2), a serum prostate-specific antigen level > 1.4 ng/ml (HR = 2.8, 95% CI: 1.6, 4.7), a peak flow rate < 12 ml/second (HR = 1.9, 95% CI: 1.1, 3.4), and an AUASI > 7 (HR = 1.6, 95% CI: 1.0, 2.7). Androgen receptor gene polymorphisms may have a potential role in the pathogenesis of benign prostatic hyperplasia.

cohort studies; polymorphism (genetics); prostate; prostatic hyperplasia; receptors, androgen; risk factors; signs and symptoms; urinary retention

Abbreviations: AUASI, American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.
has been associated with reduced androgen receptor expression (3). Therefore, it is hypothesized that a low number of repeats may increase the risk of BPH.

The functional effects of the GGN repeat polymorphisms on androgen receptor transactivation are not clear. In one study, deletion of the entire GGN repeat segment of the gene was associated with decreased transactivating action of the gene (4). In epidemiologic studies, inconsistent associations with prostate cancer, including an increased risk of prostate cancer for men with a short number of GGN repeats (5, 6), with 16 repeats (7), or with a high number of GGN repeats (8, 9), have been reported. To our knowledge, although no association has been reported between number of GGN repeats and BPH, the importance of the androgen receptor in BPH, and the reported associations between number of GGN repeats and prostate cancer (also hormonally mediated), suggest that the association with BPH needs to be investigated.

Findings from previous studies investigating the association of CAG and androgen receptor gene polymorphisms with BPH have been inconsistent. While some studies have reported an association between BPH and short CAG repeat length (10–12), others have reported no association (13, 14). Differences in the criteria used to define BPH or a narrow disease spectrum among BPH study subjects may have contributed to these inconsistencies. Use of different criteria, including surgery for treatment of BPH (11, 12), self-reported history of an enlarged prostate (11), prostate adenoma weight (10), and lower urinary tract symptom severity (11), makes it difficult to compare findings across studies. Studies based on men from clinical series present a potential for referral bias due to a narrow disease spectrum from overrepresentation of men with severe symptoms. In contrast, a randomly selected cohort provides a representative cohort with a broad disease spectrum. In recent years, a number of surrogate measures have been used to characterize BPH. However, because of variability in these surrogate measures, particularly symptom severity (15, 16) and peak urinary flow rate (17, 18), a single cross-sectional measurement may not correctly identify men with BPH, and evaluation of the association between androgen receptor gene polymorphisms and the BPH phenotype may not be valid. The current study evaluated the association of CAG and GGN repeat length polymorphisms in the androgen receptor gene and surrogate measures of BPH using multiple measurements assessed prospectively in a cohort of community-dwelling men.

MATERIALS AND METHODS

Many details of the study design have been published previously (19, 20). Briefly, subjects were participants in a longitudinal study of lower urinary tract symptoms initiated in 1989–1990. From a sampling frame of Olmsted County, Minnesota, males aged 40–79 years by 1990, a sample of 5,135 men was randomly selected. Criteria were established to exclude men who had previously received surgical treatment for genitourinary conditions. Men were excluded if they had a history of prostate or bladder cancer or surgery or if they had other surgical or medical conditions other than BPH that could affect normal urinary function. Of the 3,874 men eligible, 2,115 agreed to participate (55 percent participation rate). From this group, a 25 percent random sample (n = 537) was invited to participate in a more detailed urologic study, and 471 men agreed to do so (88 percent participation rate) (20, 21). In 1992 and 1994, men lost to follow-up were replaced with men randomly selected from the community by using the same protocol as at baseline (22). Thus, this study was based on data for 510 baseline and replacement men who participated in the detailed urologic study in 1994.

Measurements

Baseline. At the baseline assessment in 1990, participants completed a previously validated study questionnaire that assessed lower urinary tract symptom severity using questions that approximated the American Urological Association Symptom Index (AUASI), and a composite AUASI was estimated (23). A standard uroflowmeter was used to measure urine flow rates in a standing position in private. Each subject underwent a blood draw to determine serum prostate-specific antigen (PSA) level prior to any prostatic manipulation. The remaining aliquots of blood were stored in a −70°C freezer. Subjects also underwent a digital rectal examination and a transrectal ultrasonography to estimate prostate volume. Men found to have prostate cancer on the basis of this evaluation and a biopsy confirmation were excluded from the study. Prostate volume was estimated from the anterior posterior, transverse, and superior inferior diameters of the transrectal ultrasound measurements by using the formula for a prolate ellipsoid (volume = 0.52(transverse × anterior posterior × superior inferior)) (24).

Follow-up. Follow-up assessments were performed biennially after the 1990 baseline assessment. At each, lower urinary tract symptom severity was estimated from questionnaire responses, and urine flow rates, serum PSA level, and prostate volume were determined by using the same protocol as at baseline. Acute urinary retention requiring catheterization and medical or surgical treatment for BPH were assessed from the study questionnaire and also from a detailed review of the participant’s community medical record through the date of last follow-up in 2000. Measurements of AUASI, peak urinary flow rate, prostate volume, and serum PSA level following surgical treatment for BPH were not included in the analyses.

Androgen receptor genotyping. DNA was extracted from the buffy-coat cell layer of blood samples obtained and stored at −70°C in 1994. The number of CAG and GGN repeats in the androgen receptor gene was determined by a polymerase chain reaction–based fragment analysis. Fluorescently labeled primers were applied to a standard polymerase chain reaction protocol and were cycled on a TETRAD thermocycler (MJ Research, Waltham, Massachusetts), with annealing temperatures of 55°C for CAG repeats and 58°C for GGN repeats. Each 15-µl polymerase chain reaction contained 15 ng of leukocyte DNA, 2 mM of magnesium chloride (MgCl2) 200 µl of deoxynucleotide triphosphates (dNTPs), 0.67 µM of each primer, and 0.5 U of
AmpliTaq Gold (Applied Biosystems, Foster City, California). The polymerase chain reaction products were resolved on an ABI 3100 DNA Sequencer (Applied Biosystems) and were analyzed by using Genotyper 3.1 (Applied Biosystems) software. The primers used for the CAG assays were as follows: forward—FAM/CCG AGG AGC TTT CCA GAA TC; reverse—tailed/TTG GGG AGA ACC ATC CTC AC. The GGN primers used were as follows: forward—FAM/ACA GCC GAA GAA GGC CAG TT; reverse—tailed/CCG AGT GTA GCC GTA GGG G.

**Quality control.** Accuracy of genotypes was assessed by comparing fragment (allele) size with an internal reference for each capillary and by the fragment sizes generated for control samples included in every plate. The 21 internal references ranged from 50 base pairs to 400 base pairs, labeled with ROX (Applied Biosystems). Controls included two known DNA samples and a blind control; if the controls failed to amplify, the entire data were rejected and the assays repeated. For the study, the control and reference peaks were 100 percent reproducible.

**Statistical analyses**

When all available longitudinal data were used, the worst measurement of a surrogate measure of BPH ever attained from baseline through 2000 was used to characterize men as ever having the BPH phenotype. BPH phenotype/events were defined as follows: AUASI >7 (moderate or severe lower urinary tract symptoms), peak urinary flow rate (Qmax) <12 ml/second (impaired peak flow rate), prostate volume >30 ml (enlarged prostate), serum PSA level >1.4 ng/ml (75th percentile for the cohort at baseline), or an acute urinary retention during follow-up. In addition, we examined associations with cutpoints based on the 75th and 25th percentiles from the baseline distributions of surrogate measures as well as cutpoints of AUASI >19 (severe lower urinary tract symptoms), peak urinary flow rate <10 ml/second, prostate volume >40 ml, and serum PSA level >2.5 ng/ml. The findings were robust to changes in cutpoint, and only one set of data are presented in this paper. Measurements following medical or surgical treatment for BPH were censored. For each surrogate measure, a slope was estimated for each participant from four longitudinal measurements from 1990 through 1996 as the annualized percentage change in the measure. Estimation of slope takes into account fluctuating values of a measure. A slope event for a surrogate measure was defined as a value exceeding the 75th percentile determined from the distribution of slopes for the entire cohort. Spearman’s correlation coefficients between androgen receptor genotype (number of CAG or GGN repeats) and BPH event (maximum value of AUASI, prostate volume, serum PSA level, minimum Qmax ever attained over approximately 10 years of follow-up of 510 men who participated at baseline. § Slope represents the annualized percentage change in the surrogate measure during follow-up.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (25th, 75th percentile)</th>
<th>Spearman’s correlation coefficient</th>
<th>Androgen receptor CAG</th>
<th>Androgen receptor GGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>51.4 (44.6, 61.2)</td>
<td>0.065</td>
<td>0.066</td>
<td>0.066</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>59.9 (53.6, 70.1)</td>
<td>0.062</td>
<td>0.070</td>
<td>0.070</td>
</tr>
<tr>
<td>BPH† surrogate measures‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUASI†</td>
<td>10.0 (6, 14)</td>
<td>0.089*</td>
<td>–0.082</td>
<td></td>
</tr>
<tr>
<td>Qmax† (ml/second)</td>
<td>12.8 (8.9, 17.9)</td>
<td>–0.065</td>
<td>–0.007</td>
<td></td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>33.2 (26.2, 41.7)</td>
<td>–0.011</td>
<td>–0.008</td>
<td></td>
</tr>
<tr>
<td>Serum PSA† level (ng/ml)</td>
<td>1.4 (0.8, 2.5)</td>
<td>–0.032</td>
<td>–0.019</td>
<td></td>
</tr>
<tr>
<td>Slope (%/year)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUASI</td>
<td>0.2 (–0.2, 0.8)</td>
<td>0.099*</td>
<td>–0.074</td>
<td></td>
</tr>
<tr>
<td>Qmax</td>
<td>–2.1 (–6.2, 2.0)</td>
<td>–0.011</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Prostate volume</td>
<td>1.2 (–1.5, 4.3)</td>
<td>0.054</td>
<td>–0.021</td>
<td></td>
</tr>
<tr>
<td>Serum PSA level</td>
<td>5.8 (0.0, 10.3)</td>
<td>0.012</td>
<td>0.012</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05 for test of the null hypothesis that the true correlation equals zero.
† BPH, benign prostatic hyperplasia; AUASI, American Urological Association Symptom Index; Qmax, peak urinary flow rate; PSA, prostate-specific antigen.
‡ Maximum AUASI, prostate volume, serum PSA level, and minimum Qmax ever attained over approximately 10 years of follow-up of 510 men who participated at baseline.
§ Slope represents the annualized percentage change in the surrogate measure during follow-up.
TABLE 2. Associations of BPH† surrogate measures with CAG repeat pattern for men (n = 510) in the Olmsted County Study, Olmsted County, Minnesota, 1990–2000

<table>
<thead>
<tr>
<th>BPH event‡</th>
<th>No. of CAG repeats§</th>
<th>No.</th>
<th>Median age (years) at BPH event†</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>Median age (years) at BPH event†</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>Median age (years) at BPH event†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUASI† &gt;7</td>
<td>≥24</td>
<td>324</td>
<td>1.0</td>
<td>63</td>
<td>1.1</td>
<td>0.8, 1.4</td>
<td>63</td>
<td>1.0</td>
<td>0.7, 1.3</td>
</tr>
<tr>
<td>Qmax† &lt;12 ml/second</td>
<td>227</td>
<td>1.0</td>
<td>71</td>
<td>0.9</td>
<td>0.6, 1.2</td>
<td>71</td>
<td>1.2</td>
<td>0.8, 1.6</td>
<td>69</td>
</tr>
<tr>
<td>Prostate volume &gt;30 ml</td>
<td>292</td>
<td>1.0</td>
<td>66</td>
<td>1.2</td>
<td>0.9, 1.5</td>
<td>65</td>
<td>1.4</td>
<td>1.0, 1.9*</td>
<td>62</td>
</tr>
<tr>
<td>Serum PSA† level &gt;1.4 ng/ml</td>
<td>252</td>
<td>1.0</td>
<td>69</td>
<td>1.1</td>
<td>0.8, 1.5</td>
<td>66</td>
<td>1.5</td>
<td>1.1, 2.0*</td>
<td>65</td>
</tr>
</tbody>
</table>

* p ≤ 0.05, hazard ratio significantly different from 1.0.
† BPH, benign prostatic hyperplasia; CI, confidence interval; AUASI, American Urological Association Symptom Index; Qmax, peak urinary flow rate; PSA, prostate-specific antigen.
‡ Defined as occurrence of AUASI >7, Qmax <12 ml/second, prostate volume >30 ml, or serum PSA level ≥1.4 ng/ml during follow-up.
§ Hazard ratios and 95% confidence intervals from Cox proportional hazards model, modeling age at BPH event as a function of CAG repeat pattern for men with 21–23 (n = 202) and <21 (n = 156) CAG repeats compared with ≥24 repeats (n = 147).
¶ Based on Kaplan-Meier survival curve.

RESULTS

The characteristics of the 510 men in the clinical cohort are presented in table 1. The median ages at baseline and at the last examination in 2000 were 51.4 and 59.9 years, respectively. The medians of the maximum AUASI, peak urinary flow rate, prostate volume, and serum PSA level attained during follow-up were 10.0, 12.8 ml/second, 33.2 ml, and 1.4 ng/ml, respectively. More than half of the cohort had an AUASI >7 (n = 324, 65 percent) and a prostate volume >30 ml (n = 292, 58 percent); 50 men (10 percent) had an AUASI >19, 227 (45 percent) had a peak urinary flow rate <12 ml/second, and 252 (50 percent) had a serum PSA level >1.4 ng/ml. Seventeen men (3 percent) developed an acute urinary retention during follow-up. The median annualized percentage change (slope) in surrogate measures of BPH was greatest for serum PSA level (5.8 percent per year), was lower for peak urinary flow rate (–2.1 percent per year) and prostate volume (1.2 percent per year), and was smallest for AUASI (0.2 percent per year) (table 1).

Association of number of CAG repeats with measures of BPH

A significant positive correlation was found between number of CAG repeats and AUASI (r = 0.09, p = 0.05) and AUASI slope (r = 0.10, p = 0.03) but not with peak urinary flow rate (r = –0.07), prostate volume (r = –0.01), or serum PSA level (r = –0.03) (table 1). The median (25th, 75th percentile) number of CAG repeats was 21 (20, 24) (figure 1). In Cox proportional hazards models, the risk of an enlarged prostate (volume >30 ml) increased with decreasing number of CAG repeats. Men with <21 CAG repeats were 1.4 times more likely to have an enlarged prostate compared with men with a repeat length of ≥24 (95 percent confidence interval: 1.0, 1.9); the risk of a serum PSA level >1.4 ng/ml was increased 1.5 times (95 percent CI: 1.1, 2.0) for men with <21 CAG repeats compared with ≥21 CAG repeats (table 2). The median age at assessment of an enlarged prostate or serum PSA level >1.4 ng/ml was 4 years earlier for men with <21 CAG repeats than for men with ≥24 repeats (table 2). In a model with CAG as a continuous variable, the risk of an enlarged prostate decreased 3 percent with each additional increase in CAG repeat (hazard ratio (HR) = 0.97, 95 percent CI: 0.93, 1.01), although the confidence interval included 1. When linear regression models were used, no significant associations were found between genotype and annualized percentage change in surrogate measures (slopes, data not presented). The risks of an acute urinary retention were not significantly associated with number of CAG repeats: 0.75 (95 percent CI: 0.3, 2.1) and 0.5 (95 percent CI: 0.1, 2.0) for men with 21–23 and <21 CAG repeats, respectively, compared with men with ≥24 CAG repeats.
The median (25th, 75th percentile) number of GGN repeats was 16 (16, 17) (figure 2). No significant correlations were observed between number of GGN repeats and surrogate measures of BPH (table 1). However, two surrogate measures of BPH were significantly associated with <16 GGN repeats (table 3). Compared with men with ≥17 GGN repeats, men with <16 GGN repeats were more likely to have an AUASI >7 (HR = 1.6, 95 percent CI: 1.1, 2.3) or a serum PSA level >1.4 ng/ml (HR = 1.5, 95 percent CI: 1.0, 2.3). The risk of a peak urinary flow rate <12 ml/second or a prostate volume >30 ml was also elevated for men with <16 GGN repeats, but the confidence intervals all included 1. Median age at BPH events was earlier in men with <16 GGN repeats compared with ≥17 repeats (n = 199).

Association of number of GGN repeats with measures of BPH

The median (25th, 75th percentile) number of GGN repeats was 16 (16, 17) (figure 2). No significant correlations were observed between number of GGN repeats and surrogate measures of BPH (table 1). However, two surrogate measures of BPH were significantly associated with <16 GGN repeats (table 3). Compared with men with ≥17 GGN repeats, men with <16 GGN repeats were more likely to have an AUASI >7 (HR = 1.6, 95 percent CI: 1.1, 2.3) or a serum PSA level >1.4 ng/ml (HR = 1.5, 95 percent CI: 1.0, 2.3). The risk of a peak urinary flow rate <12 ml/second or a prostate volume >30 ml was also elevated for men with <16 GGN repeats, but the confidence intervals all included 1. Median age at BPH events was earlier in men with <16 GGN repeats compared with men with ≥17 GGN repeats: 5, 7, 8, and 11 years earlier for an enlarged prostate, serum PSA level >1.4 ng/ml, peak urinary flow rate <12 ml/second, and AUASI, respectively. No significant associations were observed in linear regression models assessing the association between genotype and slopes (data not presented). No significant association was found between acute urinary retention and having 16 (HR = 2.1, 95 percent CI: 0.7, 5.9) or <16 (HR = 1.0, 95 percent CI: 0.1, 8.9) GGN repeats compared with ≥17 GGN repeats.

Association of number of CAG repeats and/or GGN repeats with measures of BPH

When a CAG repeat length of <21 and a GGN repeat length of <16 were considered simultaneously, 25 (5 percent) men had both, 149 (30 percent) men had only one, and 325 (65 percent) men had neither. Compared with men negative for both markers, men with both markers were at increased risk of all four surrogate measures of BPH; hazard ratios were 1.6 (95 percent CI: 1.0, 2.7) for an AUASI >7, 1.9 (95 percent CI: 1.1, 3.4) for a peak urinary flow rate <12 ml/second, 2.5 (95 percent CI: 1.5, 4.2) for a prostate volume >30 ml, and 2.8 (95 percent CI: 1.6, 4.7) for a serum PSA level >1.4 ng/ml (table 4). The risk for men with a single

![FIGURE 1. Distribution of androgen receptor gene CAG repeat polymorphism among men in the Olmsted County Study, Olmsted County, Minnesota, 1990–2000.](image1)

![FIGURE 2. Distribution of androgen receptor gene GGN repeat polymorphism among men in the Olmsted County Study, Olmsted County, Minnesota, 1990–2000.](image2)
marker did not differ significantly from that for men negative for both markers. BPH events occurred a median of 5–9 years earlier in men with two markers compared with men negative for both markers (table 4, figure 3). Men with two markers had a more rapid decrease in peak urinary flow rate than did men with no marker (HR = 3.1, 95 percent CI: 1.5, 6.5). The presence of one marker was not associated with an increased risk of acute urinary retention (HR = 0.71, 95 percent CI: 0.23, 2.19), whereas the risk associated with the presence of two markers could not be assessed because none of the men with two markers developed acute urinary retention.

**DISCUSSION**

The study findings are consistent with previous studies suggesting that polymorphisms in the androgen receptor gene may influence the development of BPH. The risk of BPH, as defined by our surrogate measures, was increased 1.6–2.8 times for men with both $<21\text{CAG}$ repeats and $<16\text{GGN}$ repeats, and BPH events occurred 5–9 years earlier than in men with neither. The effect of having both high-risk alleles was greater than the independent effects of either polymorphism. A high number of $\text{CAG}$ repeats has been associated with decreased transactivating activity of the androgen receptor and with decreased androgen receptor mRNA expression (1, 3), low virilization, and decreased fertility (1, 25). On the other hand, a small number of repeats has been associated with increased transcriptional activity of the androgen receptor, resulting in increased androgen receptor meditated effects, including prostate growth. It is conceivable that $\text{GGN}$ repeats could also influence the transcriptional activity of the androgen receptor gene. The rationale for evaluating the effects of having both high-risk alleles was based on the hypothesis that, since the androgen receptor is located on the X chromosome, there is only one copy of the gene. Thus, the presence of both high-risk alleles was based on the hypothesis that, since the androgen receptor is located on the X chromosome, there is only one copy of the gene. Thus, the presence of both high-risk alleles could result in sufficient shortening of the androgen receptor gene to considerably alter gene function. The impact on target genes, therefore, could exceed that due to the presence of just one polymorphism, or what would have been observed if the gene were located on an autosomal chromosome. To our knowledge, the association of number of $\text{GGN}$ repeats and BPH has not been examined extensively. Thus, the role of both a short $\text{GGN}$ repeat length and a short $\text{CAG}$ repeat length in the pathogenesis of BPH should be investigated further.

The findings suggest that the androgen receptor gene polymorphisms may be associated with prostate growth. The significant associations between a short number of repeats and an enlarged prostate or a serum PSA level $>1.4$ ng/ml.
may be indicative of an association with prostate size, with potential effects on the static obstruction component of BPH. Within the scope of this study, it was not possible to determine any associations with dynamic obstruction due to smooth muscle tone in the bladder neck, prostatic stroma, or prostate capsule. However, both the static and dynamic components of obstruction could contribute to irritative or obstructive lower urinary tract symptoms, impaired peak flow rate, or both. Therefore, the elevated risks of moderate or severe lower urinary tract symptoms (AUASI >7) and impaired peak flow rates (peak urinary flow rate <12 ml/second) observed for men with a short number of both \( CAG \) and \( GGN \) repeats in the present study support the hypothesis that these polymorphisms could influence prostatic growth.

The report of decreased androgen receptor activity with deletion of the entire \( GGN \) repeat segment (4) is inconsistent with our findings. Possibly, shortening of the repeat segment as opposed to deletion of an entire segment has different effects on the transactivating function of the gene. Although the association between \( GGN \) repeat length and BPH has not received much attention, the association with prostate cancer has been examined by several investigators (5–7, 9, 26). A \( GGN \) repeat length of \( \leq 16 \) (5, 6) and a \( GGN \) repeat length of 23 (7) have been associated with an increased risk of prostate cancer. Since prostate cancer and BPH are different conditions, the associations observed with prostate cancer may not be the same as with BPH. Nonetheless, the distribution of \( GGN \) repeat length in the present study is comparable to other studies (5, 26), but the median of 16 is shorter than the median of 23 reported in certain others (7, 27).

The relation between number of \( CAG \) repeats and prostate size in men without prostate cancer has been reported consistently in the literature. The present study findings are in keeping with reports of an inverse association between number of \( CAG \) repeats and self-report of an enlarged prostate (11), moderate or severe lower urinary tract symptoms (11), or surgery for BPH (11, 12). Mitsumori et al. (10) also observed a significant decrease in number of \( CAG \) repeats with increasing adenoma weight. Men in the fourth quartile of adenoma size had fewer \( CAG \) repeats than men in the first quartile and men with no BPH. Shibata et al. (28) also reported a reduced risk of prostatic enlargement with longer \( CAG \) repeat length. However, study subjects were men with prostate cancer; thus, relevance of the findings to BPH is not clear. On the other hand, Bousema et al. (14) found no difference in the mean number of \( CAG \) repeats between BPH patients and controls. Use of a convenience group as controls could have biased the study findings because convenience samples may not be representative of the population being studied. Similarly, Schatzl et al. (13) found no significant differences in mean AUASI, peak urinary flow rate, or prostate volume across four groups of men categorized by increasing number of \( CAG \) repeats and no significant trend in serum PSA level across increasing \( CAG \) repeat length. Mononen et al. (29) also found no difference in mean number of \( CAG \) repeats between men with BPH and controls in a prostate cancer study. They reported that, compared with controls, men with BPH were less likely to have a short \( CAG \) repeat length. However, control DNA had been obtained from anonymous, healthy, male blood donors. Since the BPH status of these men is not known, the relevance of the association is not clear.

It is important to recognize certain potential limitations of the study findings. BPH is likely a multifactorial condition influenced by several genes. While we did not investigate other genes, our findings provide insights into a potential role of androgen receptor gene polymorphisms in the pathogenesis of BPH. Another potential limitation is that the high prevalence of BPH in the study cohort may have precluded the ability to demonstrate significant differences between BPH and each polymorphism. This high prevalence is realistic, however. Estimates based on recommendations from the Agency for Health Care Policy and Research in 1995 suggested that 17 percent, 27 percent, and 35 percent of men aged 50–59, 60–69, and 70–79 years, respectively, would be eligible to discuss treatment options for BPH (30). The baseline response rate for the entire cohort suggests a potential for nonparticipation bias. Although participants were slightly older and had slightly more urologic conditions than nonparticipants did (31), these baseline differences have had no impact on long-term outcomes during follow-up (32). Furthermore, it is unlikely that participation would be related to androgen receptor genotype. The lack of an association between acute urinary retention (a hard outcome of BPH) and number of \( CAG \) or \( GGN \) repeats may be in part due to the lack of power. Longer follow-up of the cohort may yield more BPH events and thereby provide greater precision and increased power to detect significant differences.

In conclusion, these findings suggest that the presence of both a low number of \( CAG \) repeats and a low number of \( GGN \) repeats in the androgen receptor gene may be associated with an increased risk of surrogate measures of BPH. The consistency of the elevated risks across all four surrogate measures of BPH suggests that the associations should be investigated further.

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The association between androgen receptor gene polymorphisms and benign prostatic hyperplasia was investigated among 510 men randomly selected from Olmsted County, Minnesota. From 1990 through 2000, lower urinary tract symptom severity was assessed by the American Urological Association Symptom Index (AUASI), and peak urinary flow rate, prostate volume, and serum prostate-specific antigen level were measured. Androgen receptor CAG and GGN genotyping was performed. A CAG repeat length of <21 was associated with an enlarged prostate (hazard ratio (HR) = 1.4, 95% confidence interval (CI): 1.0, 1.9) and a serum prostate-specific antigen level >1.4 ng/ml (HR = 1.5, 95% CI: 1.1, 2.0). A GGN repeat length of <16 was associated with an AUASI >7 (HR = 1.6, 95% CI: 1.1, 2.3) and a serum prostate-specific antigen level >1.4 ng/ml (HR = 1.5, 95% CI: 1.0, 2.3). Having <21 CAG repeats and <16 GGN repeats compared with having neither was associated with an enlarged prostate (HR = 2.5, 95% CI: 1.5, 4.2), a serum prostate-specific antigen level >1.4 ng/ml (HR = 2.8, 95% CI: 1.6, 4.7), a peak flow rate <12 ml/second (HR = 1.9, 95% CI: 1.1, 3.4), and an AUASI >7 (HR = 1.6, 95% CI: 1.0, 2.7). Androgen receptor gene polymorphisms may have a potential role in the pathogenesis of benign prostatic hyperplasia.

cohort studies; polymorphism (genetics); prostate; prostatic hyperplasia; receptors, androgen; risk factors; signs and symptoms; urinary retention

Abbreviations: AUASI, American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

Benign prostatic hyperplasia (BPH) is a condition affecting a large percentage of elderly men. To date, the only established risk factors are age and an intact androgen system. It is hypothesized that age-related changes in both androgens and estrogens could influence the development of BPH. However, the specific pathophysiologic mechanisms by which androgens influence the development of symptomatic BPH in aging males are not clear. Associations between serum androgen levels and BPH-related symptoms have not been consistent possibly because serum androgen levels may not reflect intracellular levels. The effects of androgens on prostatic tissue are mediated by the androgen receptor through the androgen receptor-androgen complex, at the intracellular level. Thus, intracellular factors that affect either intracellular androgen levels or the androgen receptor, or both, may be important in the pathogenesis of BPH.

Variations in the androgen receptor gene may influence androgenic action and thereby influence prostatic growth and other BPH-related outcomes. Two main polymorphisms in the androgen receptor gene, a variable CAG repeat that encodes a polyglutamine repeat and a variable GGN repeat that encodes a polyglycine repeat, have been described previously. Both are located in exon 1, at the NH2-transactivation domain terminal of the gene. A short CAG repeat length has been associated with increased androgen receptor transcriptional activity (1, 2), and a long CAG repeat length

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has been associated with reduced androgen receptor expression (3). Therefore, it is hypothesized that a low number of repeats may increase the risk of BPH.

The functional effects of the GGN repeat polymorphisms on androgen receptor transactivation are not clear. In one study, deletion of the entire GGN repeat segment of the gene was associated with decreased transactivating action of the gene (4). In epidemiologic studies, inconsistent associations with prostate cancer, including an increased risk of prostate cancer for men with a short number of GGN repeats (5, 6), with 16 repeats (7), or with a high number of GGN repeats (8, 9), have been reported. To our knowledge, although no association has been reported between number of GGN repeats and BPH, the importance of the androgen receptor in BPH, and the reported associations between number of GGN repeats and prostate cancer (also hormonally mediated), suggest that the association with BPH needs to be investigated.

Findings from previous studies investigating the association of CAG and androgen receptor gene polymorphisms with BPH have been inconsistent. While some studies have reported an association between BPH and short CAG repeat length (10–12), others have reported no association (13, 14). Differences in the criteria used to define BPH or a narrow disease spectrum among BPH study subjects may have contributed to these inconsistencies. Use of different criteria, including surgery for treatment of BPH (11, 12), self-reported history of an enlarged prostate (11), prostate adenoma weight (10), and lower urinary tract symptom severity (11), makes it difficult to compare findings across studies. Studies based on men from clinical series present a potential for referral bias due to a narrow disease spectrum from overrepresentation of men with severe symptoms. In contrast, a randomly selected cohort provides a representative cohort with a broad disease spectrum. In recent years, a number of surrogate measures have been used to characterize BPH. However, because of variability in these surrogate measures, particularly symptom severity (15, 16) and peak urinary flow rate (17, 18), a single cross-sectional measurement may not correctly identify men with BPH, and evaluation of the association between androgen receptor gene polymorphisms and the BPH phenotype may not be valid. The current study evaluated the association of CAG and GGN repeat length polymorphisms in the androgen receptor gene and surrogate measures of BPH using multiple measurements assessed prospectively in a cohort of community-dwelling men.

MATERIALS AND METHODS

Many details of the study design have been published previously (19, 20). Briefly, subjects were participants in a longitudinal study of lower urinary tract symptoms initiated in 1989–1990. From a sampling frame of Olmsted County, Minnesota, males aged 40–79 years by 1990, a sample of 5,135 men was randomly selected. Criteria were established to exclude men who had previously received surgical treatment for genitourinary conditions. Men were excluded if they had a history of prostate or bladder cancer or surgery or if they had other surgical or medical conditions other than BPH that could affect normal urinary function. Of the 3,874 men eligible, 2,115 agreed to participate (55 percent participation rate). From this group, a 25 percent random sample (n = 537) was invited to participate in a more detailed urologic study, and 471 men agreed to do so (88 percent participation rate) (20, 21). In 1992 and 1994, men lost to follow-up were replaced with men randomly selected from the community by using the same protocol as at baseline (22). Thus, this study was based on data for 510 baseline and replacement men who participated in the detailed urologic study in 1994.

Measurements

Baseline. At the baseline assessment in 1990, participants completed a previously validated study questionnaire that assessed lower urinary tract symptom severity using questions that approximated the American Urological Association Symptom Index (AUASI), and a composite AUASI was estimated (23). A standard uroflowmeter was used to measure urine flow rates in a standing position in private. Each subject underwent a blood draw to determine serum prostate-specific antigen (PSA) level prior to any prostatic manipulation. The remaining aliquots of blood were stored in a −70°C freezer. Subjects also underwent a digital rectal examination and a transrectal ultrasonography to estimate prostate volume. Men found to have prostate cancer on the basis of this evaluation and a biopsy confirmation were excluded from the study. Prostate volume was estimated from the anterior posterior, transverse, and superior inferior diameters of the transrectal ultrasound measurements by using the formula for a prolate ellipsoid (volume = 0.52(transverse × anterior posterior × superior inferior)) (24).

Follow-up. Follow-up assessments were performed biennially after the 1990 baseline assessment. At each, lower urinary tract symptom severity was estimated from questionnaire responses, and urine flow rates, serum PSA level, and prostate volume were determined by using the same protocol as at baseline. Acute urinary retention requiring catheterization and medical or surgical treatment for BPH were assessed from the study questionnaire and also from a detailed review of the participant’s community medical record through the date of last follow-up in 2000. Measurements of AUASI, peak urinary flow rate, prostate volume, and serum PSA level following surgical treatment for BPH were not included in the analyses.

Androgen receptor genotyping. DNA was extracted from theuffy-coat cell layer of blood samples obtained and stored at −70°C in 1994. The number of CAG and GGN repeats in the androgen receptor gene was determined by a polymerase chain reaction–based fragment analysis. Fluorescently labeled primers were applied to a standard polymerase chain reaction protocol and were cycled on a TETRAD thermocycler (MJ Research, Waltham, Massachusetts), with annealing temperatures of 55°C for CAG repeats and 58°C for GGN repeats. Each 15-µl polymerase chain reaction contained 15 ng of leukocyte DNA, 2 mM of magnesium chloride (MgCl₂), 200 µl of deoxynucleotide triphosphates (dNTPs), 0.67 µM of each primer, and 0.5 U of...
Androgen Receptor Polymorphisms and BPH

AmpliTaq Gold (Applied Biosystems, Foster City, California). The polymerase chain reaction products were resolved on an ABI 3100 DNA Sequencer (Applied Biosystems) and were analyzed by using Genotyper 3.1 (Applied Biosystems) software. The primers used for the CAG assays were as follows: forward—FAM/CCG AGG AGC TTT CCA GAA TC; reverse—tailed/TTG GGG AGA ACC ATC CTC AC. The GGN primers used were as follows: forward—FAM/ACA GCC GAA GAA GGC CAG TT; reverse—tailed/CCG AGT GTA GCC GTA GGG G.

Quality control. Accuracy of genotypes was assessed by comparing fragment (allele) size with an internal reference for each capillary and by the fragment sizes generated for control samples included in every plate. The 21 internal references ranged from 50 base pairs to 400 base pairs, labeled with ROX (Applied Biosystems). Controls included two known DNA samples and a blind control; if the controls failed to amplify, the entire data were rejected and the assays repeated. For the study, the control and reference peaks were 100 percent reproducible.

Statistical analyses

When all available longitudinal data were used, the worst measurement of a surrogate measure of BPH ever attained from baseline through 2000 was used to characterize men as ever having the BPH phenotype. BPH phenotype/events were defined as follows: AUASI >7 (moderate or severe lower urinary tract symptoms), peak urinary flow rate (Qmax) <12 ml/second (impaired peak flow rate), prostate volume >30 ml (enlarged prostate), serum PSA level >1.4 ng/ml (75th percentile for the cohort at baseline), or an acute urinary retention during follow-up. In addition, we examined associations with cutpoints based on the 75th and 25th percentiles from the baseline distributions of surrogate measures as well as cutpoints of AUASI >19 (severe lower urinary tract symptoms), peak urinary flow rate <10 ml/second, prostate volume >40 ml, and serum PSA level >2.5 ng/ml. The findings were robust to changes in cutpoint, and only one set of data are presented in this paper. Measurements following medical or surgical treatment for BPH were censored. For each surrogate measure, a slope was estimated for each participant from four longitudinal measurements from 1990 through 1996 as the annualized percentage change in the measure. Estimation of slope takes into account fluctuating values of a measure. A slope event for a surrogate measure was defined as a value exceeding the 75th percentile determined from the distribution of slopes for the entire cohort. Spearman’s correlation coefficients between androgen receptor genotype (number of CAG or GGN repeats) and BPH event (maximum value of AUASI, prostate volume, serum PSA level, minimum peak urinary flow rate) were assessed.

Associations of androgen receptor genotype with age at first BPH event were assessed by using life table methods. Hazard ratios and 95 percent confidence intervals were estimated for each BPH event by using Cox proportional hazards models, modeling the hazard ratio for a BPH event from age 40 years, for genotype subgroups. Since age is strongly related to BPH, age, as opposed to time on study, was used as the time scale. Time in this study was arbitrary since the cohort was not being followed subsequent to a...
diagnosis or initiation of treatment but rather consisted of a random group of men whose follow-up began from ages 40 to 79 years. The probability of a BPH event was also compared for genotype subgroups by using Kaplan-Meier survival curve methods. The median age at onset of a BPH event for each genotype subgroup was estimated from the curves as the age at which 50 percent of the group had attained the particular BPH event. Men were categorized into three genotype groups based on number of CAG repeats: <21 (<50th percentile), 21–23 (50th–<75th percentile), and ≥24 (≥75th percentile, reference group). For GGN genotype, men were categorized by number of GGN repeats: <16 (<10th percentile), 16 (10th–<75th percentile), and ≥17 (≥75th percentile, reference group). The robustness of these associations was examined in models using different cutoffpoints made at the median or the tertiles and with the repeat length as a continuous variable. The associations between genotype and annualized percentage change in BPH surrogate measures (slopes) were investigated by using linear regression methods, with adjustment for age.

RESULTS

The characteristics of the 510 men in the clinical cohort are presented in table 1. The median ages at baseline and at the last examination in 2000 were 51.4 and 59.9 years, respectively. The medians of the maximum AUASI, peak urinary flow rate, prostate volume, and serum PSA level attained during follow-up were 10.0, 12.8 ml/second, 33.2 ml, and 1.4 ng/mL, respectively. More than half of the cohort had an AUASI >7 (n = 324, 65 percent) and a prostate volume >30 ml (n = 292, 58 percent); 50 men (10 percent) had an AUASI >19, 227 (45 percent) had a peak urinary flow rate <12 ml/second, and 252 (50 percent) had a serum PSA level >1.4 ng/mL. Seventeen men (3 percent) developed an acute urinary retention during follow-up. The median annualized percentage change (slope) in surrogate measures of BPH was greatest for serum PSA level (5.8 percent per year), was lower for peak urinary flow rate (~2.1 percent per year) and prostate volume (1.2 percent per year), and was smallest for AUASI (0.2 percent per year) (table 1).

Association of number of CAG repeats with measures of BPH

A significant positive correlation was found between number of CAG repeats and AUASI (r = 0.09, p = 0.05) and AUASI slope (r = 0.10, p = 0.03) but not with peak urinary flow rate (r = −0.07), prostate volume (r = −0.01), or serum PSA level (r = −0.03) (table 1). The median (25th, 75th percentile) number of CAG repeats was 21 (20, 24) (figure 1). In Cox proportional hazards models, the risk of an enlarged prostate (volume >30 ml) increased with decreasing number of CAG repeats. Men with <21 CAG repeats were 1.4 times more likely to have an enlarged prostate compared with men with a repeat length of ≥24 (95 percent confidence interval (CI): 1.0, 1.9); the risk of a serum PSA level >1.4 ng/mL was increased 1.5 times (95 percent CI: 1.1, 2.0) for men with <21 CAG repeats compared with ≥21 CAG repeats (table 2). The median age at assessment of an enlarged prostate or serum PSA level >1.4 ng/mL was 4 years earlier for men with <21 CAG repeats than for men with ≥24 repeats (table 2). In a model with CAG as a continuous variable, the risk of an enlarged prostate decreased 3 percent with each additional increase in CAG repeat (hazard ratio (HR) = 0.97, 95 percent CI: 0.93, 1.01), although the confidence interval included 1. When linear regression models were used, no significant associations were found between genotype and annualized percentage change in surrogate measures (slopes, data not presented). The risks of an acute urinary retention were not significantly associated with number of CAG repeats: 0.75 (95 percent CI: 0.3, 2.1) and 0.5 (95 percent CI: 0.1, 2.0) for men with 21–23 and <21 CAG repeats, respectively, compared with men with ≥24 CAG repeats.

### TABLE 2: Associations of BPH† surrogate measures with CAG repeat pattern for men (n = 510) in the Olmsted County Study, Olmsted County, Minnesota, 1990–2000

<table>
<thead>
<tr>
<th>BPH event‡</th>
<th>No.</th>
<th>≥24</th>
<th>21–23</th>
<th>&lt;21</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUASI† &gt;7</td>
<td>324</td>
<td>1.0</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Qmax† &lt;12 ml/second</td>
<td>227</td>
<td>1.0</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Prostate volume &gt;30 ml</td>
<td>292</td>
<td>1.0</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Serum PSA† level &gt;1.4 ng/ml</td>
<td>252</td>
<td>1.0</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>Median age (years) at BPH event†</th>
<th>Hazard ratio</th>
<th>Median age (years) at BPH event†</th>
<th>Hazard ratio</th>
<th>Median age (years) at BPH event†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>63</td>
<td>1.1</td>
<td>0.8, 1.4</td>
<td>1.0</td>
<td>0.7, 1.3</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>71</td>
<td>0.6</td>
<td>1.2, 1.2</td>
<td>1.2</td>
<td>0.8, 1.6</td>
</tr>
<tr>
<td>Prostate volume &gt;30 ml</td>
<td></td>
<td></td>
<td>1.2</td>
<td>0.9, 1.5</td>
<td>1.4</td>
<td>1.0, 1.9*</td>
</tr>
<tr>
<td>Serum PSA† level &gt;1.4 ng/ml</td>
<td></td>
<td></td>
<td>1.1</td>
<td>0.8, 1.5</td>
<td>1.5</td>
<td>1.1, 2.0*</td>
</tr>
</tbody>
</table>

* p ≤ 0.05, hazard ratio significantly different from 1.0.
† BPH, benign prostatic hyperplasia; CI, confidence interval; AUASI, American Urological Association Symptom Index; Qmax, peak urinary flow rate; PSA, prostate-specific antigen.
‡ Defined as occurrence of AUASI >7, Qmax <12 ml/second, prostate volume >30 ml, or serum PSA level ≥1.4 ng/mL during follow-up.
§ Hazard ratios and 95% confidence intervals from Cox proportional hazards model, modeling age at BPH event as a function of CAG repeat pattern for men with 21–23 (n = 202) and <21 (n = 156) CAG repeats compared with ≥24 repeats (n = 147).
¶ Based on Kaplan-Meier survival curve.
Association of number of GGN repeats with measures of BPH

The median (25th, 75th percentile) number of GGN repeats was 16 (16, 17) (figure 2). No significant correlations were observed between number of GGN repeats and surrogate measures of BPH (table 1). However, two surrogate measures of BPH were significantly associated with <16 GGN repeats. Compared with men with ≥17 GGN repeats, men with <16 GGN repeats were more likely to have an AUASI >7 (HR = 1.6, 95 percent CI: 1.1, 2.3) or a serum PSA level >1.4 ng/ml (HR = 1.5, 95 percent CI: 1.0, 2.3). The risk of a peak urinary flow rate <12 ml/second or a prostate volume >30 ml was also elevated for men with <16 GGN repeats, but the confidence intervals all included 1. Median age at BPH events was earlier in men with <16 GGN repeats compared with ≥17 repeats (n = 199).

Association of number of CAG repeats and/or GGN repeats with measures of BPH

When a CAG repeat length of <21 and a GGN repeat length of <16 were considered simultaneously, 25 (5 percent) men had both, 149 (30 percent) men had only one, and 325 (65 percent) men had neither. Compared with men negative for both markers, men with both markers were at increased risk of all four surrogate measures of BPH: hazard ratios were 1.6 (95 percent CI: 1.0, 2.7) for an AUASI >7, 1.9 (95 percent CI: 1.1, 3.4) for a peak urinary flow rate <12 ml/second, 2.5 (95 percent CI: 1.5, 4.2) for a prostate volume >30 ml, and 2.8 (95 percent CI: 1.6, 4.7) for a serum PSA level >1.4 ng/ml (table 4). The risk for men with a single
marker did not differ significantly from that for men negative for both markers. BPH events occurred a median of 5–9 years earlier in men with two markers compared with men negative for both markers (table 4, figure 3). Men with two markers had a more rapid decrease in peak urinary flow rate than did men with no marker (HR = 3.1, 95 percent CI: 1.5, 6.5). The presence of one marker was not associated with an increased risk of acute urinary retention (HR = 0.71, 95 percent CI: 0.23, 2.19), whereas the risk associated with the presence of two markers could not be assessed because none of the men with two markers developed acute urinary retention.

**DISCUSSION**

The study findings are consistent with previous studies suggesting that polymorphisms in the androgen receptor gene may influence the development of BPH. The risk of BPH, as defined by our surrogate measures, was increased 1.6–2.8 times for men with both <21 \( CAG \) repeats and <16 \( GGN \) repeats, and BPH events occurred 5–9 years earlier than in men with neither. The effect of having both high-risk alleles was greater than the independent effects of either polymorphism. A high number of \( CAG \) repeats has been associated with decreased transactivating activity of the androgen receptor and with decreased androgen receptor mRNA expression (1, 3), low virilization, and decreased fertility (1, 25). On the other hand, a small number of repeats has been associated with increased transcriptional activity of the androgen receptor, resulting in increased androgen receptor mediated effects, including prostate growth. It is conceivable that \( GGN \) repeats could also influence the transcriptional activity of the androgen receptor gene. The rationale for evaluating the effects of having both high-risk alleles was based on the hypothesis that, since the androgen receptor is located on the X chromosome, there is only one copy of the gene. Thus, the presence of both high-risk alleles was based on the hypothesis that, since the androgen receptor is located on the X chromosome, there is only one copy of the gene. Thus, the presence of both high-risk alleles could result in sufficient shortening of the androgen receptor gene to considerably alter gene function. The impact on target genes, therefore, could exceed that due to the presence of just one polymorphism, or what would have been observed if the gene were located on an autosomal chromosome. To our knowledge, the association of number of \( GGN \) repeats and BPH has not been examined extensively. Thus, the role of both a short \( GGN \) repeat length and a short \( CAG \) repeat length in the pathogenesis of BPH should be investigated further.

The findings suggest that the androgen receptor gene polymorphisms may be associated with prostate growth. The significant associations between a short number of repeats and an enlarged prostate or a serum PSA level >1.4 ng/ml

<table>
<thead>
<tr>
<th>BPH event‡</th>
<th>No. of high-risk patterns§</th>
<th>Hazard ratio</th>
<th>Median age (years) at BPH event¶</th>
<th>95% CI†</th>
<th>Median age (years) at BPH event¶</th>
<th>Hazard ratio</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUASI &gt;7</td>
<td>0</td>
<td>1.0</td>
<td>63</td>
<td>0.9</td>
<td>0.7, 1.2</td>
<td>63</td>
<td>1.6</td>
</tr>
<tr>
<td>Qmax &lt;12 ml/second</td>
<td>1</td>
<td>1.0</td>
<td>71</td>
<td>1.1</td>
<td>0.9, 1.5</td>
<td>70</td>
<td>1.9</td>
</tr>
<tr>
<td>Prostate volume &gt;30 ml</td>
<td>1</td>
<td>1.0</td>
<td>65</td>
<td>1.1</td>
<td>0.8, 1.4</td>
<td>64</td>
<td>2.5</td>
</tr>
<tr>
<td>Serum PSA† &gt;1.4 ng/ml</td>
<td>1</td>
<td>1.0</td>
<td>67</td>
<td>1.2</td>
<td>0.9, 1.6</td>
<td>66</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* \( p \leq 0.05 \), hazard ratio significantly different from 1.0.
† BPH, benign prostatic hyperplasia; CI, confidence interval; AUASI, American Urological Association Symptom Index; Qmax, peak urinary flow rate; PSA, prostate-specific antigen.
‡ Defined as occurrence of AUASI >7, Qmax <12 ml/second, prostate volume >30 ml, or serum PSA level >1.4 ng/ml during follow-up.
§ Hazard ratios and 95% confidence intervals from Cox proportional hazards model, modeling age at BPH event as a function of the number of high-risk patterns (\( CAG <21 \), \( GGN <16 \)) for men with 1 \((n = 149)\) and 2 \((n = 25)\) compared with 0 \((n = 325)\) high-risk patterns.
¶ Based on Kaplan-Meier survival curve.

**FIGURE 3.** Cumulative probability of a benign prostatic hyperplasia event using 1-Kaplan-Meier. a) Prostate volume >30 ml, b) serum prostate-specific antigen level >1.4 ng/ml, c) peak urinary flow rate <12 ml/second, and d) American Urological Association Symptom Index >7 for men with 0, 1, or 2 markers (neither, \( CAG \) repeat length of <21 or \( GGN \) repeat length of <16, or both, respectively), Olmsted County Study, Olmsted County, Minnesota, 1990–2000.
may be indicative of an association with prostate size, with potential effects on the static obstruction component of BPH. Within the scope of this study, it was not possible to determine any associations with dynamic obstruction due to smooth muscle tone in the bladder neck, prostatic stroma, or prostate capsule. However, both the static and dynamic components of obstruction could contribute to irritative or obstructive lower urinary tract symptoms, impaired peak flow rate, or both. Therefore, the elevated risks of moderate or severe lower urinary tract symptoms (AUASI >7) and impaired peak flow rates (peak urinary flow rate <16 ml/second) observed for men with a short number of both CAG and GGN repeats in the present study support the hypothesis that these polymorphisms could influence prostatic growth.

The report of decreased androgen receptor activity with deletion of the entire GGN repeat segment (4) is inconsistent with our findings. Possibly, shortening of the repeat segment as opposed to deletion of an entire segment has different effects on the transactivating function of the gene. Although the association between GGN repeat length and BPH has not received much attention, the association with prostate cancer has been examined by several investigators (5–7, 9, 26). A GGN repeat length of ≤16 (5, 6) and a GGN repeat length of 23 (7) have been associated with an increased risk of prostate cancer. Since prostate cancer and BPH are different conditions, the associations observed with prostate cancer may not be the same as with BPH. Nonetheless, the distribution of GGN repeat length in the present study is comparable to other studies (5, 26), but the median of 16 is shorter than the median of 23 reported in certain others (7, 27).

The relation between number of CAG repeats and prostate size in men without prostate cancer has not been reported consistently in the literature. The present study findings are in keeping with reports of an inverse association between number of CAG repeats and self-report of an enlarged prostate (11), moderate or severe lower urinary tract symptoms (11), or surgery for BPH (11, 12). Mitsumori et al. (10) also observed a significant decrease in number of CAG repeats with increasing adenoma weight. Men in the fourth quartile of adenoma size had fewer CAG repeats than men in the first quartile and men with no BPH. Shibata et al. (28) also reported a reduced risk of prostatic enlargement with longer CAG repeat length. However, study subjects were men with prostate cancer; thus, relevance of the findings to BPH is not clear. On the other hand, Bouwema et al. (14) found no difference in the mean number of CAG repeats between BPH patients and controls. Use of a convenience group as controls could have biased the study findings because convenience samples may not be representative of the population being studied. Similarly, Schatzl et al. (13) found no significant differences in mean AUASI, peak urinary flow rate, or prostate volume across four groups of men categorized by increasing number of CAG repeats and no significant trend in serum PSA level across increasing CAG repeat length. Mononen et al. (29) also found no difference in mean number of CAG repeats between men with BPH and controls in a prostate cancer study. They reported that, compared with controls, men with BPH were less likely to have a short CAG repeat length. However, control DNA had been obtained from anonymous, healthy, male blood donors. Since the BPH status of these men is not known, the relevance of the association is not clear.

It is important to recognize certain potential limitations of the study findings. BPH is likely a multifactorial condition influenced by several genes. While we did not investigate other genes, our findings provide insights into a potential role of androgen receptor gene polymorphisms in the pathogenesis of BPH. Another potential limitation is that the high prevalence of BPH in the study cohort may have precluded the ability to demonstrate significant differences between BPH and each polymorphism. This high prevalence is realistic, however. Estimates based on recommendations from the Agency for Health Care Policy and Research in 1995 suggested that 17 percent, 27 percent, and 35 percent of men aged 50–59, 60–69, and 70–79 years, respectively, would be eligible to discuss treatment options for BPH (30). The baseline response rate for the entire cohort suggests a potential for nonparticipation bias. Although participants were slightly older and had slightly more urologic conditions than nonparticipants did (31), these baseline differences have had no impact on long-term outcomes during follow-up (32). Furthermore, it is unlikely that participation would be related to androgen receptor genotype. The lack of an association between acute urinary retention (a hard outcome of BPH) and number of CAG or GGN repeats may be in part due to the lack of power. Longer follow-up of the cohort may yield more BPH events and thereby provide greater precision and increased power to detect significant differences.

In conclusion, these findings suggest that the presence of both a low number of CAG repeats and a low number of GGN repeats in the androgen receptor gene may be associated with an increased risk of surrogate measures of BPH. The consistency of the elevated risks across all four surrogate measures of BPH suggests that the associations should be investigated further.

ACKNOWLEDGMENTS

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