Genetic Sequence Variants are Associated with Severity of Lower Urinary Tract Symptoms and Prostate Cancer Susceptibility

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Purpose: While a clear heritable component underlies lower urinary tract symptoms and benign prostatic hyperplasia, few studies have identified specific genetic factors. In contrast, recent genome-wide association studies identified single nucleotide polymorphisms that increase prostate cancer risk. Some of these single nucleotide polymorphisms may also predispose to surgical intervention for benign prostatic hyperplasia. We determined whether these single nucleotide polymorphisms are also associated with lower urinary tract symptom severity and benign prostatic hyperplasia medication use.

Materials and Methods: The genotypes of 38 single nucleotide polymorphisms previously associated with prostate cancer risk were determined for 1,168 healthy white male volunteers. American Urological Association symptom index score and medication for benign prostatic hyperplasia were documented prospectively. Statistical analyses were done to compare the frequency of the single nucleotide polymorphisms with American Urological Association symptom index and benign prostatic hyperplasia medication use.

Results: Several single nucleotide polymorphisms, including rs2736098 on chromosome 5p15, showed a significant relationship with benign prostatic hyperplasia medication. After adjusting for the other genetic variants, patient age and medication use, rs1571801 on chromosome 9q33.2 (OR 1.31, 95% CI 1.0–1.74) and rs5945572 on chromosome Xp11 (OR 1.28, 95% CI 1.04–1.59) were significantly associated with increased urinary symptoms. In contrast, rs445114 on chromosome 8q24 was marginally associated with decreased urinary symptoms (OR 0.83, 95% CI 0.66–1.01).

Conclusions: Of 38 single nucleotide polymorphisms that predispose to prostate cancer we identified 3 that are also associated with a well characterized lower urinary tract symptom phenotype. These single nucleotide polymorphisms may aid in the improved characterization of men with lower urinary tract symptoms/benign prostatic hyperplasia.

Key Words: prostate; prostatic neoplasms; prostatic hyperplasia; polymorphism, single nucleotide; lower urinary tract symptoms

Abbreviations and Acronyms

5ARI = 5α-reductase inhibitor
AUA-SI = American Urological Association symptom index
BPH = benign prostatic hyperplasia
GWAS = genome-wide association study
LMTK2 = lemur tyrosine kinase 2
LUTS = lower urinary tract symptoms
PCa = prostate cancer
PSA = prostate specific antigen
SNP = single nucleotide polymorphism

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SUBSTANTIAL evidence suggests a strong genetic component underlying common prostatic diseases such as PCa and BPH.[1–5] PCa is considered one of the most heritable diseases.[6] The relative risk of the disease is more than twofold higher in first-degree relatives of affected men.[7] Similarly, evi-

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dence suggests strong genetic components to BPH and LUTS.[3] For example, in a case-control study in which participants underwent surgery for LUTS secondary to BPH there was a fourfold to sixfold increased age specific risk of surgery for benign prostate disease among all male relatives of cases.[4] In addition, monozygotic twin concordance rates of 63% and 26% were observed for LUTS and BPH, respectively, and 1 study estimated that genetic factors may contribute as much as 72% to the risk of moderate or severe LUTS in older men.[1,3] Despite these findings, to our knowledge no group has documented a genetic variant that is reproducibly involved in susceptibility to bothersome LUTS related to BPH.

A powerful approach for identifying the genetic loci involved in complex diseases is by a GWAS.[8] Recently a GWAS identified more than 35 SNPs associated with PCa susceptibility in men of European ancestry.[9] Each SNP was independently associated with a modestly increased risk of PCa diagnosis relative to the general population (OR 1.1–1.8).[9] However, there is a strong cumulative relationship among these SNPs.[10] Interestingly, recent studies showed that some of these SNPs are associated with aggressive or nonaggressive PCa variants.[11–13]

Excluding the mentioned studies of PCa, almost no studies have been performed to identify heritable factors involved in other prostatic diseases, including male LUTS/BPH. In a multi-institutional collaboration with deCODE Genetics, Inc. our research group recently evaluated whether there is an association between PCa susceptibility SNPs and surgical intervention for LUTS/BPH.[14] This series revealed a modest association between SNP rs2736098 on chromosome 5p15 and surgical treatment for LUTS/BPH, predominantly transurethral prostate resection. However, men may possibly undergo a procedure for bladder outlet obstruction who may in fact have nonprostate centric LUTS. Thus, the study may have underestimated the association between some minor alleles and LUTS.

Using a surgical outcome as an estimate of LUTS likely underestimates the prevalence of the disease. Basing LUTS outcomes on the actual symptoms measured has intrinsic appeal. Given that most men with LUTS defer any surgical intervention by accepting conservative therapy or medical treatment for symptoms, there is a need to understand which genetic factors drive symptom development. To our knowledge no previous group has evaluated whether any other PCa susceptibility SNPs are associated with LUTS severity and/or medication use.

MATERIALS AND METHODS

Our study cohort consisted of 1,168 men of European ancestry with PSA less than 4.0 ng/ml and normal digital rectal examination who were recruited as healthy subjects for genetic studies from the 2007 National Prostate Cancer Coalition screening study, as previously described.[15] The study was approved by the Northwestern University institutional review board. All participants provided written informed consent for study participation and genetic analysis.

The demographic features of our study population were prospectively documented, including PSA and BPH medication (α-adrenergic antagonists and 5ARIs) as well as previous surgical treatment, ie transurethral prostate resection. All men were asked to complete the AUA-SI.[16] Total AUA-SI score was used as a continuous (total points on 7 questions ranging from 0 to 35 points) or as a categorical variable grouped based on the number of points (none/mild—0 to 7, moderate—8 to 19 and severe—20 to 35).[16]

DNA was extracted from whole blood, as previously described.[17,18] Each sample was genotyped for 38 PCa susceptibility SNPs (supplementary table 1, jurology.com). Statistical analyses were performed to compare allele frequency of the PCa susceptibility SNPs in men with varying degrees of LUTS, as determined by the AUA-SI score. In addition, bivariate analyses using the chi-square test were done to compare SNP frequency in men who did vs did not use BPH medication. Logistic regression analyses were used to compare SNP frequency to categorical AUA-SI score. All 3 categories (mild, moderate and severe) were treated as ordinal variables. Finally, to evaluate associations between an individual SNP and LUTS severity, multivariate analyses were done, controlling for baseline characteristics (patient age and BPH medication use) and the presence of the other SNPs. Statistical significance was considered at $p < 0.05$. All statistical analyses were performed using SAS® 9.2.

RESULTS

The 1,168 white men who met study inclusion criteria had no known diagnosis of PCa, PSA less than 4.0 ng/ml and normal digital rectal examination. Mean age was 59 years and median PSA was 1.1 ng/ml. Overall, 746 (63.9%), 344 (29.4%) and 78 men (6.7%) reported mild, moderate and severe symptoms on the AUA-SI. Study cohort genotypes were determined for 38 genetic variants previously associated with PCa risk (supplementary table 1, jurology.com).

Medication use for LUTS/BPH was reported by 82 men (7.0%), including α-adrenergic antagonists in 72 (6.2%) and 5ARIs in 36 (3.1%). Of the patients 34 (2.9%) used combination therapy with an α-blocker and 5ARI. Comparisons between men who did vs did not use these medications revealed significantly higher AUA-SI scores in medication users vs nonusers (mean $\pm$ SD 17.2 $\pm$ 9.1 vs 8.3 $\pm$ 7.5, $p < 0.0001$). Specifically, 4.3%, 9.4% and 31.6% of men with no/mild, moderate and severe symptoms, respectively, reported using medications for BPH ($p < 0.001$). Bivariate analyses revealed significant differences in the frequencies of 4 SNPs between medication users and nonusers, including SNP rs12621278 on chromosome 2q31.1, SNP rs2736098 on chromosome 5p15, SNP rs6465657 on chromosome 7q21.3 and SNP