SRD5A1 and *SRD5A2* are Associated with Treatment for Benign Prostatic Hyperplasia with the Combination of 5α-Reductase Inhibitors and α-Adrenergic Receptor Antagonists

Xin Gu,* Rong Na,* Tao Huang, Li Wang, Sha Tao, Lu Tian, Zhuo Chen, Yang Jiao,† Jian Kang, Siqun Zheng, Jianfeng Xu, Jielin Sun and Jun Qi‡

From the Department of Urology, Xinhua Hospital, Medical School of Shanghai Jiaotong University (XG, TH, YJ, JK, JQ), Shanghai and Fudan-VARI Center for Genetic Epidemiology, Fudan University (JX), Shanghai, People's Republic of China, and Center for Cancer Genomics and Center for Genomics and Personalized Medicine Research, Wake Forest University School of Medicine (RN, LW, ST, LT, ZC, SZ, JX, JS), Winston-Salem, North Carolina

Purpose: Common treatments for benign prostatic hyperplasia include 5α-reductase inhibitors and α-adrenergic receptor antagonists. However, these treatments can only partially decrease the risk of benign prostatic hyperplasia progression. *SRD5A1* and *SRD5A2* are 5α-reductase inhibitor targets. We investigated the association between drug efficacy and single nucleotide polymorphisms in the *SRD5A1* and *SRD5A2* genes in a Chinese population.

Materials and Methods: We genotyped 11 tagging single nucleotide polymorphisms in the *SRD5A1* and *SRD5A2* genes in a total of 426 benign prostatic hyperplasia cases and 1,008 controls from Xinhua Hospital, Shanghai, People's Republic of China. Cases were treated with type II 5α-reductase inhibitors and α-adrenergic receptor antagonists. We tested the association of tagging single nucleotide polymorphisms with benign prostatic hyperplasia risk/progression, clinical characteristics at baseline, including the I-PSS (International Prostate Symptom Score) and total prostate volume, and changes in clinical characteristics after treatment.

Results: The 11 tagging single nucleotide polymorphisms were not significantly associated with benign prostatic hyperplasia risk or progression (each $p > 0.05$). In the *SRD5A1* gene rs6884552 and rs3797177 were significantly associated with baseline I-PSS ($p = 0.04$ and 0.003, respectively). In the *SRD5A2* gene rs523349 (V89L) and rs9332975 were significantly associated with baseline total prostate volume ($p = 0.01$ and 0.001, respectively). In *SRD5A1* rs166050 was significantly associated with the posttreatment change in total prostate volume ($p = 0.04$). In *SRD5A2* rs523349 and rs612224 were significantly associated with the posttreatment I-PSS change ($p = 0.03$ and 0.009, respectively).

Conclusions: *SRD5A1* and *SRD5A2* single nucleotide polymorphisms are significantly associated with the clinical characteristics of benign prostatic hyperplasia and the efficacy of benign prostatic hyperplasia treatment.

Key Words: prostate; prostatic hyperplasia; SRD5A1 protein, human; SRD5A2 protein, human; polymorphism, single nucleotide

Abbreviations and Acronyms

3′-UTR = 3′-untranslated region
BPH = benign prostatic hyperplasia
DHT = 5α-dihydrotestosterone
fPSA = free PSA
PSA = prostate specific antigen
SNP = single nucleotide polymorphism
SRD5A1 = Homo sapiens steroid-5-α-reductase, α polypeptide 1
SRD5A2 = Homo sapiens steroid-5-α-reductase, α polypeptide 2
$(TA)_n$ repeat = thymine-adenine di-nucleotide repeat
TPV = total prostate volume
tPSA = total PSA
tSNP = tagging SNP

Accepted for publication March 5, 2013.
Supported by National Science Foundation of China 81070600 (JQ) and a Fudan University intramural fund (JX).
* Equal study contribution.
† Deceased.
‡ Correspondence: Department of Urology, Xinhua Hospital, Medical School of Shanghai Jiaotong University, 1665 Kongjiang Rd., Shanghai, People's Republic of China (telephone: 86-21-25078999; e-mail: jasonqi@sh163.net).

BENIGN prostatic hyperplasia is one of the most common diseases and an important cause of lower urinary tract symptoms in older men. These symptoms may deeply affect quality of life.[1–4] In some cases BPH progression may cause acute urinary retention, urinary incontinence, urinary

0022-5347/13/1902-0615/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.03.024
Vol. 190, 615-619, August 2013
Printed in U.S.A.

tract infections or kidney dysfunction.[5] Currently available BPH treatments include medication (5α-reductase inhibitors, α-adrenergic receptor antagonists, herbal mixtures, etc) and invasive therapies (transurethral prostate resection, surgery, etc). Invasive therapies are typically used for rapidly progressive BPH.[1] Medication is the preferred treatment for most men with BPH. Type II 5α-reductase inhibitors, dual 5α-reductase inhibitors (types I and II) and α-adrenergic receptor antagonists are the most commonly prescribed drugs globally.

Type I and II 5α-reductase inhibitors are testosterone analogues.[6] In prostate tissue testosterone is converted into DHT by the enzyme 5α-reductase and DHT is a more powerful androgen than testosterone. The major function of DHT is to stimulate prostate tissue proliferation. Type I and II 5α-reductase inhibitors can bind to the enzyme and prevent testosterone from being metabolized to DHT, which may lead to a reduction in prostate volume and improvement in BPH.[6,7] The α-adrenergic receptor antagonists bind to the α1-adrenergic receptor and reduce smooth muscle constriction in the bladder and urethral sphincter, which helps to relieve BPH symptoms.[8]

Treatment with type II 5α-reductase inhibitors or α-adrenergic receptor antagonists may only partially decrease the risks of rapidly progressive forms of BPH by 34% to 50%.[9–11] The combination of the 2 drugs decreased 66% of the risks.[9] In recent studies treatment with a combination of type I and II 5α-reductase inhibitors showed similar decreases in the rate of BPH progression compared with type II treatment alone.[12]

Genetic polymorphisms on type I and II 5α-reductase genes may affect enzyme activity and, thus, lead to individual variability in drug efficacy. Previous studies demonstrated that several mutations on the *SRD5A* gene changed the 5α-reductase expression level.[13] To our knowledge no pharmacogenetic studies of the *SRD5A* gene with BPH treatment have been done. Therefore, we performed a comprehensive association study of SNPs on the *SRD5A1* and *SRD5A2* genes, and the efficacy of BPH treatment in a Chinese population. We also evaluated the association of SNPs on the *SRD5A1* and *SRD5A2* genes with the risk of BPH and rapidly progressive BPH.

MATERIALS AND METHODS

Study Population and Design

A total of 426 patients with BPH (cases) were recruited from the department of urology at a tertiary health institution (Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China) from July 2010 to July 2012. Study inclusion criteria were 1) BPH with lower urinary tract symptoms, 2) age greater than 45 years, 3) prostate gland size greater than 30 ml, 4) I-PSS 7 or greater, 5) post-void residual urine volume 150 ml or less and 6) PSA less than 4 ng/ml or, if PSA was 4 ng/ml or greater, prostate cancer identified by active surveillance with stable PSA, digital rectal examination and prostate biopsy. Exclusion criteria were 1) a history of urinary tract infection, 2) previous lower tract surgery and 3) neurogenic bladder dysfunction. A total of 1,008 men were included in the control group from community populations in Shanghai. We previously reported a detailed description of the control group.[14] Written informed consent was obtained from each patient for participation and for information to be stored in the hospital database and used for research.

Clinical information was collected for all cases, including the I-PSS quality of life questionnaire, post-void residual urine volume evaluated by ultrasound, TPV evaluated by transrectal ultrasound and serum PSA, including total and free PSA. Patients had to meet standard criteria, ie no ejaculation, no manipulation such as catheterization, cystoscopy or transurethral resection, and no urinary tract infections, as well as liver function, renal function and blood glucose levels, and routine urine examination. I-PSS was classified as moderate—8 or greater to 19 or less and severe—20 or greater to 35 or less.

A combination of type II 5α-reductase inhibitors (5 mg once daily) and α-adrenergic receptor antagonists (4 mg once each night) was administered to cases for at least 9 months. After treatment, patients were classified into 2 groups based on progression after medical treatment, including 184 with rapidly progressing BPH requiring treatment and 242 with stable/improved BPH. Patients with rapidly progressive BPH after medical therapy were defined by a significant (2 points or greater) increase in I-PSS, a decrease in the maximum urinary flow rate or surgery. Patients who did not complain about progressive symptoms were defined as having stable/improved BPH.

SNP Selection and Genotyping

The *SRD5A1* and *SRD5A2* genes are located on chromosome 5 from 6,633,500 to 6,669,675 bp, and on chromosome 2 from 31,749,656 to 31,806,040 bp (National Center for Biotechnology Information build 37), respectively. We included regions covering all exons and introns, and 10 kb upstream and downstream of the 2 genes. A total of 22 SNPs from *SRD5A1* and 24 from *SRD5A2* with a minor allele frequency of greater than 0.05 were catalogued based on HapMap 3 data from the CHB population, release 27 (http://hapmap.ncbi.nlm.nih.gov/). We selected tSNPs using Haploview software[15] with aggressive 2 and 3-marker tagging methods.

tSNPs were genotyped for all study subjects using the MassARRAY® iPLEX system at Fudan University, Shanghai, People's Republic of China. Two duplicates and 2 water samples were included in each 96-well plate as polymerase chain reaction negative controls. All assays were performed in blinded fashion. The rate of missing genotypes was 0.7%.

Statistic Analysis

The genotype distribution of each SNP was tested for Hardy-Weinberg equilibrium. The main effects of the