Int J Clin Exp Pathol 2017;10(8):8660-8676
www.ijcep.com /ISSN:1936-2625/IJCEP0054200

Original Article

Associations of *SRD5A2/CYP17/CYP19/VDR* gene polymorphisms with the development and clinical progression of benign prostatic hyperplasia: a case-control study in northern Chinese population

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Received March 30, 2017; Accepted May 27, 2017; Epub August 1, 2017; Published August 15, 2017

Abstract: This study aims to explore the effect of gene polymorphisms of 5a-reduction enzyme (*SRD5A2),* steroidogenic cytochrome P-450 17alpha-hydroxylase (*CYP17)*, aromatase cytochrome P450 family 19 (*CYP19)* and vitamin D receptor (*VDR)* on benign prostatic hyperplasia (BPH) susceptibility and clinical progress. A total of 452 BHP patients and 501 healthy individuals were selected in Harbin Medical University Daqing School from October 2014 and December 2015 as the case and control groups. All BPH patients received drug treatment and were subsequently divided into the progression and non-progression groups based on their therapeutic efficacy. PCR-RFLP was applied to detect the genotype distributions of *SRD5A2/CYP17/CYP19/VDR*, which were further tested with Hardy-Weinberg (H-W) equilibrium. Logistic regression analysis was applied to determine the risk factors for BPH progression. Compared with subjects carrying VV genotype and V allele at *SRD5A2* V89L, those with LL genotype and L allele at *SRD5A2* V89L may have reduced risk of BPH susceptibility or progression (all $P < 0.05$). Compared with subjects carrying TT genotype and T allele at *CYP17* -34T>C, those with CC genotype and C allele at *CYP17* -34T>C may have increased risk of BPH susceptibility or progression (all $P < 0.05$). Compared with individuals carrying FF genotype and F allele at *VDRVDR* Fok I, those with ff genotype and f allele at *VDRVDR* Fok I may have increased susceptibility to BPH (all $P < 0.05$). Logistic regression analysis showed that *SRD5A2* V89L and *CYP17 -34T>C* polymorphisms and *CYP17* -34T>C (TC + CC)/*SRD5A2* V89L (VV) combined genotypes were significantly related with the clinical progression of BHP. These results revealed that *SRD5A2* V89L and *CYP17* -34T>C polymorphisms were associated with the risk of BPH and its clinical progression.

Keywords: *SRD5A2, CYP17, CYP19, VDR,* benign prostatic hyperplasia, gene polymorphisms

Introduction

Benign prostatic hyperplasia (BPH) usually represents the urologic diagnosis that occurs most frequently in elderly males [1]. It is a histologic diagnosis which refers to epithelial cell and smooth muscle proliferation in the prostatic transition zone [2]. BPH is also a kind of proliferative abnormality of the human prostate, which is often related with age [3]. BPH occurs in about 50% of men by the age of 50, the incidence of which usually increases with age [4]. Report suggested that the incidence rate of this disease is about 2.96 per 1000 man among patients in their forties, while 34.46 per 1000 man among patients in their seventies [5]. There are mainly two established risk factors in the development of this disease: aging and androgens [3]. Laser technology has been adopted to treat BPH for years [6]. Pharmacological therapy is most commonly applied for patients with moderate to severe BPH, which aims to improve symptoms and identify patients who are at risk of disease progression so as to optimize their management [7, 8]. And the number of BPH patients seeking treatment is expected to increase in the next few years because of the ageing male population [9]. Certain alleles of some genes are associated with BPH [10, 11].

The gene encoding steroid 5-alpha reductase type II (*SRD5A2*) is proved to be located on chromosome 2p23 and has ive exons and four introns [12, 13]. Steroidogenic cytochrome P-450 17alpha-hydroxylase (*CYP17*) encodes an enzyme with activities of 17-hydroxylase and 17,20-lyase, which is a step with rate limiting in the biosynthesis of testosterone [14]. Aromatase Cytochrome P450 family 19 (*CYP-19*) is a key enzyme in the estrogen metabolism and *CYP19* polymorphisms usually cause changes in enzyme activity and can influence the estrogen synthesis [15]. Vita-min D receptor (*VDR*) belongs to the trans-acting transcriptional regulatory factors family and can modulate many biological activities of the endocrine, immune and neural systems, including apoptosis, cell differentiation, calcium and phosphorous homeostasis [16]. *VDR* polymorphisms have been proved to be associated with many diseases such as the leprosy phenotypes and ovarian cancer [17, 18]. Similarly, the variants in *SRD5A2* are reported to be connected with the quality of semen [19]. It is also proved that variants in *CYP17* and *CYP19* genes are related with the onset of Alzheimer's disease [20].

However, little can be found on the genetics and mechanism of *SRD5A2*, *CYP17*, *CYP19* and *VDR* polymorphisms influencing BPH, especially in northern Chinese population. In order to further understand the genetic characteristics of BPH, this study targets to explore the association of BPH with *SRD5A2*, *CYP17*, *CYP19* and *VDR* polymorphisms among northern Chinese men, hoping to provide a new sight for the diagnosis and treatment of BPH.

Materials and methods

Ethical statement

The present study was performed in accordance with the guidelines established by Medicine Ethics Review Committee at Harbin Medical University Daqing School. All patients have signed written forms of consent.

Study subjects

A total of 452 BPH patients were selected into the case group in the urological department at Harbin Medical University Daqing School from October 2014 to December 2015. The inclusion criteria were as follows: patients who (1) met the BPH diagnosis criteria recommended by the 5th International Benign Prostatic Hyperplasia Advisory Committee in 2001 [21]; (2) had no abnormal echo in abdominal or rectal prostate ultrasound; (3) had a prostate specific antigen (PSA) concentration greater than 4 ng/mL; (4) had a prostate volume (PV) greater than 30 mL; (5) had a postvoiding residue (PVR) greater than 30 mL; (6) went through pathological examination of prostate and were confirmed by two experienced pathophysicians in Harbin Medical University Daqing School; (7) were permanent residents of northern China (lived in the local community for more than 2 years); (8) received no formal treatment before this study. Exclusion criteria were as follows: patients who (1) were confirmed as prostate cancer and prostate sarcoma in immunohistochemical examination; (2) had previous history of surgery in the prostate, urethra and bladder; (3) had neurological diseases that may affect the urinary tract functions; (4) had urinary tract infection; (5) used medications that may affect the urinary functions. During the same period, 501 healthy individuals who underwent physical examinations at Harbin Medical University Daqing School were enrolled into the control group. The subjects in the control group were all permanent residents of northern China (lived in the local community for more than 2 years) and had no blood relationship with the case group. Blood samples from all subjects were collected and detailed clinical data were recorded.

Treatment regimen and grouping

BPH patients were treated with combined therapy of Terazosin (National medicine permission number: H20023659, Abbott (Shanghai) Pharmaceutical Co., Ltd., Shanghai, China) and Finasteride tablets (National medicine permission number: J20090145, Merck (Hangzhou) Pharmaceutical Co., Ltd., Hangzhou, China). Treatment regimen: one tablet of Terazosin (2 mg) and 1 tablet of Finasteride (5 mg) were given orally per day before sleep for 3 months consecutively. For patients who showed significant improvement, Finasteride tablets were given alone. The case group was further divided into clinical progression group and non-progression group according to the following assessment indicators for clinical progress of BPH after drug treatment [22]: (1) decreased

Table 1. Primer sequence for each SNP

Locus	Gene	Forward primer	Reverse primer
A49T	SRD5A2	5'-ACCCTTGGGGCACTGGCCTTG-3'	5'-GTCAGCTCCTGCAGGAACCAG-3'
V89L	SRD5A2	5'-CCACCTGGGACGGTACTTCT-3'	5'- CTCCACGCTGCGCTCCTGGA-3'
-34T>C	CYP17	5'-CATTCGCaccTCTGGAGTC-3'	5'-GGCTCTTGGGGTACTTG-3'
+19C>T	CYP19	5'-GGTACTTAGTTAGCTACAATC-3'	5'-GGGTGATAGAGTCAGAGCCT-3'
Apa I	VDR	5'-CAACCAAGACTACAAGTACCGCGTCAGTGA-3'	5'- CACTTCGAGCACAAGGGGCGTTAGC-3'
Fok I	VDR	5'-AGCTGGCCCTGGCACTGACTCTGCTCT-3'	5'-ATGGAAACACCTTGCTTCTTCTCCCTC-3'

Note: SNP, single nucleotide polymorphism.

dynamic maximum urinary flow rate; (2) presence of complications such as acute urinary retention, hematuria, urinary tract infection, bladder stones and renal dysfunction.

Sample collection

Ten ml fasting venous blood were collected from all subjects in the morning. Ethylenediamine tetraacetic acid (EDTA) was added to 4 ml blood samples as anticoagulant and stored in refrigerator at -80°C. The genomic DNA was extracted using a conventional phenol extraction method and was diluted to a final concentration of 10 ng/μl. Two ml blood samples were used for routine blood examination, which covered: total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and PSA concentration. Clinical data, including age, height, weight, PV, maximum flow rate (Qmax) and PVR, were obtained from all subjects.

Single nucleotide polymorphism (SNP) screening and sequencing

The candidate loci identified in this study were 5 PV-associated SNPs selected in a previous prostate cancer genome-wide association study (GWAS), including *SRD5A2* A49T and V89L, *CYP17* -34T>C, *CYP19* +19C>T, *VDR* Apa I and Fok I. The relevant gene sequences were obtained from Genbank, and their primers were designed by Oligo 6.0 and Primer 5.0 software. The relevant primers were shown in **Table 1**.

The genomic DNA was extracted using a phenol/chloroform method and analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The PCR reaction system included: 10 ng of template DNA (batch number: KN1014, C&M Biolabs, Richmond, CA, USA), 10 × PCR buffer, 15 pmol of each primer, 0.2 mmol/L dNTPs, 0.12 U Tag enzyme (batch number: K1321, Shanghai Runcheng Biotechnology Co., Ltd., Shanghai, China). The above components were diluted with double distilled water to a final volume of 15 μl. A touchdown PCR reaction was performed on a C100 PCR apparatus (Bio-Rad, Hercules, CA, USA). The amplification conditions were: 94°C for 2 min, 94°C for 30 s, 63°C for 1 min and 72°C for 1 min; and 94°C for 30 s, 57°C for 1 min, 72°C for 1 min and 72°C for 7 min. The amplification products were transferred to 1.5% agarose gel electrophoresis (2117 Multiphor II, Bio-Rad, Hercules, CA, USA). The purity of the amplified bands were observed under an ultraviolet lamp and the concentration was estimated. A total of 3 μl of each PCR amplification product was added with different endonucleases at the following reaction condition was as follows: 45 min at 37°C and 15 min at 85°C. The PCR product was then kept at 4°C. A reverse primer (1 μl) and BDT (1 μl) were added into purified PCR products using a Prism BigDyeTerminator (BDT) Cycle Sequencing kit (lot number: N73144, ABI, Thermo Fisher, Waltham, MA, USA).

Follow-up

BPH patients were followed up every 3 months for 3 to 12 months through phone calls, outpatient service and medical record evaluation. The follow-up ended in February, 2016. Altogether, 6 patients were lost to follow-up and the follow-up rate was 99.50%. Detailed information about the clinical progression of BPH was closely monitored, including: (1) Qmax; (2) the incidence of complications such as acute urinary retention, hematuria, urinary tract infection, bladder stones and renal function impairment.

Table 2. Comparison of baseline characteristics between the control group and the BPH group

Item	BPH group (n = 452)	Control group (n = 501)	*P*
Age (years)	58.02 ± 7.38	57.28 ± 7.61	0.129
BMI (kg/m^2)	22.46 ± 3.55	24.14 ± 3.63	< 0.001
TC (mmol/L)	4.75 ± 0.91	4.72 ± 0.99	0.628
TG (mmol/L)	2.18 ± 0.91	1.98 ± 1.22	0.005
LDL-C (mmol/L)	3.21 ± 0.77	3.14 ± 0.81	0.173
HDL-C (mmol/L)	1.58 ± 0.31	1.63 ± 0.35	0.02
PV (mL)	69.59 ± 20.49	66.68 ± 17.76	0.019
PSA (ng/L)	2.02 ± 1.11	1.71 ± 0.81	< 0.001
Qmax (mL/s)	6.35 ± 1.91	6.59 ± 1.79	0.046
PVR (mL)	62.89 ± 20.71	58.51 ± 21.05	0.001

Notes: BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoproteincholesterol; HDL-C, high-density lipoproteincholesterol; PV, prostate volume; PSA, prostate specific antigen concentration; Qmax, maximum flow rate; PVR, postvoiding residue; the t test was performed.

Statistical method

SPSS 17.0 software was used for data analysis. The measurement data were expressed as mean ± SD. The *t* test was used for comparison between two groups in normal distribution. One-way ANOVA was applied for comparison among multiple groups with variance homogeneity and normality. Nonparametric Kruskal-Wallis rank-sum test was used for comparison among multiple groups without variance homogeneity and normality. Count data were expressed in percentage or rate and were compared using X^2 test. The comparison of alleles and genotypes and the Hardy-Weinberg equilibrium of alleles were verified using X^2 test. The relative risk was expressed with odds ratio (OR) and 95% confidence interval (CI). Logistic regression analysis was carried out to analyze the risk factors for clinical progression of BPH. $P < 0.05$ was considered statistically significant.

Results

Comparisons of baseline characteristics between the control group and the BPH group

The BMI, HDL-C and Qmax in the BPH group were significantly lower than those in the control group (all $P < 0.05$). The levels of TG, PV, PSA and PVR in the BPH group were significantly higher than those in the control group (all $P < 0.05$). There was no significant difference in age, TC and LDC-C between the two groups (all $P > 0.05$) (**Table 2**).

Electrophoresis results of SRD5A2 A49T and V89L, CYP17 -34T>C, CYP19 +19C>T, VDR Apa I and Fok I

In the *SRD5A2* A49T locus, AA, AT and TT genotypes were detected after Rsai digestion: a single restriction site was found in the wild type homozygous (AA), which was cut into bands of 169 bp, 105 bp and 64 bp; the wild-type homozygous (TT) was cut into bands of 169 bp, 105 bp and 83 bp; the mutant heterozygote (AT) only showed a 169 bp band (**Figure 1A**).

In the *SRD5A2* V89L locus, VV, VL and LL genotypes were detected after HYF10VI digestion: wild-type homozygous (VV) had no digestion site and only showed a 89 bp band; the mutant homozygous (LL) only showed a 124 bp band; the mutant heterozygous (VL) was cut into bands of 124 bp and 89 bp (**Figure 1B**).

After $MspA_1I$ digestion, the *CYP17* -34T>C site showed TT, CC and TC genotypes: the wild-type homozygote (TT) had no digestion site and only showed a 459 bp band; the mutant homozygote (CC) had one digestion site and was cut into bands of 336 bp and 123 bp; the mutant heterozygous (TC) was cut into bands of 459 bp, 336 bp and 123 bp (**Figure 1C**).

After Bsp1286 I digestion, the *CYP19* +19C>T site showed TT, CC and TC genotypes: the mutant homozygote (TT) had no digestion site and only showed a 202 bp band; the wild-type homozygote (CC) had one digestion site and was cut into bands of 172 bp and 30 bp; the mutant heterozygous (TC) was cut into bands of 202 bp, 172 bp and 30 bp (**Figure 1D**).

In the *VDR* Apa I locus, AA, Aa and aa genotypes were detected after Apa I digestion: the mutant homozygous (aa) and wild-type homozygous (AA) both only showed a 495 bp band; the mutant heterozygote (Aa) had one digestion

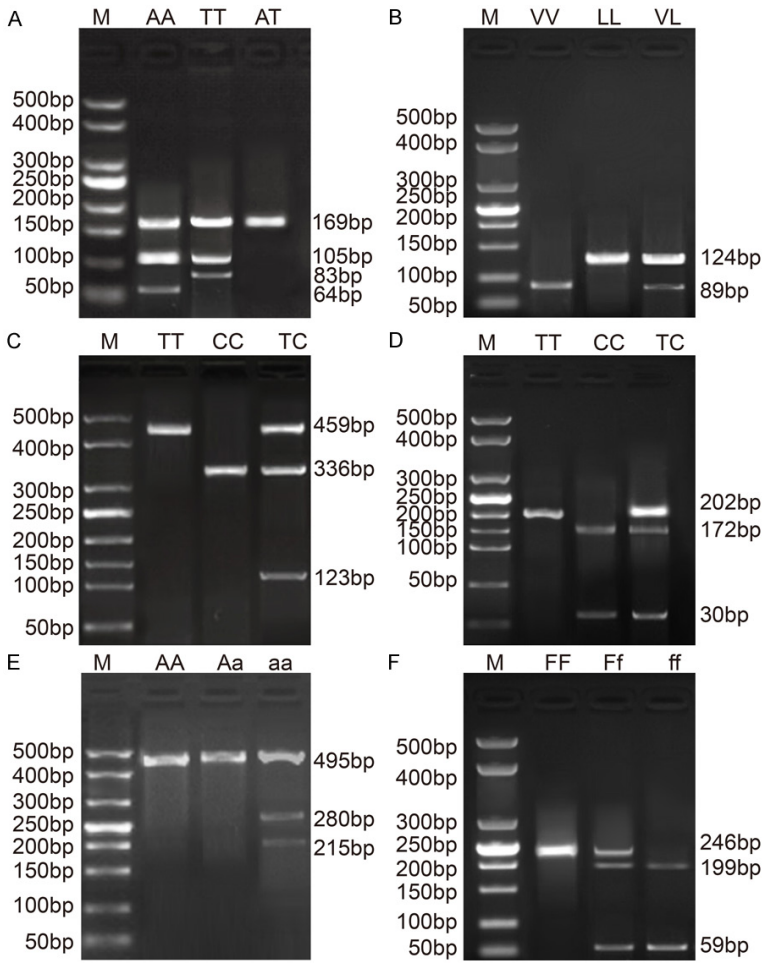

Figure 1. Electropherogram of PCR products at each gene locus. Notes: A: Electropherogram of SRD5A2 A49T locus after Rsai enzyme digestion, M: Marker; AA: Wild-type homozygote; AT: Mutant heterozygote; TT: Mutant homozygote; B: Electropherogram of SRD5A2 V89L locus after HYF10VI enzyme digestion; M: Marker; VV: Wild-type homozygote; VL: Mutant heterozygote; LL: Mutant homozygote; C: Electropherogram of CYP17 -34T>C locus after $MspA_1I$ enzyme digestion, CC: Mutant homozygote; TC: Mutant heterozygote; TT: Mutant homozygote; D: Electropherogram of CYP19 +19C>T locus after BSP1286 I enzyme digestion, CC: Mutant homozygote; TC: Mutant heterozygote; TT: Mutant homozygote; E: Electropherogram of VDR Apa I locus post Apa I enzyme digestion; M: Marker; AA: Wild-type homozygote; Aa: Mutant heterozygote; aa: Mutant homozygote; F: Electropherogram of VDR Fok I locus post Fok I enzyme digestion, FF: Wild-type homozygote; Ff: Mutant heterozygote; ff: Mutant heterozygote; M: Marker; PCR = polymerase chain reaction.

site and was cut into bands of 495 bp, 280 bp and 215 bp (**Figure 1E**).

In the *VDR* Fok I locus, FF, Ff and ff genotypes were detected after Fok I digestion: the mutant homozygous (ff) genotype had two digestion sites and was cut into two bands of 199 bp and 59 bp; the wild-type homozygous (FF) had no digestion site and only showed a 246 bp band; the mutant heterozygous (Ff) had one digestion site and was cut into bands of 59 bp, 199 bp and 246 bp (**Figure 1F**).

Hardy-Weinberg equilibrium test for SRD5A2 A49T and V89L, CYP17 -34T>C, CYP19 +19C>T, VDR Apa I and Fok I

Hardy-Weinberg equilibrium analysis was carried out for different loci in the control group. No significant difference was found between the actual and expected values of *SRD5A2* A49T, *SRD5A2* V89L, *CYP17* -34T>C, *CYP19* +19C>T, *VDR* Apa I and *VDR* Fok I (all $P > 0.05$) (**Table 3**), indicating that the distribution frequency of each gene locus is representative.

Distribution frequency of SRD5A2/CYP17/CYP19/VDR SNPs between the BPH group and the control group

There was no significant difference in the distribution frequency of *SRD5A2* A49T, *VDR* Apa I and *CYP19* +19C>T between the BPH and control group (all $P > 0.05$). The frequency of *SRD5A2* V89L was significantly different between the control group and the BPH group (all $P < 0.05$). Compared with the VV genotype, the LL genotype may reduce the risk of BPH (OR = 0.401, 95% CI = 0.190-0.845, $P = 0.013$); compared with the V allele, the L allele also tended to reduce the risk of BPH (OR = 0.787, 95% CI = 0.622-0.994, $P = 0.044$). The distribution frequency of *CYP17* -34T>C was significantly different between the BPH and control groups (all $P < 0.05$). Compared with the TT genotype, the CC genotype may increase the risk of BPH (OR = 9.064, 95% CI = 2.687-30.580, $P < 0.001$); compared with the T allele, the C allele also tended to increased the risk of BPH (OR = 1.584, 95% CI = 1.233-2.035, $P < 0.001$). The distribution frequency of *VDR* Fok I

Table 3. Hardy-Weinberg equilibrium for the representativeness of *SRD5A2* A49T and V89L, *CYP17* -34T>C, *CYP19* +19C>T, *VDR* Apa I and Fok I

Locus	Genotype	Predicted value n (%)	Actual value n (%)	X^2	*P*
SRD5A2 A49T	AA	421 (84.03)	417 (83.23)	4.322	0.115
	AT	77 (14.78)	84 (16.77)		
	TT	4 (0.80)	0 (0.00)		
SRD5A2 V89L	VV	320 (63.87)	326 (65.07)	1.303	0.521
	VL	161 (32.14)	149 (29.74)		
	LL	20 (3.99)	26 (5.19)		
CYP17 -34T>C	TT	382 (76.25)	377 (75.25)	2.737	0.255
	TC	111 (22.16)	121 (25.15)		
	CC	8 (1.60)	3 (0.60)		
CYP19 +19C>T	CC	337 (67.27)	343 (68.46)	1.507	0.471
	TC	148 (29.54)	136 (27.15)		
	TT	16 (3.19)	22 (4.39)		
VDR Apa I	AA	356 (71.06)	363 (72.46)	2.321	0.313
	Aa	132 (26.35)	119 (23.75)		
	aa	12 (2.40)	19 (3.79)		
VDR Fok I	FF	390 (77.78)	390 (77.78)	0	1
	Ff	104 (20.76)	104 (20.76)		
	ff	7 (1.40)	7 (1.40)		

Note: the chi-square test was performed.

was significantly different between the control group and the BPH group (all $P < 0.05$). Compared with the *VDR* FF genotype, the ff genotype may increase the risk of BPH (OR = 1.587, 95% CI = 1.266-2.053, $P = 0.007$); compared with the F allele, the f allele also tended to increase the risk of BPH (OR = 1.587, 95% CI = 1.266-2.053, $P < 0.001$) (**Table 4**).

Relationship between SRD5A2 A49T and V89L, CYP17 -34T>C, CYP19 +19C>T, VDR Apa I and Fok I gene polymorphisms and clinical progression of BPH

No significant difference was found in the distribution frequencies of *SRD5A2* A49T, *CYP19* +19C>T, *VDR* Apa I and *VDR* Fok I between the progression group and the non-progression group (all $P > 0.05$). The distribution frequency of *SRD5A2* V89L genotypes and alleles was not significantly different between the progression group and the non-progression group (all $P > 0.05$). Compared with the VV genotype, the LL genotype might decrease the risk of clinical progression in BPH patients (OR = 0.235, 95% CI = 0.049-1.123, $P = 0.049$); compared with the V allele, the L allele might also reduce the risk of clinical progression (OR = 0.534, 95% CI = 0.330-0.865, $P = 0.010$). The distribution of genotype and allele of *CYP17* -34T>C was significantly different between the progression group and the non-progression group (all $P < 0.05$). Compared with the TT genotype, the CC genotype may increase the risk of clinical progression in BPH patients (OR = 4.821, 95% CI = 1.732-13.420, $P = 0.001$); compared with the T allele, the C allele might also increase the risk of clinical progression in BPH patients (OR = 2.261, 95% CI = 1.546-3.306, $P < 0.001$) (**Table 5**).

Relationship between a combination of SRD5A2 V89L/CYP17 -34T>C and clinical progression of BPH

The relationship between various combinations of *SRD5A2* V89L/*CYP17* -34T>C SNPs and the risk of clinical progression in BPH patients was anlyzed (**Table 6**). The distribution frequency of *SRD5A2* V89L (VL + LL)/*CYP17* -34T>C (TT) genotype combination was significantly lower in the progression group (14.4%) than that in the non-progression group (27.4%), indicating that *SRD5A2* V89L (VL + LL)/*CYP17* -34T>C (TT) genotype combination may be a protective factor during the clinical progression of BPH (OR = 0.429, 95% CI = 0.266-0.693, $P < 0.001$). The distribution frequency of genotype combination *SRD5A2* V89L (VV)/*CYP17* -34T>C (TC + CC) was significantly higher in the progression group (32.6%) than that in the non-progression group (18.6%), indicating that *SRD5A2* V89L (VV)/*CYP17* -34T>C (TC + CC) genotype combination may be a risk factor during the clinical progression of BPH (OR = 2.118, 95% CI = 1.371-3.629, $P = 0.001$). No signifi-

Table 4. Distribution frequency of *SRD5A2/CYP17/CYP19/VDR* SNPs between the BPH group and the control group

Genotype	BPH group (N = 452)		Control group (N = 501)		OR (95% CI)	*P*
	Cases	%	Cases	%		
SRD5A2 A49T						
AA	385	85.18	417	83.21	1 (Reference)	
AT	64	14.16	84	16.79	1.137 (0.851-1.726)	0.286
TT	3	0.66	0	0	7.851 (0.390-147.30)	0.072
AT + TT	67	14.82	84	16.77	1.158 (0.816-1.642)	0.412
A	834	92.26	918	91.62	1 (Reference)	
T	70	7.74	84	8.38	1.090 (0.783-1.518)	0.609
SRD5A2 V89L						
VV	313	69.25	326	65.07	1 (Reference)	
VL	129	25.54	149	29.74	0.902 (0.680-1.196)	0.472
LL	10	2.21	26	5.19	0.401 (0.190-0.845)	0.013
VL + LL	121	30.75	175	34.93	0.720 (0.545-0.952)	0.021
V	755	85.52	801	79.94	1 (Reference)	
L	149	16.48	201	20.06	0.787 (0.622-0.994)	0.044
CYP17 -34T>C						
TT	305	67.48	377	75.25	1 (Reference)	
TC	125	27.65	121	24.15	1.277 (0.954-1.710)	0.101
CC	22	4.87	3	0.6	9.064 (2.687-30.580)	< 0.001
TC + CC	147	32.52	124	24.75	1.454 (1.096-1.928)	0.009
T	735	81.31	875	87.33	1 (Reference)	
C	169	18.69	127	12.67	1.584 (1.233-2.035)	< 0.001
CYP19 +19C>T						
CC	310	68.58	343	68.37	1 (Reference)	
TC	121	26.77	136	27.25	0.984 (0.737-1.315)	0.915
TT	21	4.65	22	4.38	0.947 (0.511-1.756)	0.862
TC + TT	142	31.42	159	31.54	0.988 (0.752-1.299)	0.932
C	741	81.97	823	82.04	1 (Reference)	
T	163	18.03	181	17.96	1.000 (0.791-1.263)	0.998
VDR Apa I						
AA	307	67.92	363	72.46	1 (Reference)	
Aa	125	27.65	119	23.75	1.242 (0.926-1.666)	0.147
aa	20	4.42	19	3.79	1.245 (0.652-2.375)	0.506
Aa + aa	145	32.08	137	27.54	1.251 (0.947-1.654)	0.114
A	740	81.75	845	84.33	1 (Reference)	
a	164	18.25	155	15.67	1.208 (0.950-1.537)	0.123
VDR Fok I						
FF	312	69.03	389	77.64	1 (Reference)	
Ff	122	26.99	105	20.96	1.466 (1.085-1.981)	0.012
ff	18	3.98	7	1.4	3.214 (1.325-7.795)	0.007
Ff + ff	140	30.97	112	22.36	1.577 (1.179-2.108)	0.002
F	746	82.52	883	88.12	1 (Reference)	
f	158	17.48	119	11.88	1.587 (1.226-2.053)	< 0.001

Notes: BPH, benign prostatic hyperplasia; OR, odds ratio; 95% CI, 95% confidence interval; the chi-square test was performed.

Table 5. Relationship between *SRD5A2* A49T and V89L, *CYP17* -34T>C, *CYP19* +19C>T, *VDR* Apa I and Fok I gene *polymorphisms* and clinical progression of BPH

Genotype	Progression group (N = 215)		Non-progression group (N = 237)		OR (95% CI)	*P*
	Cases	%	Cases	%		
SRD5A2 A49T						
AA	190	88.37%	195	82.28%	1 (Reference)	
AT	24	11.16%	40	16.88%	0.616 (0.357-1.061)	0.079
TT	1	0.47%	2	0.84%	0.513 (0.046-5.710)	0.58
AT + TT	25	11.63%	42	17.72%	0.611 (0.358-1.042)	0.068
A	404	93.95%	430	90.72%	1 (Reference)	
T	37	8.60%	44	9.28%	0.895 (0.566-1.415)	0.635
SRD5A2 V89L						
VV	162	75.35%	152	64.14%	1 (Reference)	
VL	51	23.72%	77	32.49%	0.621 (0.409-0.943)	0.025
LL	2	0.93%	8	3.38%	0.235 (0.049-1.123)	0.049
VL + LL	53	24.65%	85	35.86%	0.585 (0.389-0.880)	0.01
V	232	53.95%	324	68.35%	1 (Reference)	
L	26	6.05%	68	14.35%	0.534 (0.330-0.865)	0.01
CYP17 -34T>C						
TT	122	56.74%	173	73.00%	1 (Reference)	
TC	76	35.35%	59	24.89%	1.827 (1.210-2.757)	0.004
CC	17	7.91%	5	2.11%	4.821 (1.732-13.42)	0.001
TC + CC	93	43.26%	64	27.00%	2.061 (1.390-3.055)	< 0.001
T	320	74.42%	405	85.44%	1 (Reference)	
C	110	25.58%	69	14.56%	2.261 (1.546-3.306)	< 0.001
CYP19 +19C>T						
CC	148	68.84%	172	72.57%	1 (Reference)	
TC	58	26.98%	53	22.36%	1.272 (0.825-1.960)	0.275
TT	9	4.19%	12	5.06%	0.872 (0.357-2.127)	0.763
TC + TT	67	31.16%	65	27.43%	1.198 (0.798-1.798)	0.383
C	354	82.33%	327	68.99%	1 (Reference)	
T	76	17.67%	65	13.71%	1.080 (0.751-1.554)	0.678
VDR Apa I						
AA	145	67.44%	162	68.35%	1 (Reference)	
Aa	61	28.37%	64	27.00%	0.939 (0.619-1.424)	0.767
aa	9	4.19%	11	4.64%	0.914 (0.368-2.269)	0.846
Aa + aa	70	32.56%	75	3418.00%	0.959 (0.646-1.424)	0.836
A	351	81.63%	388	81.86%	1 (Reference)	
a	79	18.37%	86	18.14%	0.985 (0.702-1.381)	0.929
VDR Fok I						
FF	149	69.30%	163	68.78%	1 (Reference)	
Ff	59	27.44%	63	26.58%	0.976 (0.642-1.484)	0.91
ff	7	3.26%	11	4.64%	0.696 (0.263-1.843)	0.464
Ff + ff	66	30.70%	74	31.22%	0.976 (0.654-1.455)	0.904
F	357	83.02%	389	82.07%	1 (Reference)	
f	413	96.05%	85	17.93%	0.936 (0.663-1.320)	0.706

Notes: OR, odds ratio; 95% CI, 95% confidence interval; the chi-square test was performed.

Table 6. Relationship between a combination of *SRD5A2* V89L/*CYP17* -34T>C and clinical progression of BPH

Combination of genotypes	Progression group (n = 215)	Non-progression group (n = 237)	OR	95% CI	*P*
SRD5A2 V89L (VL + LL)/*CYP17* -34T>C (TT)	30 (14.0%)	65 (27.4%)	0.429	0.266-0.693	< 0.001
SRD5A2 V89L (VL + LL)/*CYP17* -34T>C (TC + CC)	24 (11.2%)	23 (9.7%)	1.169	0.639-2.140	0.612
SRD5A2 V89L (VV)/*CYP17* -34T>C (TC + CC)	70 (32.6%)	44 (18.6%)	2.118	1.371-3.629	0.001
SRD5A2 V89L (VV)/*CYP17* -34T>C (TT)	91 (42.3%)	105 (44.3%)	0.923	0.636-1.339	0.672

Notes: OR, odds ratio; 95% CI, 95% confidence interval; the chi-square test was performed.

Table 7. Logistic regression analysis to determine the related risk factors for clinical progression in BPH patients

Variables	B	Wald	Sig	Exp (B)	95% CI
BMI	0.236	2.065	0.151	1.267	0.918-1.749
TG	-2.64	20.397	< 0.001	0.071	0.023-0.224
HDL-C	-8.94	18.445	< 0.001	0.001	0.000-0.008
PSA	3.01	14.065	< 0.001	20.289	4.208-97.822
PV	0.104	5.927	0.015	1.109	1.020-1.206
Qmax	-0.47	5.151	0.013	0.626	0.431-0.906
PVR	-0.05	3.975	0.046	0.955	0.913-0.999
SRD5A2 V89L	2.914	23.097	< 0.001	18.438	5.617-60.521
CYP17 -34T>C	-2.45	25.86	< 0.001	0.087	0.034-0.222
SRD5A2 V89L (VL + LL)/*CYP17* -34T>C (TT)	-4.27	10.02	0.002	0.014	0.001-0.196
SRD5A2 V89L (VV)/*CYP17* -34T>C (TT)	3.573	11.209	0.001	35.619	4.398-288.439

Notes: 95% CI, 95% confidence interval; BPH, benign prostatic hyperplasia; BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoproteincholesterol; PV, prostate volume; PSA, prostate specific antigen concentration; Qmax, maximum flow rate; PVR, postvoiding residue; the logistic regression analysis was performed.

cant correlation was found between the other genotype combinations and the clinical progression in BPH patients (all $P > 0.05$).

Logistic regression analysis for risk factors for clinical progression of BPH

A logistic regression analysis was performed using BPH progression as a dependent variable. The following factors were included in the analysis as independent variables: varied factors in clinical data of subjects (such as BMI, TG, HDL-C, PV, PSA, Qmax and PVR), polymorphism of *SRD5A2* V89L and *CYP17* -34T>C, and the genotype combinations of *SRD5A2* V89L (VL + LL)/*CYP17* -34T>C (TT) and *CYP17* -34T>C (TC + CC)/*SRD5A2* V89L(VV). It was found that PSA, the VV genotype of *SRD5A2* V89L, and the genotype combination of *CYP17* -34T>C (TC + CC)/*SRD5A2* V89L (VV) were all the risk factors for the clinical progression in BPH patients (all $P < 0.05$). TG, HDL-C, PV, Qmax, PVR and *CYP17* -34T>C were all protective factors for the clinical progression in BPH patients (all $P < 0.05$) (**Table 7**).

Discussion

BPH is a common urological problem among elderly men and is mainly perceived as a proliferative stromal disease featured with lower urinary tract and prostate enlargement symptoms [23]. Symptoms of BPH will not usually threat life, however, they often drastically affect life quality [9]. Previous studies have demonstrated that the gene polymorphisms were largely applied into the researches of BPH [24, 25]. For further supplementation, this paper explored the association of BPH with *SRD5A2/CYP17/CYP19/VDR* gene polymorphisms in northern Chinese population.

It was found in this study that the BMI, HDL-C and Qmax were significantly lower, while the levels of TG, PV, PSA and PVR were significantly higher in the BPH group when compared with those the control group. Consistent with the

result of our study, Mehmet Murat Baykam et al. have researched the correlation between prostatic resistive index and cardiovascular risk factors in BPH patients, in which HDL-C and Qmax were demonstrated to be risk factors of BPH [26]. And it is also reported that levels of BMI, TG were greater while HDL-C was lower in BPH patients [27]. Qmax and PVR were significantly correlated with BPH [28].

Furthermore, it was also found that in SRD5A2 V89L, compared with the VV genotype and V allele, LL genotype and L allele may reduce the risk of BPH and its clinical progression. As revealed in a previous study, *SRD5A2* is the target of 5-reductase inhibitor which may affect the enzyme activity and lead to individual variability in the efficacy [29]. *SRD5A2* can encode testosterone, a primary androgen in males, into dihydrotestosterone which is necessary for the prostatic growth and male external genitalia development [13]. Besides, L allele in the SRD5A2 is connected with reduced androstanediol glucuronide concentrations, and L/L genotype of V89L polymorphism was significantly related to lower concentrations of free testosterone and testosterone [30]. It was reported that when compared with the V/V genotype, the L/L genotype makes a 42% reduction in the activity of 5 a-reductase enzyme [31].

Another important finding from this study is that compared with the TT genotype and T allele at *CYP17* -34T>C, CC genotype and C allele at *CYP17* -34T>C may increase the risk of disease and its clinical progression. CYP17 is a key enzyme in the steroid biosynthesis which contains a heme prosthetic group at the active site and it can inhibit the treatment of prostatic diseases such as BPH [32, 33]. CYP17 enzyme mediates two steps in steroid hormone biosynthesis, which are 17 a-hydroxylase and 17, 20-lyase activities; CYP17 contains a single-base pair (bp) T to C polymorphism which can create a Sp-1 site (CCACC box) at 34 bp upstream from the beginning of translation and downstream from the transcription site, which can provide an additional promoter activity with increased CYP17 transcription [24]. One study conducted by Tigli H et al. have demonstrated that in the risk allele, the T to C transition would create a new recognition site for restriction enzyme $MspA_1$ [34]. All of these studies were in accordance with the result of this study.

This study also found that the *SRD5A2* V89L and *CYP17 -34T>C* polymorphisms, *CYP17* -34T>C (TC + CC)/*SRD5A2* V89L (VV) combined genotypes were significantly related with the clinical progression of BHP.A relevant research has revealed that SRD5A2-V89L and CYP17-A1/A2 are involved in the biosynthesis of testosterone and dihydrotestosterone, V89L polymorphism of the SRD5A2 gene has been proved to be an important determinant of hypospadias risk, and *CYP17-A1/A2* and *SRD-5A2-V89L* are both involved in the biosynthesis of dihydrotestosterone and testosterone, which are in related with hypospadias [14].

In conclusion, these results have confirmed that *SRD5A2/CYP17/CYP19/VDR* gene polymorphisms are associated with the susceptibility and clinical progress of BPH. However, there are still some deficiencies in this study for various constraints. For examples, certain deviation in the statistical results may arise due to limited research time and sample size. Therefore, further studies are needed to verify our findings. Nevertheless, this study might shed some light on the future treatment of BPH.

Acknowledgements

This study was supported by Guiding Science and Technology Program of Daqing (szdy-20-15-03).

Disclosure of conflict of interest

None.

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