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Original Article

Clinical significance of single nucleotide polymorphisms of adiponectin gene in Chinese benign prostatic hyperplasia patients

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Abstract: Epidemiologic studies indicated that Benign Prostatic Hyperplasia (BPH) is closely associated with metabolic syndrome (MetS), which commonly associated with decreased serum adiponectin level. The presented study evaluated the clinical significance of a set of tag Single Nucleotide Polymorphisms (SNPs) of adiponectin gene in a cohort of Chinese BPH patients. 1008 healthy controls and 426 BPH patients, who received combination treatment of α-adrenergic blockers and 5α-reductase inhibitors for at least 9 months, were included in this study. Associations between SNPs and BPH risk, BPH aggressiveness, and clinical response to the combination treatment were tested by log-linear analysis. At least four SNPs were identified with clinical significance in BPH outcomes. For example, minor allele "A/A" of SNP rs16861205 was found significantly associated with an overall increased risk of BPH, and impaired clinical response to the treatment. In conclusion, our study showed a set of adiponectin SNPs may serve as risk indicators and prognosis predictors for Chinese BPH patients.

Keywords: Adiponectin, BPH, SNPs, risk indicator, prognosis predictor

Introduction

Benign prostatic hyperplasia (BPH), one of the most common age-related disorders, is a non-malignant proliferative abnormality affecting elder male throughout the world. Although the high prevalence and the modifiable risk factors of BPH have been noticed, the outcome of BPH remains difficult to predict [1]. It is important to find a useful and easy indicator to estimate the risk and predict the prognosis in BPH patients who received treatments.

Adiponectin is one of the most abundant adipokine that derived from adipose tissue and plays a role in several physiologic processes, including cell proliferation and apoptosis and metabolism of glucose and fatty acids [2, 3]. Adiponectin is well known to be associated with the development of hormonally-sensitive malignancies. Recent epidemiologic studies have examined serum adiponectin level is in relation to BPH severity [4-7]. Adiponectin level were also found negatively associated with BPH development and also negatively related with prostate volume as assessed by ultrasound [8, 9]. Notably, there are increasing evidences of both direct and indirect effects of adiponectin on BPH pathogenesis. For instance, cell surface receptors of adiponectin were found highly expressed in human prostate (named AdopoR1 and R2) and contribute in the regulation of cell growth, proliferation, and apoptosis in prostate [10]. In addition to that, adiponectin enhances insulin sensitivity and indirectly affects BPH risk. Decreased insulin sensitivity leads to high levels of fasting glucose, which are associated with prostate gland enlargement and lower urinary tract symptoms [11].

It has been estimated that genetic variants significantly influenced the circulating levels of adiponectin in plasma samples [12]. Gene mutations significantly alter the serum adiponectin level, which lead to disruption of cell metabolism and abnormal growth of prostate cells [13, 14]. To our best knowledge, how genetic variants and genotype differences of adiponectin gene associate with BPH development or its prognosis was not clear. Given that single nu-

Table 1. The clinical characteristics of the study subjects

	Patient N=426		Control N=1008
	Aggressive	Non-Aggressive	
Age (y)			
Mean ± SD	73.84±7.97	70.45±7.44	61.24±8.96
IPSS score			
Mean ± SD	18±6.3	14±6.2	N/A
PSA level			
tPSA (ng/ml)			
<4%	107 (58.2)	139 (57.4)	N/A
≥4%	77 (41.8)	103 (42.6)	N/A
fPSA (ng/ml)			
<25%	125 (67.9)	100 (41.3)	N/A
≥25%	58 (31.5)	141 (58.3)	N/A
TPV (ml)	10±3.7	74±14.6	N/A

cleotide polymorphisms (SNPs), are the most common type of genetic variations that generate biological variation between people, we performed a comprehensive study to exam the associations between the adiponectin SNPs and the clinical outcomes of BPH in a Chinese population.

Materials and methods

Study subjects

All the study participants were of Han Chinese descent and local residents of Shanghai. All 426 BPH patients were selectively enrolled from the department of Urology at Xinhua Hospital from July 2010 to July 2012 while 1,008 healthy controls were recruited randomly from four local communities between April 2010 and November 2010. The informed consent were reviewed and documented before the start of this study. This study was approved by ethics committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine.

The following clinical measurements or exams were collected from the BPH patients: International Prostate Symptom Score (IPSS), post-void residual urine volume, total prostate volume (TPV), serum prostate-specific antigen (PSA) level, blood glucose level, liver and renal function evaluation, routine urine exam, and questionnaire of life quality. The inclusion criteria were as follows: (1) benign prostatic enlargement with lower urine tract syndromes; (2) age >45 yr; (3) total prostate volume >30 mL; (4) IPSS≥7; (5) post-void residual urine volume ≤150 mL and (6) PSA<4 ng/mL, or if PSA≥4 ng/mL, prostate cancer should be identified by active surveillance with stable PSA level, digital rectal examination and prostate biopsy. The exclusion criteria were as follows: (1) history of urinary tract infection; (2) previous lower tract surgery and (3) neurogenic bladder dysfunction. Detailed information for controls was previously reported in Ma et al [15].

All BPH patients received combination drug therapy for at least nine months, including type II 5α-reductase inhibitors (5 mg/day) and α-adrenergic-receptor antagonists (4 mg/day at bedtime). After receiving the treatments, patients suffering from a significant BPH related complications (acute urinary retention, bladder stone or recurrent hematuria, etc), with a significant IPSS score increase, or in need of an operation were classified into “aggressive” BPH group. In contrast, patients with stable status were assigned to the “non-aggressive” BPH group.

SNP genotyping

The adiponectin gene locates in 3q27 (old nomenclature: NCBI build 37). All SNP genotyping was performed via MassARRAY iPLEX system (Sequenom, San Diego, CA) at Fudan University, Shanghai. Our genotyping covered all the exons, introns, as well as 5 kb upstream and downstream regions. A total of 7 Tag SNPs (tSNPs) with allele frequencies over 0.05 were selected through Haploview (Broad Institute, Cambridge, MA) with aggressive-tagging methods (2- and 3-marker). Hapmap data from the CHB population (public Release #27) was included as a reference. All assays were performed blinded. Two blank samples were included as PCR-negative controls. Missing genotypes rate was 1.9%.

Statistical analysis

Genotypic distribution of each SNP was tested in Hardy-Weinberg equilibrium (HWE). The associations between SNPs and BPH risk (BPH vs controls), as well as SNPs and BPH aggressiveness (aggressive vs non-aggressive) were measured by logistic regression analysis. Clinical response to the combinational treatment

Table 2. Associations between SNPs of adiponectin gene with BPH risk

Chr	SNP (M/m)[1]	BP[2]	RA[3]	Minor allele frequency		OR (95% CI)[4]	*P*[4]
				Case	Control		
3q27	rs182052 (G/A)	186560782	A	0.47	0.43	1.17 (0.98-1.41)	0.09
3q27	rs16861205 (G/A)	186561634	A	0.18	0.10	1.88 (1.43-2.47)	6.42E-06**
3q27	rs822391 (T/C)	186563803	C	0.09	0.11	0.89 (0.66-1.23)	0.50
3q27	rs1501299 (G/T)	186571123	T	0.29	0.26	1.14 (0.93-1.40)	0.19
3q27	rs2241767 (A/G)	186571169	G	0.22	0.22	1.02 (0.82-1.27)	0.89
3q27	rs3774261 (A/G)	186571559	G	0.43	0.44	1.01 (0.85-1.21)	0.90
3q27	rs7639352 (C/T)	186578474	T	0.31	0.28	1.18 (0.97-1.45)	0.10

[1]Genotypes were indicated by major/minor alleles (M/m); [2]BP: Base Pair; [3]RA: Risk Allele; [4]OR and *P* value were calculated based on logistic regression and adjusted for age; ***P*<0.01.

Table 3. Associations between SNPs of adiponectin gene with BPH aggressiveness

Chr	SNP (M/m)[1]	BP	RA	Minor allele frequency		OR (95% CI)[4]	*P*[4]
				Aggressive[2]	Non-aggressive[3]		
3q27	rs182052 (G/A)	186560782	A	0.49	0.45	1.12 (0.85-1.48)	0.42
3q27	rs16861205 (G/A)	186561634	A	0.19	0.17	1.03 (0.73-1.47)	0.85
3q27	rs822391 (T/C)	186563803	C	0.07	0.11	0.61 (0.36-1.03)	0.07
3q27	rs1501299 (G/T)	186571123	T	0.24	0.20	1.26 (0.89-1.77)	0.19
3q27	rs2241767 (A/G)	186571169	G	0.40	0.53	0.88 (0.6-1.17)	0.38
3q27	rs3774261 (A/G)	186571559	G	0.41	0.45	0.97 (0.66-1.15)	0.33
3q27	rs7639352 (C/T)	186578474	T	0.33	0.29	1.19 (0.87-1.61)	0.23

[1]Genotypes were indicated by major/minor alleles (M/m); [2]Patients suffered from a significant increase of BPH related complications or continuous decrease in maximum urinary flow Rate were defined as aggressive BPH; [3]Patients with stable disease and no indications to receive invasive treatments were considered as nonaggressive BPH; [4]OR and *P* value were calculated based on logistic regression and adjusted for age.

was defined by the change of clinical traits such as IPSS, TPV, total prostate-free antigen (tPSA), and free prostate-free antigen (fPSA) were transformed through log transformations. Associations between SNPs and clinical response to the treatment were analyzed by log-linear analysis. All analyses were conducted through PLINK software (Plink v 1.07) [15]. *P*-values less than 0.05 were considered as statistical significance.

Results

The overall demographic characteristics of the study subjects are showed in **Table 1**. The average ages of two patients groups (aggressive and non-aggressive BPH) are both beyond 70 yrs (73.84 yrs in aggressive BPH and 70.45 yrs in non-aggressive BPH) while the average age of health control is 61.24 yrs. The clinical characteristics related to BPH aggressiveness showed significant difference between two patient groups.

Firstly, the genotype distributions of all SNPs included in this study were tested in Hardy-Weinberg equilibrium (HWE). The associations between several SNPs with BPH risk were analyzed (**Table 2**). Our results indicated SNP rs16861205, out of seven SNPs, was significantly associated with BPH risk (*P*=6.42E-06). In particular, subjects carrying the allele "A" of rs16861205 had 1.8-fold higher risk of the BPH than subjects who carrying "G" allele (OR=1.88, 95% CI: 1.43-2.47). Similar analyses were performed to exam if any of these SNPs were correlated with the aggressiveness of BPH. No significant association between the SNPs and BPH aggressiveness was noticed in our analysis (**Table 3**).

Next, we investigated the associations between SNPs and all the clinical responses to the combinational treatments. Clinical variables like IPSS score, PV, TPV and PSA levels were assessed during the post-treatment follow up. Normally, the IPSS score were signifi-

Table 4. Associations between SNPs and TPV change in response to the combinational treatment

SNP (M/m)	BP	RA	Mean GG/GA/AA	*P* (Add)[1]	*P* (Dom)[2]	*P* (Rec)[3]
rs182052 (G/A)	186560782	A	-1.64/0.54/0.97	0.03*	0.04*	0.15
rs16861205 (G/A)	186561634	A	-3.61/0.98/1.58	0.04*	0.06	0.01*

[1-3]The *P* values were obtained via analysis with the additive model, dominant model, or recessive model respectively; *, *P*<0.05.

Table 5. Associations between SNPs and other clinical response to the combinational treatment

SNP (M/m)	RA	IPSS change[1]		PV change[1]		t-PSA change[1]		f-PSA change[1]	
		Beta (SE)	*P*[2]	Beta (SE)	*P*[2]	Beta (SE)	*P*[2]	Beta (SE)	*P*[2]
rs182052 (G/A)	A	0.29 (0.31)	0.34	2.4 (0.93)	0.03*	0.09 (0.26)	0.71	0.16 (0.11)	0.13
rs16861205 (G/A)	A	0.11 (0.39)	0.79	2.43 (1.17)	0.04*	-0.44 (0.33)	0.20	-0.09 (0.14)	0.49
rs822391 (T/C)	C	-0.68 (0.56)	0.22	-1.66 (1.68)	0.32	1.19 (0.47)	0.01*	0.34 (0.19)	0.08
rs1501299 (G/T)	T	0.17 (0.35)	0.63	-0.02 (1.05)	0.9	0.16 (0.29)	0.58	0.18 (0.13)	0.15
rs2241767(A/G)	G	0.11 (0.32)	0.71	-1.14 (0.94)	0.22	-0.13 (0.27)	0.64	-0.17 (0.11)	0.14
rs3774261 (A/G)	A	-0.19 (0.31)	0.53	0.1 (0.93)	0.91	0.61 (0.26)	0.02*	0.17 (0.11)	0.12
rs7639352 (C/T)	T	0.27 (0.34)	0.42	0.97 (1.01)	0.34	-0.08 (0.29)	0.78	0.15 (0.12)	0.20

[1]The change of IPSS, TPV, fPSA and tPSA were calculated as the values after treatment minus the values at baseline; [2]The Beta (SE) and *P* values were obtained via additive model analysis; *, *P*<0.05.

cantly improved from baseline while PSA levels and PV, TPV measurements were decreased throughout the study. The results of correlation analysis indicated genotypes of rs16861205 again, as well as another rs182052, were significantly correlated with TPV improvement after the treatments (*P*=0.03 and *P*=0.04, respectively) (**Table 4**). In particular, TPV in subjects carrying normally "G/G" in rs16861205 decreased 3.61 ml in response to the treatment. In contrast to that, TPV level in subjects with "A/A" genotype (homozygous minor allele) was increased after the therapy (**Table 4**). The other SNP rs182052 showed similar pattern in post-treatment exams. These results indicated genotype of some SNPs, especially rs16861205, were highly related to the clinical status of BPH, including disease risk and prognosis.

On top of that, other clinical variables in patients with different SNPs genotypes showed different responses to BPH treatment (**Table 5**). For instance, change of t-PSA was significantly associated with genotype variants of SNPs rs822391 and rs3774261.

Discussion

BPH is the most common prostate problem for men older than age of 50. The occurrence and symptoms of BPH increase greatly with age. So it is of great importance in clinical practice to seek a useful biomarker to predict the risk and the outcome of BPH.

Protein level of adiponectin in serum has been reported to associated with high risk of prostate diseases such as prostate enlargement and prostatic malignancy [16]. Adiponectin gene expression was also found downregulated in prostate cancer tissues [17]. Little is known about the relationship of adiponectin genetic variants and the clinical signatures of BPH. Our study was the first time to report the significant associations between tag SNPs of adiponectin gene with BPH risk, aggressiveness, as well as the clinical response to BPH treatment.

Adiponectin acts as an important regulator and biological marker in metabolic syndrome. It is concluded that high adiponectin level antagonized the fatty inflammation, insulin resistance and metabolic syndrome, especially in obese people. However, the genetics studies in adiponectin SNPs yielded different conclusions in different populations [18-20]. In this cohort study of Han Chinese population, we found rs16861205, located in the intron of 3q27, was significantly associated with BPH risk (*P*= 6.42E-06). Risk allele "A" of rs16861205 indicated higher risk of BPH. In addition to that, BPH therapy failed to reduce TPV level in patients carrying "A/A" genotype in this SNP, com-

pared to patients with the "G/G" genotype. Previously, Du et al reported in Chinese Han descent "A/A" genotype was negatively related to serum glucose level as well as blood pressure on the same SNP and indicated lower risk of metabolic syndrome compared to "G/G" genotype [21]. Inspired from that, our expectation at the beginning of this study was this SNP mutation should lead to a reduced risk of BPH. Surprisingly, the results from our analysis suggested an opposite conclusion. Interestingly, Ye et al from an independent group reported there were significant correlations between rs1342387A/G and tumor location [22]. In particular, rs16861205 with the minor alleles "A/A" presented significant associations with a decreased risk of cardia cancer but an increased risk of body cancer [22]. It seems there are various aspects of risk prediction that are outside the scope of the particular SNP rs16861205. The relationship of SNP rs16861205 with disease risk should be tissue specific and interindividual variances among different populations should be taken into account.

Another adiponectin identified associated with changing of TPV in response to the therapy is SNP rs182052. Patients with "A/A" genotype showed weaker TPV improvement than "G/G" patients after 9-month treatment. An Asian cohort study reported subjects with the minor allele "A/A" of rs182052 loci genotype had 17.7% higher plasma level of adrenal medulla in patients with cardiovascular disease and diabetes [23]. High level of adrenal medullary hormone resulted in activated sympathetic nervous system and systemic inflammatory response, which consequently promote prostate cell proliferation. In consistent to that, we found patients with "A/A" genotype at rs182052 loci had higher baseline IPSS score (data not show). Another study found "A/A" genotype of rs182052 was associated with lower serum adiponectin levels which could reduce the insulin sensitivity [24]. Taken together, it is possible that serum hormone level, including adiponectin, may directly contribute to the impaired TPV improvement we observed in "A/A" genotype patients.

Several limitations need to be noted regarding the present study. Firstly, the relatively small sample size lowered the statistical power to pull significant association of SNPs with the clinical outcomes of BPH. These findings need to be validated in cohorts with larger samples size. Secondly, data of serum adiponectin level is missing in this study. Considering the rs16861205 loci locate in the intron region of adiponection gene, the SNP genotype may not affect its protein level but it should be carefully confirmed by measurements. Hence our study could not completely exclude that clinical influence of adiponectin SNPs in BPH patients may be an indirect effect due to altered adiponectin level or other hormone in serum.

Conclusion

This is the first study to identify the associations between SNPs of adiponectin gene and clinical outcomes of BPH. Our results suggested the two SNP (rs16861205 and rs182052) may serve as useful tools in risk prediction and prognosis assessment for Chinese BPH patients.

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Disclosure of conflict of interest

None.

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