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Association of polymorphism within the interleukin-28 receptor alpha gene, but not in interleukin-28B, with lower urinary tract symptoms (LUTS) in Chinese

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ABSTRACT. The aim of this study was to determine the relationship between polymorphisms in the IL-28B and IL-28R genes and lower urinary tract symptoms (LUTS) in Chinese patients. Genomic DNA was extracted from 553 whole blood samples from 233 patients with LUTS resulted from benign prostatic hyperplasia and 320 control subjects. The IL-28B rs12979860 and rs8099917, and IL-28Rα rs10903035 and rs11249006 polymorphisms were genotyped using a polymerase chain reaction-restriction fragment length polymorphism assay. For rs10903035, the frequencies of the "G" allele and the "AG/GG" genotypes in the LUTS group were significantly lower than those in the control group ("G" *vs* "A": OR = 0.655, 95%CI = 0.506-0.849;

AG/GG *vs* "AA": OR = 0.538, 95%CI = 0.379-0.764, respectively). Combined effects analysis of rs12979860 and rs10903035 showed that the "CC+AG/GG" and "CT+AA" genotypes were significantly less frequent in the LUTS group ("CC+AG/GG" *vs* "CC+AA": OR = 0.553, 95%CI = 0.381-0.801; "CT+AG/GG" *vs* "CC+AA": OR = 0.429, 95%CI = 0.198-0.927, respectively). In addition, the combined effects of the rs8099917 and rs10903035 "TT+AG/GG" and "GT+AG/GG" genotypes were also significantly lower in the LUTS group ("TT+AG/GG" *vs* "TT+AA": OR = 0.569, 95%CI = 0.395-0.821; "GT+AG/GG" *vs* "TT+AA": OR = 0.318, 95%CI = 0.128-0.788, respectively). Stratification analysis revealed that the frequencies of the rs11249006 "AG/GG" genotypes in the subgroups of size ≤4.11 and IPSS ≤ 28 were significantly higher than those in the subgroups of size >4.11 and IPSS > 28. Therefore, the *IL-28Rα* gene polymorphism might be involved in the development of LUTS.

Key words: Benign prostatic hyperplasia; Interleukin-28B; Interleukin-28B receptor α; Single nucleotide polymorphism; Lower urinary tract symptoms

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common benign disease that leads to lower urinary tract symptoms (LUTS) in mid-aged or aged men. The major clinical manifestations include LUTS and bladder outlet obstruction (Wu and Gu, 1991; Rowhrborm and McConnell, 2002). Histological enlargement of the prostate generally initiates around 40 years of age and LUTS occurs at over fifty-five years of age. The LUTS become more severe with increasing age, which greatly impacts the quality of life of aged men (Berry et al., 1984; Gu et al., 1994). Eventually, patients must have surgery to relieve the urinary obstruction. In certain studies, moderate and severe LUTS seemed to occur more readily in Asian than in American men (Homma et al., 1997; Arvanitis et al., 2004). Furthermore, there was a tendency for LUTS to occur in families, and the incidence of LUTS was found to be higher in homozygotic than in heterozygotic twins. Together, these studies suggested that the development of LUTS consequent to BPH is partially determined by individual genetic background. However, the exact mechanism of BPH-associated LUTS is still unknown.

Interleukin-28B (IL-28B) has been identified as a novel member of the interferon-lambda family with biological functions of antiviral, anti-hyperplasia, and immune mediation. (Robek et al., 2005; Sato et al., 2006; Zitzmann et al., 2006; Jordan et al., 2007; Numasaki et al., 2007; Siebler et al., 2007; Li et al., 2008; Dellgren et al., 2009). High expression of *IL-28Rα* mRNA in human pancreas, thyroid, prostate, and testis has been observed (Kotenko et al., 2003; Sheppard et al., 2003). Previous study has shown that *IL-28B* gene polymorphisms play a role in the development of viral hepatitis and in the response to antiviral treatment (Cheng et al., 2012; Osaki et al., 2012). Additionally, the IL-28 family resembles IL-10 in function and construction (Dumoutier and Renauld, 2002; Chen et al., 2006). Of note, the other subunit receptor of IL-28B, IL-10R2, is also an IL-10 receptor family member and forms a heterodimer together with IL-28Rα. Research has also shown that IL-10 exhibits elevated expression in BPH concomitant with inflammation (Kotenko, 2002). Based on this informa-

tion, it has been assumed that *IL-28B* or *IL-28Rα* gene polymorphisms might play a role in the development of LUTS. In this study, four single nucleotide polymorphisms (SNPs) in the *IL-28B* and *IL-28Rα* genomic loci in 233 patients with BPH with serious LUTS and in 320 non-LUTS subjects were investigated, on the assumption that these gene polymorphisms might function as susceptibility markers for the development of LUTS.

MATERIAL AND METHODS

Study population

We enrolled 233 patients with BPH and moderate to severe LUTS, between the age of 48 and 86, and who underwent surgery in the West China Hospital of Sichuan University, in this study (Table 1). We also enrolled 320 non-LUTS control subjects between the age of 22 and 68 in the same hospital. The diagnosis of BPH in patients was based on medical history, physical examination, prostatic ultrasonography, and pathological evidence. Individuals with a history of acute/chronic urine retention, LUTS, or repeated hematuria were intentionally excluded as controls.

Table 1. Common parameters of the LUTS and control groups.

	LUTS (N = 233)	Controls (N = 320)	P value
Age (years)	70.59 ± 6.77	41.96 ± 12.74	<0.05
Size* (cm)	4.16 ± 0.76	-	-
PSA# (ng/mL)	7.19 ± 7.18	-	-
IPSS	27.76 ± 6.04	-	-

Antero-posterior diameter of the prostate measured by ultrasonography. #Prostatic-specific antigen; total PSA is given. IPSS = international prostatic symptoms score. LUTS = lower urinary tract symptoms. Data are reported as means ± standard deviation.

Genotyping

The genomic DNA of each individual was extracted from 200-µL EDTA-anticoagulated peripheral blood samples using a whole blood DNA isolation kit from BioTeke Corporation (Beijing, China). The procedure was carried out according to the manufacturer instructional manual. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was employed to determine the genotypes of the *IL-28B* and *IL-28Rα* gene polymorphisms. The rs12979860 polymorphism genotype was determined using the following primers: 5'- GCC CCT AAC CTC TGC ACA GTC T -3' (forward) and 5'- AGT GCA ATT CAA CCC TGG TGC -3' (reverse). The PCR product (1 µL sample DNA, 5 µL 2X Taq PCR MasterMix, 0.2 µL specific pair primers, 3.8 µL ddH_2O in 10 µL reaction volume. The reactants were from JinBo (BeiJing, China). The sample DNAs were amplified by PCR. The amplification process was performed in a Mastercycler Nexus PCR (Eppendorf, Germany). It comprised a denaturation step at 94ºC for 4 min, 34 cycles (denaturation for 45 s at 94ºC, renaturation for 45 s at 61ºC, extention for 3 minutes at 72ºC) and an extention step at 72ºC for 10 min.

The PCR product was digested with 10 U *Apa*I at 37°C for 4 h. The "C" and "T" alleles were assigned based on the presence of a 151-bp (undigested) fragment and 20- and 131-bp (digested) fragments, respectively. The rs8099917 genotype was determined using the following primers: 5'- AAG TCT TGT ATT TCA CCT CCT GGA GG -3' (forward) and 5'- GCA TGG TTC CAA

TTT GGG AGA -3' (reverse). The PCR product was digested with 10 U *Bsm*AI at 55°C for 4 h and the "T" and "G" alleles were assigned based on the presence of a 107-bp (undigested) fragment and 16- and 91-bp (digested) fragments, respectively. The rs10903035 genotype was determined using the following primers: 5'- AGC TCC TTT GCA ACA AAA GGA CTG -3' (forward) and 5'- TTT CAC CAG AGC AGC CTC ACT G -3' (reverse). The PCR product was digested with 10 U *Bsr*I at 65°C for 4 h and the "C" and "T" alleles were assigned based on the presence of a 125-bp (undigested) fragment and 26- and 99-bp (digested) fragments, respectively. The rs11249006 genotype was determined using the following primers: 5'- CGG GTG AAA ACT CAG CTA CGC TC -3' (forward) and 5'- GGC ACG TTA GAC TCT TGG TTG GC -3' (reverse). The PCR product was digested with 10 U *Hae*III at 65°C for 4 h and the "A" and "G" alleles were assigned based on the presence of a 177-bp (undigested) fragment and 155- and 22-bp (digested) fragments, respectively. In addition, the exact genomic sequences of undigested amplified genomic fragments were confirmed by direct sequencing. The exact genomic sequences of undigested amplified genomic fragments were confirmed by Sanger sequencing (Invitrogen, Shanghai, China), and the analysis was performed by the Chromas software version 2.1.1 (Technelysium Ltd., Helensvale, Queensland, Australia) .

Statistical analysis

All statistical calculations were performed using the SPSS 19.0 statistical software (SPSS, Chicago, IL, USA). Comparisons between groups were performed using the chi-square test and the Fisher exact test when appropriate. Contingency tables were used to analyze qualitative results. Hardy-Weinberg equilibrium was calculated by using the χ^2 test (with one degree of freedom). The level of statistical significance was set at $P < 0.05$.

RESULTS

Genotype distributions were in accord with Hardy-Weinberg equilibrium in patients with LUTS and control subjects. The results of the four gene polymorphisms for the 233 patients with LUTS and the 320 control subjects are shown in Table 2. The combined effects of *IL-28B* and *IL-28Rα* genotypes are shown in Table 3.

In the present study, the significant differences in the genotypes and frequencies of the alleles of the *IL-28B* and *IL-28Rα* polymorphisms were identified between the patients with LUTS and the control subjects. It was found that the rs10903035 genotypes "AA" and "AG/GG" occurred in patients with LUTS with the frequencies of 45.06 and 54.94%, and in the control group with the frequencies of 30.62 and 69.38% respectively. The "AG/GG" genotypes of the rs10903035 locus in the LUTS group were significantly less frequent than in the control group (OR = 0.538, 95%CI = 0.379-0.764, P = 0.001). Similarly, the frequency of the rs10203035 "G" allele in the LUTS group was significantly lower than that in the control group (OR = 0.655, 95%CI = 0.506-0.849, P = 0.001). However, there were no significant differences between the allele or genotype frequencies of the other three loci between the groups.

In the *IL-28B* rs12979860 and *IL-28Rα* rs10903035 interaction analysis, it was found that the "CC+AG/GG" and "CT+AG/GG" genotypes were significantly less frequent in the patient than in the control group ("CC+AG/GG" *vs* "CC+AA": OR = 0.553, 95%CI = 0.381-

0.801, P = 0.002; "CT+AG/GG" *vs* "CC+AA": OR = 0.429, 95%CI = 0.198-0.927, P = 0.028, respectively). Similarly, in the *IL-28B* rs8099917 and *IL-28Rα* rs10903035 interaction analysis, it was found that the "TT+AG/GG" and "GT+AG/GG" genotypes were also significantly less frequent in the patient than in the control group ("TT+AG/GG" *vs* "TT+AA": OR = 0.569, 95%CI = 0.395-0.821, P = 0.002; "GT+AG/GG" *vs* "TT+AA": OR = 0.318, 95%CI = 0.128-0.788, P = 0.01, respectively).

To evaluate the effect of the distribution frequencies of the genotypes in patients with LUTS, the LUTS group was separated into six subgroups according to size, prostatic specific antigen (PSA), and international prostatic symptoms score (IPSS) of the prostate, respectively (Tables 4-6). In subgroups based on prostate size, the distributions of the rs11249006 "AG/GG" genotypes in the subgroup of size ≤4.11 were significantly higher than those in the subgroup of >4.11 (OR = 1.726, 95%CI = 1.018-2.929, P = 0.042). Similarly, the frequencies of the "AG/GG" genotypes were also significantly higher in the subgroup of IPSS ≤ 28 than in the subgroup of IPSS > 28 (OR = 2.009, 95%CI = 1.175-3.436, P = 0.01).

Table 2. *IL-28B* and *IL-28Rα* genotype and allele frequencies of the groups studied.

Genotype	LUTS (N = 233)	Control (N = 320)	OR (95%CI)	P value
IL-28 rs12979860				
CC	210 (90.103%)	285 (89.060%)	1	
CT	23 (9.870%)	35 (10.940%)	0.892 (0.512-1.554)	0.686
C allele frequency	443 (95.060%)	605 (94.530%)	1	
T allele frequency	23 (4.940%)	35 (5.470%)	0.897 (0.523-1.540)	0.695
IL-28 rs8099917				
TT	219 (94.000%)	292 (91.250%)	1	
GT	14 (6.000%)	28 (8.750%)	0.667 (0.343-1.296)	0.230
T allele frequency	452 (97.000%)	612 (95.630%)	1	
G allele frequency	14 (3.000%)	28 (4.370%)	0.677 (0.352-1.301)	0.239
IL-28Rα rs10903035				
AA	105 (45.060%)	98 (30.620%)	1	
AG/GG	128 (54.940%)	222 (69.350%)	0.538 (0.379-0.764)	0.001
A allele frequency	337 (72.320%)	404 (63.130%)	1	
G allele frequency	129 (27.680%)	236 (36.870%)	0.655 (0.506-0.849)	0.001
IL-28Rα rs11249006				
AA	94 (40.340%)	149 (46.560%)	1	
AG/GG	139 (59.660%)	171 (53.440%)	1.288 (0.916-1.813)	0.146
A allele frequency	317 (68.030%)	444 (69.370%)	1	
G allele frequency	149 (31.970%)	196 (30.630%)	1.065 (0.823-1.377)	0.632

LUTS = lower urinary tract symptoms; OR = odds ratio; CI = confidence interval.

Table 3. *IL-28B* genotypes combined with *IL-28Rα* genotypes in the groups studied.

	LUTS (N = 233)	Control (N = 320)	OR (95%CI)	P value
IL-28 Rs12979860 + *IL-28Rα* rs10903035				
CC+AA	93 (39.910%)	87 (27.190%)	1	
CC+AG/GG	117 (50.220%)	198 (61.880%)	0.553 (0.381-0.801)	0.002
CT+AA	12 (5.150%)	11 (3.430%)	1.021 (0.428-2.433)	0.963
CT+AG/GG	11 (4.720%)	24 (7.490%)	0.429 (0.198-0.927)	0.028
IL-28 rs8099917 + *IL-28Rα* rs10903035				
TT+AA	98 (42.060%)	89 (27.810%)	1	
TT+AG/GG	121 (51.930%)	193 (60.310%)	0.569 (0.395-0.821)	0.002
GT+AA	7 (3.000%)	8 (2.500%)	0.795 (0.277-2.280)	0.669
GT+AG/GG	7 (3.000%)	20 (6.240%)	0.318 (0.128-0.788)	0.010

LUTS = lower urinary tract symptoms; OR = odds ratio; CI = confidence interval.

Table 4. Size and genotype distribution frequencies in the LUTS groups.

Genotype	Size of LUTS*		OR (95%CI)	P value
	≤4.11 (N = 118)	>4.11 (N = 115)		
IL-28 rs12979860				
CC	102 (86.440%)	108 (93.910%)	1	
CT	16 (13.560%)	7 (6.090%)	2.42 (0.956-6.125)	0.056
C allele frequency	220 (93.22%)	223 (96.95%)	1	
T allele frequency	16 (6.780%)	7 (3.050%)	2.317 (0.935-5.742)	0.063
IL-28 rs8099917				
TT	111 (94.070%)	108 (93.910%)	1	
GT	7 (5.930%)	7 (6.090%)	0.973 (0.33-2.867)	0.96
T allele frequency	229 (97.030%)	223 (96.905%)	1	
G allele frequency	7 (2.97 0%)	7 (3.050%)	0.974 (0.336-2.821)	0.961
IL-28α rs10903035				
AA	51 (43.220%)	54 (46.960%)	1	
AG/GG	67 (56.780%)	61 (53.040%)	1.163 (0.694-1.949)	0.567
A allele frequency	169 (71.610%)	168 (73.040%)	1	
G allele frequency	67 (28.390%)	62 (26.960%)	1.074 (0.716-1.612)	0.73
IL-28α rs11249006				
AA	40 (33.900%)	54 (46.960%)	1	
AG/GG	78 (66.100%)	61 (53.040%)	1.726 (1.018-2.929)	0.042
A allele frequency	153 (64.830%)	164 (71.300%)	1	
G allele frequency	83 (35.170%)	66 (28.700%)	1.348 (0.912-1.993)	0.134

*Antero-posterior diameter of the prostate measured by ultrasonography; LUTS = lower urinary tract symptoms; OR = odds ratio; CI = confidence interval.

Table 5. PSA and genotype distribution frequencies in the LUTS groups.

Genotype	PSA of LUTS*		OR (95%CI)	P value
	≤4.2 (N = 116)	>4.2 (N = 117)		
IL-28 rs12979860				
CC	105 (90.520%)	105 (89.740%)	1	
CT	11 (9.480%)	12 (10.260%)	0.917 (0.387-2.17)	0.843
C allele frequency	221 (95.260%)	222 (94.870%)	1	
T allele frequency	11 (4.740%)	12 (5.130%)	0.921 (0.398-2.131)	0.847
IL-28 rs8099917				
TT	111 (95.690%)	108 (92.310%)	1	
GT	5 (4.310%)	9 (7.690%)	0.541 (0.176-1.665)	0.277
T allele frequency	227 (97.84%)	225 (96.150%)	1	
G allele frequency	5 (2.163%)	9 (3.850%)	0.551 (0.182-1.669)	0.285
IL-28α rs10903035				
AA	55 (47.410%)	50 (42.730%)	1	
AG/GG	61 (52.590%)	67 (57.270%)	0.828 (0.494-1.388)	0.473
A allele frequency	171 (73.710%)	166 (70.940%)	1	
G allele frequency	61 (26.290%)	68 (29.060%)	0.871 (0.58-1.307)	0.505
IL-28α rs11249006				
AA	50 (43.100%)	44 (37.610%)	1	
AG/GG	66 (56.900%)	73 (62.390%)	0.796 (0.471-1.344)	0.392
A allele frequency	159 (68.530%)	158 (67.520%)	1	
G allele frequency	73 (31.470%)	76 (32.480%)	0.954 (0.647-1.409)	0.815

*Prostatic-specific antigen; total PSA is given; LUTS = lower urinary tract symptoms; OR = odds ratio; CI = confidence interval.

Table 6. IPSS and genotype distribution frequencies in the LUTS groups.

Genotype	IPSS of LUTS		OR (95%CI)	P value
	≤28 (N = 108)	>28 (N = 125)		
IL-28 rs12979860				
CC	96 (88.89%)	114 (91.20%)	1	
CT	12 (11.110%)	11 (8.800%)	1.295 (0.547-3.068)	0.555
C allele frequency	204 (94.440%)	239 (95.600%)	1	
T allele frequency	12 (5.560%)	11 (4.400%)	1.278 (0.552-2.958)	0.566
IL-28 rs8099917				
TT	102 (94.440%)	117 (93.600%)	1	
GT	6 (5.560%)	8 (6.400%)	0.860 (0.289-2.562)	0.787
T allele frequency	210 (97.220%)	242 (96.800%)	1	
G allele frequency	6 (2.780%)	8 (3.200%)	0.864 (0.295-2.531)	0.790
IL-28Rα rs10903035				
AA	50 (46.300%)	55 (44.000%)	1	
AG/GG	58 (53.700%)	70 (56.000%)	0.911 (0.543-1.529)	0.725
A allele frequency	157 (72.690%)	180 (72.000%)	1	
G allele frequency	59 (27.310%)	70 (28.000%)	0.966 (0.643-1.452)	0.869
IL-28Rα rs11249006				
AA	34 (31.480%)	60 (48.000%)	1	
AG/GG	74 (68.520%)	65 (52.000%)	2.009 (1.175-3.436)	0.010
A allele frequency	136 (62.960%)	181 (72.400%)	1	
G allele frequency	80 (37.040%)	69 (27.600%)	1.543 (1.043-2.282)	0.029

IPSS = international prostatic symptoms score; LUTS = lower urinary tract symptoms; OR = odds ratio; CI = confidence interval.

DISCUSSION

IL-28B has been termed as interferon-λ3 and belongs to the interferon-λ family that is comprised of interferons-λ1-λ3 (Kotenko et al., 2003; Renauld, 2003; Sheppard et al., 2003). The human gene that encodes interferon-λ3 includes six exons and is located on chromosome 19 (19q13.13) (Lasfar et al., 2006). Its receptor IL-28Rα has also been termed as IFN-λ R1 or CRF2-12, and is a member of the class II cytokine receptor family (CRF2).

The IL-28Rα subunit and the IL-l0R β subunit make up the receptor heterodimer and mediate signal transduction in the cells. After binding of the ligand to the heterodimer, the Janus kinase-signal transducer and activator of transcription pathway is activated (Vilcek, 2003). Additionally, this signal pathway is simultaneously activated by IFN-α; therefore, interferon-λ3 appears to resemble IFN-α in antiviral, inhibition of cell proliferation, and regulation of immune activity biological functions (Dellgren et al., 2009). This similarity seems to explain the observation that variation of interferon-λ3 can lead to alterations in the inhibition of cell proliferation and regulation of immune activity. The biological activity of IFN-λ3 depends on the specificity of the distribution of its receptors. The IL-l0R β subunit has ubiquitous ligand binding activity, whereas IL-28Rα is specific for IL-28B. *IL-28Rα* mRNA has been shown to exhibit high levels of expression in pancreas, thyroid, skeletal muscle, heart, prostate, and testis (Sheppard et al., 2003), which seems to suggest that interferon-λ3 plays a role in these organs. In addition, the presence of the IL-l0R β subunit in the IL-28R heterodimer suggests that IFN-λ3 bound to its receptor can also transmit information through the IL-10 signal pathway. IL-10 expression has also been shown to be elevated in BPH concomitant with inflammation (Miller et al., 2002; Shoskes et al., 2002), which further implies a correlation between IFN-λ3, LUTS, and inflammation. At present, the factors which caused the inflammation have been considered as the suspected cause for BPH (Sciarra et

al., 2007). IFN-λ3 has been shown to both cause and regulate inflammation in the liver upon infection by hepatitis C virus (Barreiro et al., 2011). Therefore, it has been considered that *IL-28B* gene polymorphism, which has been shown to be involved in inflammatory diseases (Bierne et al., 2012), might also play a role in the development of BPH with serious LUTS, and therefore *IL-28B* and *IL-28R* genetic variations have been considered to be potentially associated with LUTS. Additionally, Homma et al. (1997) reported that moderate and severe LUTS seemed to occur more readily in Asian compared to American men; furthermore, a tendency was observed for LUTS to cluster in families, and the incidence of LUTS was shown to be higher in homozygous than in heterozygous twins. These findings together suggest that genetic factors might play a role in the development of LUTS.

Recently, several studies have described the association between polymorphisms of *IL-28B* and *IL-28Rα* and the outcomes of antiviral therapy in patients who were infected by hepatitis B or C viruses (HBV or HCV) (Rauch et al., 2010; Eurich et al., 2012; Lampertico et al., 2012). Cui et al. (2011) reported that *IL-28Rα* polymorphism was associated with the outcomes of HCV infection in a high-risk Chinese population. Lampertico et al. (2012) reported that *IL-28B* polymorphism was strongly associated with HBsAg seroclearance in patients who were chronically infected by HBV with the D genotype. Eurich et al. (2012) reported that the "C" allele of *IL-28B* plays a protective role in the development of HCV-induced hepatocellular carcinoma. In contrast, Barreiro et al. (2011) reported that the *IL-28B* rs12979860 "CC" genotype was associated with a higher prevalence of cirrhosis. However, the relationship between the *IL-28B* and *IL-28Rα* gene polymorphisms and LUTS has not been reported. In the present study, it was observed that the most common genotypes were "CC" and "TT" in the *IL-28B* rs12979860 and *IL-28B* rs8099917 loci (90.13 and 94%, respectively), which differs from the observation of Lampertico et al. (2012). We considered that these differences might result from different ethnicities of the populations studied. Similarly, it was also observed in this study that the most common genotypes were "AG" in the *IL-28Rα* rs10903035 and rs11249006 loci (54.51 and 55.36%, respectively). Similar to the report of Cui et al. (2011) that the *IL28Rα* rs10903035 and rs11249006 haplotype "GG" played a protective effect for HCV infection, in this study it was also observed that the *IL-28Rα* rs10903035 "AG/GG" genotypes were significantly less frequent in patients with LUTS. Furthermore, it was found that the frequency of the "G" allele of the rs10903035 locus in the LUTS group was also significantly lower. Together with the difference of the frequencies of the "A" or "G" alleles in the LUTS and control groups, these results seemed to suggest that the *IL-28Rα* SNP might be related to the development of LUTS in the Chinese BPH population.

After a stratification analysis according to the size, PSA, and IPSS of the prostate, it was found that the frequencies of the "AG/GG" genotypes at the *IL-28Rα* rs11249006 locus were higher in the size ≤4.11 cm and the IPSS ≤ 28 subgroups. These differences supported the trend that the patients with LUTS who carried the *IL28Rα* "AG/GG" genotype seemed to display reduced clinical numbers and severities of LUTS than did individuals carrying the "CC" variants, and suggesting that the "G" allele served a protective role in the course of development of LUTS. When the combined effects of *IL-28B* and *IL-28Rα* were further studied, it was observed that the *IL-28B* rs1279860 "CC" genotype + *IL28Rα* rs10903035 "AG/GG" were also less frequent in the LUTS group; this also seems to support the above trend. It is possible that *IL-28Rα* variant (A/G) might cause the functional alteration of IFN-stimulated genes and influence the secretion of proinflammatory cytokines in patients with BPH, and therefore be ultimately involved in the development of LUTS. Nonetheless, the exact mechanism of *IL-28Rα* gene polymorphism

involvement in the development of LUTS is still unclear.

There are, however, some limitations to this study. First, the sample size was not large enough to make definitive conclusions. Second, only subjects who had been treated in the West China Hospital of Sichuan University were analyzed. Therefore, the patients enrolled in the study might not be representative of the general Chinese BPH plus LUTS patient population. Third, the difference of age between patients with LUTS and control subjects might have had an impact on the results. Additional studies in a large number of patients with BPH and LUTS and in different populations might help to establish the exact association of *IL-28B* and *IL-28R* genetic polymorphism with the development of LUTS.

In conclusion, this study demonstrated tha*t IL-28Rα* gene polymorphism might be involved in the development of LUTS in a Chinese population.

Conflicts of interest

The authors declare no conflict of interest.

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