Positive Correlation Between Beta-3-Adrenergic Receptor (*ADRB3*) Gene and Gout in a Chinese Male Population

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ABSTRACT. ***Objective.*** The common polymorphism rs4994 [c. T387C, p. Trp64Arg (W64R)] of the lipolysis regulator beta-3-adrenergic receptor (*ADRB3*) was identified as a marker in the pathogenesis of hyperuricemia. As gout is characterized by elevated serum concentrations of uric acid, we investigated *ADRB3* as a potential candidate for gout.

Methods. This was a prospective case-control study in a group of 421 male patients with gout and 312 gout-free male controls to genotype the single-nucleotide polymorphism rs4994 of *ADRB3* gene.

Results. Our results showed that the C allele carrier confers a significantly higher risk for development of gout [chi-square = 4.91, df = 1, p = 0.027, OR 1.95 (adjusted by age, total cholesterol level, and body mass index), 95% CI 1.22–3.13 by dominant mode]. There was significantly higher uric acid level in carriers of the Arg64/Arg64 genotype in controls compared to non-carriers (480.5 mmol/l vs 315.0 mmol/l, respectively).

Conclusion. *ADRB3* rs4994 polymorphism is a potential candidate for the pathogenesis of gout in a male Chinese population. (J Rheumatol First Release Feb 1 2011; doi:10.3899/jrheum.101037)

Key Indexing Terms:
BETA-3-ADRENERGIC RECEPTOR *ADRB3* HYPERURICEMIA
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Gout is characterized by joint pain, inflammation, and painful tophi, and can result in joint destruction and disability if untreated[1]. Uric acid (UA) is the endproduct of purine metabolism in humans, and concentrations of it are primarily determined by endogenous metabolism and the rate of excretion and reabsorption in the kidney[2].

The beta-3-adrenergic receptor (*ADRB3*), located on human chromosome 8p12-p11.2, is expressed predominantly in adipose tissue and is involved in the regulation of lipolysis and thermogenesis[3]. The direct potential for this gene is to promote obesity in humans; previous studies suggested that *ADRB3*-selective agonists had an antidiabetic effect in rodent models of obesity and diabetes[4].

Trp64Arg (W64R, rs4994) variant was first reported by Walston and colleagues in Indians[5]. This single-nucleotide polymorphism has moreover been associated with obesity and insulin resistance[6,7].

Genes responsible for insulin resistance could contribute

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to the development of hyperuricemia. Cross-sectional and case-control studies[8,9,10] have suggested *ADRB3* as a possible candidate for the development of hyperuricemia. This result suggested to us that *ADRB3* may also be a potential candidate for development of gout, since hyperuricemia is characterized by elevated levels of UA, and a higher level of UA is the major cause of gout. Our objective was to assess the genetic association of rs4994 polymorphism in a Chinese Han male population.

MATERIALS AND METHODS

A total of 421 male patients with gout and 312 gout-free male controls were recruited from Qingdao University. We collected the clinical features from all the participants. The diagnosis of gout was based on the preliminary criteria for classification of gout of the American Rheumatism Association[8] for use in either clinical settings or population-based epidemiology studies. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the National Research Institute for Family Planning.

Urea nitrogen in the urine was measured from all participants. We calculated the body mass index (BMI) to assess obesity. Hyperuricemia is defined as UA concentrations > 7 mg/dl. The rs4994 and its surrounding sequences in patients and controls were amplified by polymerase chain reaction (PCR) and PCR products were sequenced using an ABI 3730XL instrument (Applied Biosystems, Foster City, CA, USA) to perform genetic analysis.

Statistical analyses were carried out using SPSS version 13.0 (Stata, College Station, TX, USA). Differences between noncontiguous variables, genotype distribution, and allele frequency were tested by chi-square analysis. Student's t test was used to compare clinical parameters between different genotypes. Significant differences between or among groups were indicated by a p value < 0.05.

RESULTS

The distributions of allele frequencies in patients with gout and controls were in Hardy-Weinberg equilibrium. The results showed that gout patients had significantly higher abnormal blood urea nitrogen levels, total cholesterol levels, blood glucose levels, obesity, hypertension, and hyperuricemia than controls ($p < 0.05$; Table 1).

There were significant differences in rs4994 genotypic and allelic frequencies between gout cases and controls (Table 2). Compared with controls, there was a higher Arg64/Arg64 genotype and Arg64 allele frequency of rs4994 polymorphism in the gout cases (2.4% vs 0.6% by genotype; 15.0% vs 10.6% by allele). The association to gout reached significance [chi-square = 4.91, df = 1, p = 0.027, OR 1.95 (adjusted by age, total cholesterol, and BMI), 95% CI 1.22–3.13 by dominant mode].

Compared with T allele carriers, there were significantly higher average uric acid levels in Arg64/Arg64 genotype carriers than in controls (480.5 mmol/l vs 315.0 mmol/l; $p < 0.001$, respectively).

DISCUSSION

The primary finding in our study was that men with *ADRB3* Arg64 allele had a significantly higher risk of the incidence of gout than men with Trp64/Trp64 genotype.

Morcillo, *et al* demonstrated that W64R polymorphism of the *ADRB3* gene predicted the risk of developing hyperuricemia in an adult population[9]. Studies in Chinese and Korean cohorts suggested that W64R polymorphism is possibly related to serum uric acid levels in populations of Asian subjects[10,11]. According to the results of our study, the carriers of the Arg64/Arg64 genotype had significantly higher serum uric acid levels than noncarriers.

W64R polymorphism is located at the first intracellular loop of *ADRB3*, considered to be extremely important for receptor movement and in subsequent coupling to the effector system. Therefore, the substitution at position 64 may lead to a lower activity of *ADRB3* protein and induce a decrease in intracellular signal transduction leading to development of metabolic syndromes such as gout[12].

We investigated the differences of allele and genotype distributions of the *ADRB3* W64R polymorphism between 412 Chinese male patients with gout and 312 gout-free controls. *ADRB3* rs4994 polymorphism is a potential candidate for the pathogenesis of gout in a male Chinese population.

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Table 1. Demographic and clinical characteristics of the study population. Data are mean ± SD.

Characteristic	Patients with Gout, n = 412	Controls, n = 312	p
Age, yrs	52.9 ± 13.4	50.0 ± 11.8	0.002
BMI, kg/m^2	25.9 ± 3.58	23.1 ± 3.31	<0.001
Systolic pressure, mm Hg	137 ± 20.2	119 ± 12.7	<0.001
Diastolic pressure, mm Hg	88.1 ± 12.1	79.7 ± 12.9	<0.001
Blood glucose, mmol/l	6.19 ± 1.85	5.08 ± 0.62	<0.001
Uric acid, mmol/l	512.6 ± 135.9	316.1 ± 66.5	<0.001
Total cholesterol, mmol/l	5.37 ± 1.35	3.49 ± 1.55	<0.001
Triglycerides, mmol/l	2.37 ± 1.85	1.99 ± 1.85	0.006
Creatinine, μmol/l	92.7 ± 38.6	96.4 ± 8.5	0.059
Urea nitrogen, mmol/l	6.14 ± 3.79	5.57 ± 1.44	0.005

BMI: body mass index.

Table 2. Genotype distribution and relative allele frequencies of Trp64Arg polymorphism in Chinese male patients with gout (n = 412) and controls (n = 312).

Group	No.	Genotype Frequency (%)			Allele Frequency (%)	
		C/C	C/T	T/T	C	T
Patients	412	10 (2.4)	104 (25.2)	298 (72.3)	124 (15.0)	700 (85.0)
Controls	312	2 (0.6)	62 (19.9)	248 (79.5)	66 (10.6)	558 (89.4)
		Chi-square 6.86, df = 2, p = 0.032, OR 1.95 (adjusted by age, TC, and BMI), 95% CI 1.22–3.13 by dominant mode (p = 0.005)			Chi-square 6.23, df = 1, p = 0.013, OR 1.50, 95% CI 1.09–2.06	

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