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Original Article

Association of *BTN2A1* rs6929846 polymorphism with central obesity in community-dwelling Chinese individuals

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Abstract: Objective(s): The aim of this study was to examine the association of polymorphism (rs6929846) of BTN2A1 gene with central obesity in Chinese individuals. Materials and methods: This study genotyped rs6929846 of BTN2A1 in 371 community-dwelling Chinese individuals in a population-based cohort study. All participants underwent anthropometric and biochemical examinations. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were evaluated by magnetic resonance imaging (MRI). Differences in clinical characteristics between individuals with CC and CT genotypes were investigated in all subjects, grouped by sex. Results: CT genotype carriers showed significantly greater waist circumference (WC) and waist circumference/height (WHtR) values than CC genotype in all subjects. Multiple linear regression analysis showed that WC and WHtR were positively associated with the CT genotype for the entire cohort. Significant positive association was found between VAT and CT genotype only in male subjects. This association remained significant after adjusting for BMI. No relationship was observed between SAT and the CT genotype. Conclusion: *BTN2A1* gene polymorphism (rs6929846, C→T) was associated with anthropometric central obesity indicators (WC, WHtR) in all individuals, but with VAT only in males. This variation may lead to increased predisposition to central obesity in Chinese individuals.

Keywords: BTN2A1, central obesity, waist circumference, visceral adipose tissue, subcutaneous adipose tissue

Introduction

Obesity is a significant public healthcare problem associated with hypertension, dyslipidemia, cardiovascular diseases (CVD), type 2 diabetes, and cancers [1, 2]. The worldwide prevalence of obesity has increased two times over the past thirty years. In 2014, more than 1.9 billion adults were overweight and over 600 million were obese [WHO]. In the United States, over two thirds of the adult population were either overweight (33%, BMI: 25-30 kg/m^2), obese (35%, 30-40 kg/m^2), or morbidly obese (6%, > 40 kg/m^2) [3]. According to a 2007-2008 China National Diabetes and Metabolic Disorders Study, prevalence of obesity was 6.02% in males and 4.92% in females [4].

Obesity is defined as abnormal or excessive fat accumulation. According to different body fat distribution, obesity can be divided into general obesity and central obesity. A recent study showed that central obesity, composed of excessive visceral adipose tissue (VAT) or subcutaneous adipose tissue (SAT), provides more useful prognostic information on CVD risk than general obesity [5]. Although WC has been used as a simple indicator of central obesity, it is incapable of distinguishing between VAT and SAT [6]. Magnetic resonance imaging has (MRI) provided a more direct and quantitative measurement of central adiposity [7].

Genetic epidemiological investigations have demonstrated that genetic factors play a key role in predisposition to obesity [6, 8]. Many genome-wide association studies (GWAS) have discovered susceptibility genes of general obesity and central obesity [9-11]. Since few studies have examined the association of genetic

Table 1. Genotype distribution and allele frequencies of BTN2A1 (rs6929846) polymorphism in female and male groups

Gene	Sex		*P*-Value
	Femal (158)	Male (213)	
CC	134 (84.8%)	181 (85%)	
CT	24 (15.2%)	32 (15%)	0.539
C	292 (92.4%)	394 (92.5)	
T	24 (7.6%)	32 (7.5%)	0.537

Genotypes distribution and allele frequencies were compared by χ analysis. Allele frequencies were in Hardy-Weinberg equilibrium. Genotypes P = 0.0.539; allele frequencies, P = 0.537.

architecture and fat distribution measured by MRI, it is important to identify candidate genes that influence fat distribution.

Previous studies have revealed that polymorphism rs6929846 of the butyrophilin, subfamily 2, member A1 gene (*BTN2A1*), is a risk factor for hypertension [12], dyslipidemia [13], chronic kidney disease [12], CVD [14], and metabolic syndrome [15] in Eastern Asian populations. Few studies have examined the association of *BTN2A1* rs6929846 polymorphism with central obesity in Chinese and other populations. Central obesity is a major risk factor for CVD and MS, therefore, this study hypothesized that *BTN2A1* rs6929846 polymorphism may be associated with central obesity. This research is a cross-sectional study of community-dwelling Chinese individuals to determine the association of *BTN2A1* rs6929846 polymorphism and central obesity measured by anthropometric parameters and MRI quantification.

Materials and methods

Study population

From September to November 2011, a total of 371 community-dwelling Chinese subjects, aged 40-65 years, were recruited for a cross-sectional study, as described previously [16]. All subjects completed a standard questionnaire including menopausal age, medical history, and use of medicine. This study protocol was approved by the Institutional Review Board of Chengdu Fifth People Hospital and each participant provided written informed consent.

Exclusion criteria

Exclusion criteria included history of cardiovascular events, tumors, hyperthyroidism and hypothyroidism, use of corticosteroid hormones, use of L-thyroxine and anti-thyroid drugs, weight reduction by lifestyle, and medical intervention within three months.

Clinical and biochemical measurements

All subjects submitted to detailed medical histories and anthropometric examinations including height, weight, WC, and blood pressure. BMI was calculated as weight/height^2 (kg/m^2). WC was assessed during expiration between the iliac crest and lower rib. Blood pressure was measured on the right arm while patients were in a sitting position at intervals of 5 minutes. Three measurements were taken and mean values were used. Blood samples were collected from an antecubital vein after an 8-hour overnight fast. All participants underwent an oral glucose tolerance test of 75 g glucose. Blood samples were obtained at baseline, 30 minutes, and 120 minutes. Glucose concentrations, triglycerides, high-density lipoprotein cholesterol levels, and low-density lipoprotein cholesterol levels were detected.

MRI quantification of VAT and SAT

MRI examinations were performed by a 1.5-T scanner (Magnetom Open Viva, Siemens AG, Erlangen, Germany). Quantification of abdominal fat was detected at the level of L3-L4 discs. SliceOmatic image analysis software (version 4.3, Tomovision, Montreal, CAN) was used to analyze MRI slices. Visceral and subcutaneous fat areas (cm^2) were measured separately. To evaluate the repeatability of the observer, a second independent observer repeated measurements using the same conventions.

Genotyping

Standard methods were used to extract DNA from the blood of the participants. Genotyping for the C→T rs6929846 polymorphism in *BTN2A1* was performed, as described previously [16].

Statistical analysis

All analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA). *P* values of < 0.05 are

Table 2. Clinical and biochemical characteristics in all individuals with CC and CT genotypes of BTN2A1 (rs6929846) polymorphism stratified by sex

	Female			Male		
	CC	CT	*P*-Value	CC	CT	*P*-value
N	134	24		181	32	
Age (years)	48.47±6.91	49.75±5.95	0.396	49.5±6.7	52.6±7.4	0.056
Height (cm)	155.06±4.92	152.19±6.29	0.213	165.9±5.9	164.5±5.0	0.207
Weight (cm)	56.88±8.10	57.21±5.61	0.844	67.7±9.5	68.9±9.7	0.498
BMI (kg/m^2)	23.64±3.09	24.75±2.53	0.099	24.6±3.1	25.5±3.4	0.147
WC (cm)	75.97±8.24	81.20±6.04	0.005	83.7±8.0	90.0±9.2	< 0.001
WHtR	0.82±0.06	0.84±0.05	0.014	0.87±0.05	0.90±0.05	0.040
SBP (mmHg)	113.81±15.45	113.71±11.46	0.976	119.7±14.9	117.3±13.0	0.398
DBP (mmHg)	75.71±9.20	74.89±8.58	0.684	80.7±10.8	79.9±9.4	0.694
TG[a]	1.30±0.92	1.32±0.85	0.721	2.0±2.2	1.9±2.0	0.833
HDL-C[a]	1.61±0.35	1.64±0.46	0.768	1.44±0.35	1.43±0.31	0.907
LDL-C[a]	2.85±0.77	2.73±0.75	0.446	2.89±0.74	2.98±0.59	0.498
HbA1C (%)[a]	5.52±0.66	5.56±0.33	0.772	5.66±0.75	5.98±1.63	0.074
FBG	5.68±7.76	4.90±0.49	0.628	5.19±1.07	7.69±12.29	0.57
30 min-PG	8.68±1.89	9.13±1.84	0.271	9.82±2.45	10.55±3.60	0.15
120 min-PG	6.45±2.27	7.33±2.44	0.086	7.41±3.58	8.17±4.45	0.285
SAT	172.57±63.10	177.58±53.83	0.715	126.45±46.48	134.54±43.47	0.355
VAT	56.36±25.89	56.03±26.40	0.955	84.96±46.23	111.70±43.48	0.002

Data are mean ± SE, unless otherwise indicated. Continuous variables were compared by ANOVA. BMI: body mass index; WC: waist circumference; WHtR: waist circumference/height; SBP: systolic blood pressure; DBP: diastolic blood pressure; Lipids (mmol/L), TG: triglycerides; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; plasma glucose (mmol/L), FBG: fasting blood glucose; 30 min-PG: plasma glucose at 30 min after the glucose load; 120 min-PG: plasma glucose at 120 minutes after the glucose load; SAT: subcutaneus adipose tissue; VAT visceral adipose tissue. [a]Logarithmic transformation was used to normalize distributions of TG, HDL-C, LDL-C, HbA1C%. P < 0.05 is considered significant.

considered significant. Data are presented as mean ± SD. Distribution of genotypes was performed by Chi-squared test. Analysis of variance (ANOVA) was performed to test variations between groups. Multiple linear regression analyses were performed to identify associations between central obesity indicators and the *BTN2A1* rs6929846 polymorphism in the two models. In the first model, an adjustment was made for age. In the second model, an adjustment was made for BMI. As a confounding variable, BMI can affect association. Quanto software was used to calculate the power [17].

Results

Genotypic and allelic frequencies

Table 1 shows allele frequencies of the SNP in samples stratified by sex. Chi-square test was used to compare genotype distributions and allele frequencies. Distributions of *BTN2A1* rs6929846 in the female group (C = major, T = minor; CC: 84.8%, CT: 15.2%, C: 92.4%, T: 7.6%) and male group (CC: 85%, CT: 15%, C: 92.5%, T: 7.5%) were all in Hardy-Weinberg equilibrium. There were no significant differences in genotype and allele frequency between females and males ($P = 0.539$ and $P = 0.537$, respectively).

Clinical characteristics

Clinical and biochemical characteristics of study participants are shown in **Table 2**. There was no TT genotype in any of the subjects. Differences in clinical characteristics between individuals with CC and CT genotypes were examined in all subjects grouped by sex. CT genotype carriers showed significantly greater WC and WHtR values than CC genotype ($P < 0.05$) in both groups (**Table 2**). Otherwise, no significant differences were found in comparing CC and CT genotypes for general obesity (weight and BMI) and other biochemical characteristics including blood pressure, lipids, blood glucose, and HbA1C.

Table 3. Multiple linear regression analysis for association between central obesity indicators and BTN2A1 (rs6929846) polymorphism

Dependent variable	Total		Femal		Male	
	β	*P*-Value	β	*P*-Value	β	*P*-Value
WC						
Model 1	0.208	0.009	0.348	0.048	0.237	0.007
Model 2	0.302	0.028	0.517	0.029	0.437	0.014
WHtR						
Model 1	0.214	0.049	0.299	0.035	0.357	0.024
Model 2	0.272	< 0.001	0.184	< 0.001	0.218	< 0.001
VAT						
Model 1	0.387	0.149	0.533	0.087	0.364	0.028
Model 2	0.481	0.084	0.652	0.065	0.272	< 0.001
SAT						
Model 1	0.493	0.097	0.781	0.143	0.476	0.078
Model 2	0.594	0.136	0.712	0.245	0.667	0.321

WC: waist circumference; WHtR: waist circumference/height; SBP: systolic blood pressure; VAT visceral adipose tissue. SAT: subcutaneus adipose tissue; Model 1: adjusted for age. Model 2: adjusted for age and BMI. P < 0.05 is considered significant.

Association with central obesity

Association between central obesity indicators and BTN2A1 rs6929846 polymorphism is presented in **Table 3**. Sex-stratified analysis showed a significant positive relationship between CT genotype and WC and (P < 0.05) in the entire cohort. After adjusting for BMI, the relationship also remained (P < 0.05). Significant positive association was found between VAT and CT genotype, only in males (P = 0.028). This association remained significant after adjusting for BMI (P < 0.001). No relationship was observed between SAT and CT genotype in all individuals.

Discussion

The present study analyzed correlation between *BTN2A1* gene polymorphism (rs6929846) and central obesity in 371 Han individuals. It was found that *BTN2A1* gene polymorphism (rs6929846, C→T) was associated with WC and WHtR, in the entire cohort, and with VAT in the male group.

BTN2A1 genes are located in a cluster of expanding B7/butyrophilin-like genes group, encoding a member of the immunoglobulin superfamily involved in lipid, fatty-acid, and sterol metabolism. Previous studies have shown that C→T mutation of *BTN2A1* gene (rs6929846) leads to increased transcription [14] and greater high sensitivity C-reactive protein concentrations among healthy individuals [18], suggesting that the mutation may speed up inflammation.

Relationships between anthropometric adiposity indicators and inflammatory factors have been thoroughly explored in many ethnic groups. Previous studies have indicated that inflammatory factors are crucial in the development, progression, and complications of central obesity. WC and WHtR may serve as optimal and reliable anthropometric indicators of obesity, as they correlated with risk of type 2 diabetes mellitus and CVD [19]. Several studies have demonstrated that, except for total body fat mass, central obesity may play a greater role in mediating insulin resistance, chronic low-grade inflammation, and cardiovascular risk [20-22]. Therefore, it was assumed that the relationship of *BTN2A1* rs6929846 polymorphism with central obesity may be related to inflammation processes.

The present study indicates that *BTN2A1* gene polymorphism (rs6929846, C→T) was associated with VAT only in the male group, suggesting a sex-specific association. This has been observed for many gene loci, such as *THNSL2* (19) and *IRS1* [23]. Sex has been widely known to show effects on phenotypic expression of genotypes in complex traits such as disease. Males have higher VAT levels but lower SAT levels than females [24]. This may contribute to differences in VAT distribution of *BTN2A1* rs6929846 polymorphism for males.

This study was performed in community-dwelling Chinese subjects. One strength of the present study was that VAT and SAT were measured by MRI. Even though WHtR is a simple and convenient epidemiological tool to measure regional distribution of body fat, it cannot distinguish between intra-abdominal fat and subcutaneous fat, a limitation of many large studies [25]. The present study had some limitations: 1)

Because study subjects were composed of Chinese individuals, a larger sample size study including ethnic groups will be required to validate the present findings; 2) Molecular mechanisms involved in the development of central obesity by *BTN2A1* gene (rs6929846) polymorphism were not detected; 3) Influence of environmental factors on obesity was not evaluated; and 4) This study only examined one SNP of *BTN2A1* that was supposedly associated with CVD and metabolic syndrome. Larger numbers of new SNPs of the *BTN2A1* gene should be investigated for association with central obesity in future studies.

In conclusion, this present study found that *BTN2A1* gene may be a predisposing gene for central obesity in Chinese individuals. *BTN2A1* gene polymorphism (rs6929846, C→T) was associated with anthropometric central obesity indicators (WC and WHtR) in all individuals, but with VAT only in the male group. Larger sample sizes for the male predominant effect of *BTN2A1* on VAT accumulation should be examined in the future. In addition, further inter-individual variation screening and research should consider sex dimorphism.

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Disclosure of conflict of interest

None.

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