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Original Article

Relation between *ADIPOQ* gene polymorphisms and type 2 diabetes in a Chinese population

Wei-Lin Wang[1], Hong Zhu[2], Yun Xie[1], Jin Li[1]

[1]2011 Collaborative Innovation Center of Tianjin for Medical Epigenetics, The Key Laboratory of Hormones and Development (Ministry of Health), Metabolic Diseases Hospital & Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin 300070, China; [2]Department of Epidemiology, School of Public Health, Tianjin Medical University, Tianjin 300070, China

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Abstract: Objective: We aimed to investigate the relation between adiponectin gene (*ADIPOQ*) polymorphisms and type 2 diabetes mellitus (T2DM) in a Chinese population. Methods: The present study included 510 subjects with normal glucose tolerant (NGT) and 510 patients with type 2 diabetic. Five SNPs (rs2241767, rs3821799, rs182052, rs1501299 and rs7627128) were genotyped by TaqMan methods. Results: Of these 5 SNPs, three SNPs (rs1501299, rs182052, and rs7627128) were found to be significantly associated with T2DM. The haplotypes AAT (Construction of rs1501299, rs182052, and rs7627128) was frequent in T2DM patients (OR=2.051, 95% CI: 1.439~2.923, P<0.001), but GAT (Construction of rs1501299, rs182052, and rs7627128) was frequent in the control group (OR=0.65, 95% CI: 0.540~0.805, P<0.001). Conclusion: The *ADIPOQ* gene variants and haplotype were associated with the risk for development of type 2 diabetes.

Keywords: *ADIPOQ*, diabetes, genetic polymorphism, case-control study

Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic disease worldwide [1]. Although the exact pathogenesis of T2DM is unclear, it is general accepted that T2DM is a multifactor disorders resulting from genetic polymorphisms and several environmental factors [2]. The previous studies indicated that genetic polymorphisms such as *SAA* gene [3], *CYP17A1* gene [4], and *CCR5* gene [5] were associated with the risk for T2DM. However, these results can only explain a small fraction of the susceptibility for T2DM.

Previous studies suggested the role of adipose tissue is of great significance where it contributes to the pathogenesis of diabetes as well as obesity by secreting a variety of secretory proteins [6]. Among them, adiponectin is the major adipocyte secretory protein most abundantly found in human plasma with potent roles in insulin sensitivity in muscle and liver, regulating energy homeostasis and glucose tolerance [7]. Adiponectin is a product of the *ADIPOQ* gene which spans approximately 16 kb with three exons on chromosome 3q27 and has been linked to metabolic syndrome, type 2 diabetes and cardiovascular disease [8, 9]. However, the relation between *ADIPOQ* genetic polymorphisms and T2DM in Chinese population is unclear. Therefore, in this study we investigate the relation between genetic polymorphism in *ADIPOQ* and T2DM in a Chinese population.

Subjects and methods

Ethnics

The present study has been performed with the approval of the ethics committee of Third Military Medical University and is in compliance with the Helsinki Declaration. The informed consents of the study were collected from all the candidate subjects.

Subjects

We recruited 1,020 unrelated study subjects, including 510 controls subjects with normal glu-

Table 1. Characteristics of participants

Groups	N	Sex ratio (Male/Female)	Age (years)	Family history (n, %)	BMI (Kg/m^2)	GLU (mmol/L)	TG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
T2DM group	510	365/145	53.3±10.2	147 (28.82)	24.8±2.7	5.52±0.49	1.61±0.27	2.85±0.68	0.89±0.22	1.45±0.49
Control group	510	37/139	53.9±10.1	15 (2.94)	23.2±1.5	4.32±0.43	1.52±0.17	2.64±0.56	0.90±0.21	1.27±0.34
P		0.987	0.321	<0.001	<0.001	<0.001	<0.001	<0.001	0.893	<0.001

cose tolerant (NGT) and 510 patients with T2DM from July 2010 to June 2013. Oral glucose tolerance test (OGTT) was utilized to confirm diabetes or NGT. According to World Health Organization (WHO) criteria, the subjects who have 2-h plasma glucose value ≥11.1 mmol/l were identified as diabetes and those with 2-h plasma glucose value <7.8 mmol/l were confirmed as NGT [10]. The characteristics of participants were shown in **Table 1**.

Phenotype measurements

We collected the characteristics of the participants including height, weight, and waist using standardized methods. Fasting plasma glucose, serum cholesterol, serum triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin (HbA1c), and serum insulin concentration were measured according to previous literatures. Total serum adiponectin was measured by radioimmunoassay.

Genetic analysis

As shown in **Figure 1**, we obtained five tagging SNPs (rs2241767, rs3821799, rs182052, rs1501299, and rs7627128) for Chinese Han, using the Haploview 4.2 software and the HapMap phrase II database. Genomic DNA was extracted from the whole blood by the phenol chloroform method. Genotyping was confirmed by TaqMan method as described previously [11].

Statistical analysis

We utilized SPSS 17.0 software (SPSS, Chicago, IL) to perform the statistical analyses. Gene counting methods were utilized to estimate the allele frequencies. And a χ^2 test was used to test the Hardy-Weinberg expectations (HWE). Student's t test was utilized to compare of the difference of the means between the two groups. We utilized the χ^2 test to compare the proportions of genotypes or alleles and utilized the one way analysis of variance to compare groups for continuous variables. We utilized the SHEsis software (http://analysis2.bio-x.cn/myAnalysis.php) [12, 13] to perform linkage disequilibrium (LD) analysis and haplotype analysis. Statistical significance was established at P<0.0125.

Results

The genotype distribution of each SNP was in line with the Hardy-Weinberg equilibrium (data not shown). For total participants, the genotype (P=0.008, P=0.006, P<0.001, respectively) and the allele (P=0.006, P=0.005, P<0.001, respectively) distribution of rs182052, rs1501299, and rs7627128 was significant different between the T2DM patients and the control subjects. The genotype and the allele distributions of other two SNPs (rs3821799, and rs2241767) were not different between the T2DM patients and the control participants (**Table 2**).

According to the |D'| and r^2 values of these five SNPs, there are three SNPs (rs1501299, rs182052, and rs7627128) are located in one haplotype block. In the haplotype-based case-control analysis, haplotypes were established through the use of all these three SNPs. As shown in **Table 3**, the haplotypes AAT (Construction of rs1501299, rs182052, and rs7627128) was frequent in T2DM patients (OR=2.051, 95% CI: 1.439~2.923, P<0.001), but GAT (Construction of rs1501299, rs182052, and rs7627128) was frequent in the control group than that in the T2DM group (OR= 0.65 95% CI: 0.540~0.805, P<0.001).

Discussion

T2DM is common geriatric diseases and their incidences increase over age. Its pathogeneses are complex and are usually influenced by genetic and environmental factors. Multiple genes have been found to be associated with T2DM. The present study found that the *ADIPOQ* gene rs1501299, rs182052, and rs7627128 genotype distribution frequencies were significant between T2DM patients and healthy control subjects, which indicated that *ADIPOQ* gene was associated with T2DM in Chinese population.

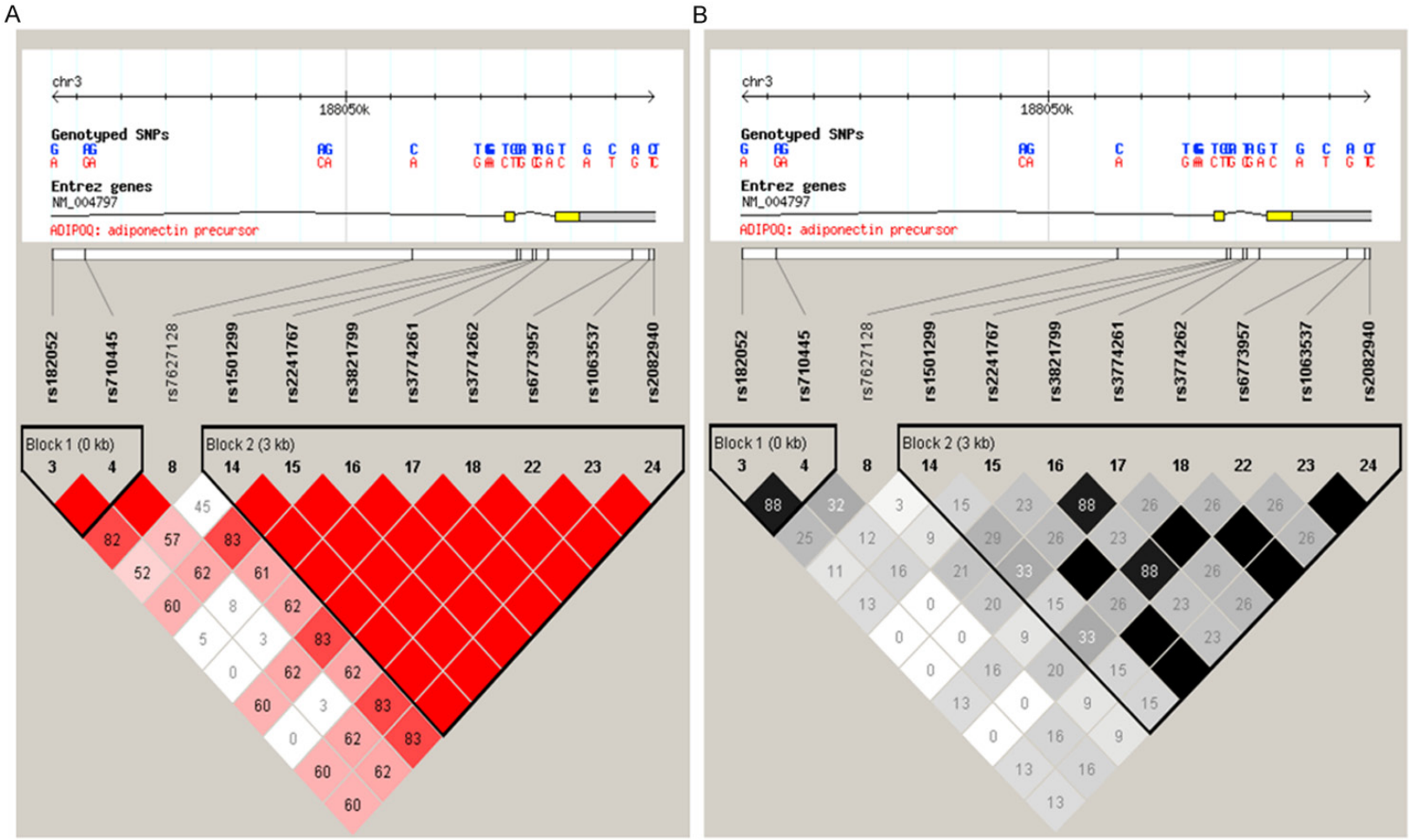

Figure 1. Genetic variation at human ADIPOQ gene. Using the Haploview 4.2 software and the HapMap phrase II database, we scanned 11 genotyped single-nucleotide polymorphisms (SNPs) in Chinese Han. Linkage disequilibrium (LD) blocks across the locus in Chinese Han. LD blocks derived by solid spline method in Haploview 4.2. A: LD value shown: |D'|×100; |D'| colour scheme: |D'|=0: white; 0<r^2<1: shades of Pink; |D'|=1: red; B: LD value shown: r^2×100; r^2 color scheme: r^2=0: white; 0<r^2<1: shades of grey; r^2=1: black.

Table 2. Distributions of ADIPOQ genotype

Groups	N	SNP	Genotypes (n, %)			*P* value	Allele		OR (95% CI)	*P* value
		rs2241767	AA	AG	GG		A	G		
T2DM group	510		265 (0.520)	180 (0.353)	65 (0.127)	0.325	710 (0.696)	310 (0.304)	0.90 (0.74-1.09)	0.307
Control group	510		271 (0.531)	189 (0.371)	50 (0.098)		731 (0.717)	289 (0.283)		
		rs3821799	CC	CT	TT					
T2DM group	510		95 (0.186)	220 (0.431)	195 (0.382)	0.231	410 (0.402)	610 (0.598)	1.05 (0.87-1.25)	0.543
Control group	510		83 (0.163)	232 (0.455)	195 (0.382)		398 (0.390)	622 (0.610)		
		rs182052	AA	AG	GG					
T2DM group	510		101 (0.198)	257 (0.504)	152 (0.298)	0.008	459 (0.450)	561 (0.550)	1.27 (1.07-1.52)	0.006
Control group	510		87 (0.171)	224 (0.439)	199 (0.390)		398 (0.390)	622 (0.610)		
		rs1501299	AA	AG	GG					
T2DM group	510		87 (0.171)	301 (0.590)	122 (0.239)	0.0006	475 (0.466)	545 (0.534)	1.28 (1.07~1.53)	0.005
Control group	510		80 (0.157)	253 (0.496)	177 (0.347)		413 (0.405)	607 (0.595)		
		rs7627128	AA	AC	CC					
T2DM group	510		61 (0.120)	293 (0.575)	156 (0.306)	<0.0001	415 (0.407)	605 (0.593)	1.40 (1.16-1.6)	0.0002
Control group	510		55 (0.108)	226 (0.443)	229 (0.449)		336 (0.329)	684 (0.671)		

Table 3. Haplotype analyses results

Variables	Case (n, frequency)	Control (n, frequency)	*P* value	OR (95% CI)
A A C	378.36 (0.371)	363.57 (0.356)	0.519032	1.061 [0.886~1.272]
A A T	96.62 (0.095)	49.43 (0.048)	<0.001	2.051 [1.439~2.923]
G A T	226.36 (0.222)	307.10 (0.301)	<0.001	0.659 [0.540~0.805]
G G C	22.98 (0.023)	23.52 (0.023)	0.929743	0.974 [0.545~1.743]
G G T	287.00 (0.281)	265.47 (0.260)	0.296449	1.110 [0.913~1.350]

Previously, Gu and the colleagues found that *ADIPOQ* gene polymorphisms were associated with T2DM in Swedish Caucasians [12]. There were several studies related to the association of *ADIPOQ* gene polymorphisms with T2DM have been carried out. However, the results from each study were found to be controversial. Ye and colleagues found there was significant association *ADIPOQ* gene polymorphism and the serum adiponectin level and the T2DM hereditary risk [13]. Sun et al. [14] also found T2DM risk was related to the *ADIPOQ* gene variant. However, Shi et al. [15] and Li et al [16] did not verify this association mentioned above.

Previous study suggested that analysis based on haplotypes has advantages over analysis based on individual SNPs for genes with multiple susceptibilities [17]. In the present study, we carried out a haplotype-based case-control study to investigate the association of *ADIPOQ* polymorphisms with T2DM, and we found rs182052, rs1501299, and rs7627128 polymorphisms were significantly associated with T2DM. In addition, the haplotypes AAT (Construction of rs1501299, rs182052, and rs7627128) was frequent in T2DM patients (OR=2.051, 95% CI: 1.439~2.923, P<0.001), but GAT (Construction of rs1501299, rs182052, and rs7627128) was frequent in the control group than that in the T2DM group (OR=0.65, 95% CI: 0.540~0.805, P<0.001).

In conclusion, we found *ADIPOQ* gene polymorphisms was associated with T2DM. The AAT haplotype appear to be a useful genetic marker and the GAT haplotype might be protective factors of T2DM in Chinese people.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wei-Lin Wang, 2011 Collaborative Innovation Center of Tianjin for Medical Epigenetics, The Key Laboratory of Hormones and Development (Ministry of Health), Metabolic Diseases Hospital & Tianjin Institute of Endocrinology, Tianjin Medical University, 66# Tongan Road, Heping District, Tianjin 300070, China. Tel: 86-02223503996; Fax: 86-0225989-8666; E-mail: wangweiil@126.com

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