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Research Paper

Association Study of *ARL15* and *CDH13* with T2DM in a Han Chinese Population

Yiping Li[1,2], Ying Yang[2], Yueting Yao[3], Xianli Li[2], Li Shi[3],Ying Zhang[2], Yuxin Xiong[2], Man Yan[2], Yufeng Yao[3] and Chunjie Xiao[1]✉

1. School of Medicine, Yunnan University, Kunming 650091, Yunnan, China;
2. Department of Endocrinology and Metabolism, The Second People's Hospital of Yunnan Province, Kunming 650021, Yunnan, China;
3. Institute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming 650118, Yunnan, China.

✉ Corresponding author: Prof. Chunjie Xiao, School of Medicine, Yunnan University, Kunming 650091, Yunnan, China. Email: chjxiao@ynu.edu.cn.

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Abstract

Several studies indicate that plasma adiponectin levels are associated with the risk of type 2 diabetes mellitus (T2DM) or T2DM risk factors in diverse populations. In addition to the adiponectin gene, several other genes have been postulated to influence plasma adiponectin levels. In this study, we investigated two single nucleotide polymorphisms (SNPs), rs4311394 and rs4783244, located intronically in the ADP-ribosylation factor-like protein 15 (ARL15) and the T-cadherin (CDH13) genes, respectively. These SNPs were detected in a Han Chinese population using a TaqMan assay and evaluated for association with T2DM as well as with individual metabolic traits. Allele frequencies for rs4311394 were significantly different in T2DM and nondiabetes (NDM) groups (χ^2 = 4.49, P = 0.034). However, neither allele nor genotype frequencies for rs4783244 were associated with T2DM (χ^2 = 0.33, P = 0.56 and χ^2 = 2.35, P = 0.31 respectively). The SNPs did not exhibit significant association with individual metabolic traits in the T2DM and NDM groups. Our results indicated that the G allele of the rs4311394 might be a susceptibility factor for T2DM in the Han Chinese population (odds ratio: 1.20; 95% confidence interval: 1.01–1.41).

Key words: SNP; T2DM; Chinese population; ARL15; CDH13.

Introduction

In China, the incidence rate for all types of diabetes increased from 2.5% in 1994 to 9.7% in 2007, during a time in which the population became more aged and urbanized and experienced notable changes in lifestyle [1]. Type 2 diabetes mellitus (T2DM), which accounts for 80–90% of all diabetes cases, is characterized by complex traits and is caused by both genetic and environmental factors.

Adiponectin, an abundant plasma protein, plays an important role in T2DM development by increasing insulin sensitivity and improving islet beta cell dysfunction and beta-oxidation of fatty acids [2-5]. Low plasma adiponectin levels have been associated with adiponectin-related diseases, such as T2DM [6], obesity [7,8], dyslipidemia [8,9], insulin resistance [2,8] and cardiovascular disease [10,11]. Moreover, varying adiponectin levels have been associated in different populations with other metabolic characteristics, such as fasting blood glucose, lipid level and insulin resistance [12,13].

The genome-wide association study (GWAS) method has been widely used to identify additional candidate genes that influence plasma adiponectin levels. One of the identified genes, *ADP-ribosylation factor-like protein 15* (*ARL15*), is structurally similar to ADP-ribosylation factors and Ras-related GTP-binding proteins [14]. *ARL15* is expressed in insulin-responsive tissues, including adipose tissue and

skeletal muscle. In 2009, Richards *et al* used GWAS to identify a single nucleotide polymorphism (SNP) located in the *ARL15*, rs4311394, which was associated with low adiponectin levels and T2DM in a European population [15]. To date, the association of *ARL15* with T2DM has not been reported for Asian populations.

T-cadherin (*CDH13*), another important candidate gene, is expressed in endothelium and smooth muscle and has been reported to be an adiponectin receptor. In 2011, Chung et al reported that an SNP (rs4783244) located in the *CDH13*, whose G allele was associated with higher plasma adiponectin and the risk of T2DM for men [16]. Subsequently, Morisaki *et al* reported that the haplotype consisting of rs12051272 and rs4783244 was significantly associated with plasma adiponectin levels in a Japanese population [17].

The aim of the current study was to evaluate the association of the *ARL15* rs4311394 and the *CDH13* rs4783244 with T2DM in a Han Chinese population. Analysis was performed to determine the mode of inheritance. In addition, we also evaluated the association of these SNPs with individual metabolic traits for both T2DM and nondiabetes (NDM) groups.

Materals and Methods

Ethics statement

All participants gave written informed consent. The protocol was in accordance with the Helsinki Declaration and was approved by the Institutional Review Boards of the Second People's Hospital of Yunnan Province.

Subjects

The study included 611 patients (389 males and 222 females) who were diagnosed with T2DM at the Second People's Hospital of Yunnan Province from December 2011 to September 2013. T2DM diagnosis was confirmed using World Health Organization criteria from 1999. The NDM group included 536 subjects (339 males and 197 females) who had no family history of diabetes mellitus and were recruited from an unselected population undergoing routine health checkups at the Second People's Hospital of Yunnan Province. Subjects with diabetes or impaired glucose tolerance were excluded from the NDM group on the basis of an oral glucose tolerance test. In addition, subjects with hypertension or coronary heart disease (CHD) were also excluded from the study. All participants (T2DM and NDM) were self-reported to be ethnically Han.

Laboratory measurements

Venous blood samples were collected in the morning after the subjects had fasted for 12 hours. Fasting plasma glucose (FPG) was assayed by the glucose oxidase method. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) were determined by enzymatic methods. Glycosylated hemoglobin (HbA1c) was determined by immunoturbidimetry. All laboratory measurements were performed on a HITACHI 7600-020 Automatic Analyzer.

SNP genotyping

Genomic DNA was extracted from peripheral lymphocytes using a standard hydroxybenzene-chloroform method. Two SNPs (rs4311394 and rs4783244) were detected by PCR amplification using a TaqMan assay (Applied Biosystems, Foster City, CA, USA). Some of the PCR products were characterized by direct sequencing on a 3100 Genetic Analyzer (Applied Biosystems, Tokyo, Japan) using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) after purification with Sephadex™ G-50 (GE Healthcare, Piscataway, NJ, USA).

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was tested for both SNPs in both the T2DM and the NDM groups. Allele and genotype frequencies for the two SNPs were calculated by the direct-counting method. A χ^2 test was used to determine differences in allele and genotype frequencies between the T2DM and NDM groups and the odds ratios (OR) with associated 95% confidence intervals (CI) of genotype-specific risks. The association between each SNP and T2DM was analyzed for mode of inheritance using SNPStats [18]. The Akaike information criterion (AIC) was used to determine the best-fit model for each SNP. Analysis of variance (ANOVA) was used to compare the difference in metabolic traits between three genotype groups of these two SNPs. Statistical analyses were performed using SPSS 13 (Chicago, IL). A P value of less than 0.05 was considered statistically significant.

Results

Subject characteristics

Table 1 lists the characteristics of the enrolled subjects. There were no age or gender differences between the T2DM and NDM groups. However, the clinical values for metabolic traits, including FPG, TC, HDL-C, TG, LDL-C and HbA1c were significantly different for T2DM and NDM subjects (Table 1).

Table 1. Clinical characteristics of the subjects enrolled in the present study (Data are mean±SD).

	Nondiabetic subject	Type 2 diabetes	P
N	536	611	
Ages (years)	49.60±10.78	50.31±11.82	0.23
Sex (M/F)	339/197	389/222	
Total cholesterol(mmol/L)	4.41±0.82	4.94±1.54	<0.01
Triglycerides (mmol/L)	1.65±1.15	2.56±1.82	<0.01
High-density lipoprotein (HDL)-cholesterol(mmol/L)	1.29±0.28	1.1±0.29	<0.01
Low-density lipoprotein (LDL)-cholesterol(mmol/L)	2.06±0.60	2.68±1.06	<0.01
Fasting plasma glucose(mmol/L)	4.92±0.58	7.94±2.52	<0.01
HbA_1c(%)	5.19±0.43	8.74±2.61	<0.01

Association of the *ARL15* rs4311394 with T2DM

The allele and genotype frequencies for the rs4311394 are listed in Table 2. The genotype frequencies for rs4311394 was in HWE for both the T2DM and NDM groups (P = 0.72 and P = 0.21, respectively). The genotype frequencies for rs4311394 AA, AG and GG were 0.283, 0.491 and 0.226, respectively in the T2DM group and 0.341, 0.463 and 0.196, respectively, for the NDM group. The genotype frequencies were not significantly different between the T2DM and NDM groups (χ^2 = 4.81, P = 0.09). The allele frequencies for rs4311394 for A and G were 0.529 and 0.471, respectively, in the T2DM group and 0.573 and 0.427, respectively, for the NDM group. The allele frequencies for the rs4311394 were significantly different between the T2DM and NDM groups (χ^2 = 4.49, P = 0.03). The G allele for *ARL15* rs4311394 occurred at a significantly higher frequency in the T2DM group compared to the NDM group (OR = 1.20; 95% CI: 1.01–1.41).

Association of the *CDH13* rs4783244 with T2DM

The allele and genotype frequencies for the *CDH13* rs4783244 are listed in Table 2. The genotype frequencies for rs4783244 was in HWE for both the T2DM and NDM groups (P = 0.64 and P = 0.13, respectively). The genotype frequencies for rs4783244 for GG, GT and TT were 0.419, 0.463 and 0.118, respectively, in the T2DM group and 0.424, 0.431 and 0.146, respectively, for the NDM group. The allele frequencies for G and T were 0.651 and 0.349, respectively, in the T2DM group and 0.639 and 0.361, respectively, for the NDM group. The allele and genotype frequencies for the rs4783244 were not significantly different between the T2DM and NDM groups (χ^2 = 0.33, P = 0.56 and χ^2 = 2.35, P = 0.31 respectively).

Mode of inheritance analysis

Tables 3 and 4 present the results of analysis to determine the mode of inheritance for the two SNPs. To compare each inheritance model (co-dominant, dominant, recessive, over-dominant and log-additive) to the most general model (co-dominant), the AIC was calculated to identify to the inheritance model that best fits the data [18]. The model with the smallest AIC value corresponds to the minimal expected entropy [18]. The best fits inheritance model with the lowest AIC for rs4311394 in *ARL15* was dominant, and rs4783244 in *CDH13* was recessive. The analysis under different genetic models revealed that the AA genotype of the *ARL15* rs4311394 was protective against T2DM under dominant models. The rs4311394 GA and GG genotype increased the susceptibility to T2DM by 1.02–1.69-fold under dominant models. No significant differences for rs4783244 were found between the T2DM and NDM groups under different genetic models.

Association between genotype and metabolic traits

No significant association was observed for rs4311394 in *ARL15* and rs4783244 in *CDH13* genotypes and metabolic traits (data not shown).

Discussion

Several groups using GWAS to identify factors influencing plasma adiponectin levels[15-17,19-24] have found that variants of the *ARL15* or *CDH13* influence the adiponectin levels [15-17,19,21-24] and are associated with T2DM. In this study, we found that the G allele of the *ARL15* rs4311394 is a risk factor for T2DM. However, we did not observe an association of the *CDH13* rs4783244 with T2DM.

Table 2. Comparison of genotypic and allelic distribution of two SNPs (rs4311394 and rs4783244) between type 2 diabetic and nondiabetic subjects.

Polymorphism	Genotypes			P	Alleles		P
rs4311394	A/A	A/G	G/G		A	G	
T2DM[n(%)]	173(28.3)	300(49.1)	138(22.6)	0.09	646(52.9)	576(47.1)	0.03
NDM[n(%)]	183(34.1)	248(46.3)	105(19.6)		614(57.3)	458(42.7)	
rs4783244	G/G	G/T	T/T		G	T	
T2DM[n(%)]	256(41.9)	283(46.3)	72(11.8)	0.31	795(65.1)	427(34.9)	0.56
NDM[n(%)]	227(42.4)	231(43.1)	78(14.6)		685(63.9)	387(36.1)	

Table 3. Different inheritance models analysis of the SNP rs4311394 in *ARL15* gene between the T2DM and NDM group.

Model	Genotype	NDM[n(%)]	T2DM[n(%)]	OR (95% CI)	P-value	AIC
Codominant	A/A	183 (34.1%)	173 (28.3%)	1.00	0.09	1586.40
	G/A	248 (46.3%)	300 (49.1%)	1.28 (0.98-1.67)		
	G/G	105 (19.6%)	138 (22.6%)	1.39 (1.00-1.93)		
Dominant	A/A	183 (34.1%)	173 (28.3%)	1.00	0.03	1584.60
	G/A-G/G	353 (65.9%)	438 (71.7%)	1.31 (1.02-1.69)		
Recessive	A/A-G/A	431 (80.4%)	473 (77.4%)	1.00	0.21	1587.60
	G/G	105 (19.6%)	138 (22.6%)	1.20 (0.90-1.59)		
Overdominant	A/A-G/G	288 (53.7%)	311 (50.9%)	1.00	0.34	1588.30
	G/A	248 (46.3%)	300 (49.1%)	1.12 (0.89-1.41)		
Log-additive	---	---	---	1.19 (1.01-1.40)	0.04	1584.80

Table 4. Different inheritance models analysis of the SNP rs4783244 in *CDH13* gene between the T2DM and NDM group.

Model	Genotype	NDM[n(%)]	T2DM[n(%)]	OR (95% CI)	P-value	AIC
Codominant	G/G	227 (42.4%)	256 (41.9%)	1.00	0.31	1588.80
	T/G	231 (43.1%)	283 (46.3%)	1.09 (0.85-1.39)		
	T/T	78 (14.6%)	72 (11.8%)	0.82 (0.57-1.18)		
Dominant	G/G	227 (42.4%)	256 (41.9%)	1.00	0.88	1589.10
	T/G-T/T	309 (57.6%)	355 (58.1%)	1.02 (0.81-1.29)		
Recessive	G/G-T/G	458 (85.5%)	539 (88.2%)	1.00	0.17	1587.30
	T/T	78 (14.6%)	72 (11.8%)	0.78 (0.56-1.11)		
Overdominant	G/G-T/T	305 (56.9%)	328 (53.7%)	1.00	0.27	1588.00
	T/G	231 (43.1%)	283 (46.3%)	1.14 (0.90-1.44)		
Log-additive	---	---	---	0.95 (0.80-1.13)	0.57	1588.80

ARL15 plays key roles in the regulation of intracellular vesicle trafficking [14] and, in particular, has been implicated in insulin signaling and insulin-stimulated glucose transport [25-28]. In 2009, Richards *et al* reported that the *ARL15* G allele at rs4311394 was consistently associated with an increased risk for T2DM and CHD [15]. The authors proposed that *ARL15* may be an upstream mediator of the relationship between insulin and adiponectin and might, thus, impact T2DM and CHD through an insulin-dependent pathway which involves, but is not entirely dependent upon, adiponectin. The results of our study agree with the trend reported for a European population by Richards *et al*. We determined that the *ARL15* rs4311394 was associated with T2DM in a Han Chinese population, that the rs4311394 G allele was a risk factor for T2DM (OR = 1.20; 95% CI: 1.01–1.41) and that the rs4311394 GA and GG genotype increases susceptibility to T2DM (OR = 1.31; 95% CI: 1.02–1.69) in T2DM patients under dominant models. Although, results from the Richards report and our study indicated that *ARL15* is a candidate gene for T2DM involvement, the role of *ARL15* in T2DM is still unknown.

CDH13, located at chromosome 16q24 [29] with 14 exons, codes T-cadherin which is expressed in endothelium and smooth muscle and has been reported as an adiponectin receptor [30]. Several studies have determined that *CDH13* SNPs are associated with adiponectin and adiponectin-related diseases in different ethnic populations [16,17,21,24,31]. Most of these reported association studies of the *CDH13* rs4783244 were performed with Asian populations. Recently, three GWAS for East Asian populations have revealed that the T allele of the *CDH13* rs4783244 was associated with lower plasma adiponectin levels [16,17,24]. In 2011, Chung *et al* reported that rs4783244 G allele was associated with the risk of metabolic syndrome (OR = 1.42, P = 0.027) and T2DM in men (OR = 3.25, P = 0.026)[16]. However, we did not find that rs4783244 in *CDH13* was associated with T2DM in a Han Chinese population in this study. We did also not find that rs4783244 in *CDH13* was associated with T2DM in male or female subjects after the gender of subjects was further stratified (data not shown). One reason for difference between Chung *et al* and our results could be our sample size was by one third smaller than that of Chung *et al*, which might lead to no association found in current study. If we tested in a larger population, we might observe an effect of rs4783244 in *CDH13*. In addition, population-specific gene variants and/or gene-environment interactions might contribute to the risk increasing of T2DM, although Asian populations have similar genetic backgrounds. Moreover, Gao *et al.* [24] reported that a genetic variant of the rs4783244 in *CDH13* did not appear to affect insulin-resistance-related metabolic traits; these authors inferred that up-regulation of

adiponectin receptors is a compensatory mechanism of adiponectin sensitivity. Thus, the fact that our study did not reveal an association between rs4783244 and T2DM might be due to adiponectin-sensitivity compensation of low adiponectin levels caused by the presence of rs4783244 in T2DM.

In 2013, Yaghootkar *et al.* reported that adiponectin is not a causal risk of insulin resistance and T2DM using the Mendelian randomization approach [32]. However, many studies have reported that adiponectin is an insulin-sensitizing hormone [33]. The human studies established that adiponectin is associated with T2DM risk or T2DM risk factors, which is not only in plasma adiponectin levels but also in genetic variations [2,3,6,13,34-39]. Moreover, adiponectin-deficient mice showed the increased susceptibility to insulin resistance [40]. The model of rhesus monkeys also proved that the changes of adiponectin levels are closely associated with changes in insulin sensitivity [41]. The reason of the difference between Yaghootkar *et al.* and previous studies might be the complex feedback loops or canalization of the body's adaptation to early physiological changes caused by subtle genetic changes, which Yaghootkar *et al.* mentioned in their paper and could not be accounted by their Mendelian randomization approach [32].

Conclusions

In this study, we did an association study of *ARL15* and *CDH13* for T2DM in a Han Chinese population, and found that the G allele of the *ARL15* rs4311394 is a risk factor for T2DM and that individuals with the rs4311394 GA and GG genotype are more susceptible to T2DM under dominant models. However, we did not observe an association of the *CDH13* rs4783244 with T2DM. Thus, compared with *CDH13*, *ARL15* may play more important role in T2DM in Han Chinese population. It is generally known that T2DM is influenced by gene-environment interactions and many genetic factors, including the *adiponectin*. Therefore, to better understand the mechanisms underlying T2DM, future research should explore the effects of gene-gene interactions, environmental factors, and individual genetic background.

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Competing Interests

The authors have declared that no competing interest exists.

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