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Association of the adiponectin gene rs1501299 G>T variant, serum adiponectin levels, and the risk of coronary artery disease in a Chinese population

Ming-Hui Gui [a,1], *Xiang Li* [b,1], *Sun-Fang Jiang* [c], *Jian Gao* [d], *Da-Ru Lu* [e], *Xin Gao* [a,*]

[a] *Department of Endocrinology and Metabolism, Zhongshan Hospital, Fudan University, Shanghai 200032, PR China*
[b] *Department of Endocrinology and Metabolism, Zhongshan Hospital, Dalian University, Dalian 116001, Liaoning Province, PR China*
[c] *Department of General Practice, Zhongshan Hospital, Fudan University, Shanghai 200032, PR China*
[d] *Department of Nutrition, Zhongshan Hospital, Fudan University, Shanghai 200032, PR China*
[e] *Institute of Genetics, School of Life Science, Fudan University, Shanghai 200433, PR China*

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ABSTRACT

Background: The present study aimed to investigate whether the single nucleotide polymorphism (SNP) 276G>T (rs1501299) of the adiponectin (*ADIPOQ*) gene was associated with the risk of coronary artery disease (CAD) and serum adiponectin levels in a Chinese population.

Methods: The rs1501299 polymorphism of the *ADIPOQ* gene was genotyped in 438 subjects with angiographically diagnosed CAD and 443 controls. Levels of serum adiponectin were determined in 152 CAD subjects and 155 controls.

Results: The CAD subjects had GT and TT genotypes more frequently, and had GG genotype less frequently than the controls. The OR increased and was significant after adjustment for known CAD risk factors. Significant difference was also observed with T allele being more frequent among the CAD subjects. The T allele at the rs1501299 polymorphism was associated with a higher risk of CAD. The mean adiponectin levels of CAD patients were lower than control subjects. No significant correlation was seen of different genotypes with serum adiponectin levels.

Conclusions: The adiponectin rs1501299 G>T variant was positively related with an increased risk of CAD, and the CAD patients had lower adiponectin levels which were not affected by the different genotypes of rs1501299 in the present study.

1. Introduction

Abundant in blood, adiponectin is an adipose specific derived cytokine that promotes fatty acid oxidation, glucose uptake, and insulin action in peripheral tissues. Adiponectin also has an antiatherogenic property, the levels of which are correlated inversely with the severity of insulin resistance, obesity [1], type 2 diabetes (T2DM) [2], cardiovascular disease [3], and metabolic syndrome [4]. The gene of adiponectin (*ADIPOQ*) is located on chromosome 3q27, consisting of three exons and two introns. Genome-wide scans have revealed some susceptible loci for type 2 diabetes [5], coronary heart disease [6], and measurement of adiposity [7] in this chromosome region.

* *Corresponding author*. Tel.: +86 13788961990x680362.
E-mail address: gao.xin@zs-hospital.sh.cn (X. Gao).

[1] Both these authors contribute equally to this work and are co-first authors.

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Intensive research has been focused on the relationship between single nucleotide polymorphisms (SNPs) of *ADIPOQ* gene and diseases related insulin resistance. One of the most commonly reported variants is the 276 G>T polymorphism in intron 2 (rs1501299). In an Italian population [8], the rs1501299 polymorphism was observed to be associated with coronary artery disease (CAD) risk in diabetic patients. However, this association was not replicated in some American [9], Swedish [10], French [11] populations, and another Italian population [12]. Therefore, the findings associated with the *ADIPOQ* loci may present considerable heterogeneity among different populations. In Asia, the *ADIPOQ* gene rs1501299 polymorphism was shown to be not only associated with type 2 diabetes [13] and cardiovascular disease [14] in Japanese patients, but also associated with metabolic syndrome in Korean subjects [15]. While this variant may not be an important determinant of type 2 diabetes mellitus or insulin resistance in another Korean population [16]. However, little is known about the association between the rs1501299 of the *ADIPOQ* gene and the risk of CAD in Chinese patients. The aim of this study was to investigate whether the rs1501299 polymorphism of the *ADIPOQ* gene was associated with the risk of CAD and serum adiponectin levels in a Chinese population.

2. Materials and methods

2.1. Subjects

The present study subjects were recruited from a consecutive sample of 1107 individuals who were undergoing coronary angiography for the confirmation of suspected myocardial ischemia and the evaluation of CAD at the department of cardiology in Zhongshan Hospital affiliated to Fudan University. Patients who had an acute coronary syndrome ($n = 215$) or had incomplete clinical information were excluded ($n = 11$). Thus, the final subjects in the study are 881, including 438 CAD subjects and 443 controls. The CAD subjects were patients with angiographically documented CAD. Significant CAD was defined as more than 50% stenosis in at least one coronary artery segment, which can be seen in more detail in previous study [17,18]. The control subjects were individuals with negative coronary angiogram results. All subjects were Chinese living in Shanghai and its neighboring areas and without blood relationship, and all gave their informed consents. The Institutional Review Board of Zhongshan Hospital approved the study protocol.

2.2. Anthropometric and blood pressure measurements

Body weight and height were measured in the morning when the subjects were fasting and not wearing shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in metres (kg/m^2). Circumferences of waist and hip were measured while the subjects were standing after normal expiration, and the waist to hip ratio (WHR) was also computed. Blood pressure was read using mercurial sphygmomanometer, while subjects remained seated after a 20 min rest. An average of 3 measurements was recorded.

2.3. Blood collection and biochemical marker determination

For economic reasons, a random sample of the study subjects, approximately 35%, were assayed for adiponectin. Venous blood specimens were collected after a 12 h overnight fasting. The blood samples were frozen at −80 °C until assayed. Fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) were determined using automatic analyzer (Hitachi 7170A, Japan). Glycosylated hemoglobin (HbA1c) was determined by high pressure liquid chromatography after removal of the labile faction (HPLC Diamat Analyzer, Bio-Rad, Richmond, CA). Levels of serum adiponectin were determined in some subjects by commercial radioimmunoassay kits (Linco Research, St. Charles, MO). Intra- and interassay coefficients of variation were 6.21 and 9.25%, respectively.

2.4. Genotyping

We used modified guanidine hydrochloride method for DNA extraction from 2 ml whole blood. We screened the rs1501299 at intron 2 of *ADIPOQ* gene in all subjects with assays using the quantitative real-time TaqMan polymerase chain reaction (Applied Biosystems, Foster City, CA, USA).

2.5. Statistical analysis

Statistical analysis was performed with SPSS version 11.5 software (SPSS, Chicago, IL, USA). Continuous variables were present as mean ± SD, and were compared by Student's *t*-test, oneway ANOVA, or Kruskal–Wallis test. Natural logarithmic transformation was used for adiponectin because of the high degree of skewing and reverted by reverse logarithm. Discrete variables were presented as total number (percentage) and were compared by the χ^2-test. Logistic regression was used to estimate the unadjusted and adjusted odds ratio (OR) of genotypic association for CAD. The allelic association estimation with CAD and OR was analyzed using the χ^2-test with the G allele as the reference allele. Hardy–Weinberg equilibrium was used to calculate the expected frequencies of the investigated heterozygous genotypes. A two-tailed *P* value of <0.05 was considered statistically significant. In some cases, adjustment was made for the effect of age, sex, BMI, WHR, smoking, blood pressure, blood glucose, blood lipid and the use of lipid lowering drugs and anti-diabetic drugs.

3. Results

3.1. Clinical characteristics of the CAD and control subjects

The clinical characteristics of the study subjects are shown in Table 1. Compared with control individuals, the CAD patients had more smokers and male subjects, who showed higher BMI, WHR, TG, FPG, 2hPG, and HbA1c ($P < 0.001$), and also showed lower levels of TC, LDL-C, and HDL-C ($P < 0.001$).