

Association of Adiponectin SNP+45 and SNP+276 with Type 2 Diabetes in Han Chinese Populations: A Meta-Analysis of 26 Case-Control Studies

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Abstract

Recently, many studies have reported that the SNP+45(T>G) and SNP+276(G>T) polymorphisms in the adiponectin gene are associated with type 2 diabetes (T2DM) in the Chinese Han population. However, the previous studies yielded many conflicting results. Thus, a meta-analysis of the association of the adiponectin gene with T2DM in the Chinese Han population is required. In the current study, we first determined the distribution of the adiponectin SNP+276 polymorphism in T2DM and nondiabetes (NDM) control groups. Our results suggested that the genotype and allele frequencies for SNP+276 did not differ significantly between the T2DM and NDM groups. Then, a meta-analysis of 23 case-control studies of SNP+45, with a total of 4161 T2DM patients and 3709 controls, and 11 case-control studies of SNP+276, with 2533 T2DM patients and 2212 controls, was performed. All subjects were Han Chinese. The fixed-effects model and random-effects model were applied for dichotomous outcomes to combine the results of the included studies. The results revealed a trend towards an increased risk of T2DM for the SNP+45G allele as compared with the SNP+45T allele (OR = 1.34; 95% CI, 1.11–1.62; $P < 0.01$) in the Chinese Han population. However, there was no association between SNP+276 and T2DM (OR = 0.90; 95% CI, 0.73–1.10; $P = 0.31$). The results of our association study showed there was no association between the adiponectin SNP+276 polymorphism and T2DM in the Yunnan Han population. The meta-analysis results suggested that the SNP+45G allele might be a susceptibility allele for T2DM in the Chinese Han population. However, we did not observe an association between SNP+276 and T2DM.

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Introduction

Diabetes mellitus comprises a group of metabolic disorders that are characterized by chronic hyperglycemia. Type 2 diabetes (T2DM) and its complications impose a tremendous burden both on individuals with diabetes and on the health care system.

Adiponectin is an important adipocytokine that is secreted by adipocytes and plays a key role in the regulation of insulin sensitivity and glucose homeostasis [1,2,3,4]. Serum adiponectin concentrations are decreased in patients with T2DM, obesity, and metabolic syndrome [4,5,6,7]. Many studies have reported that single nucleotide polymorphisms (SNPs) in the adiponectin gene are associated with T2DM in different populations [8,9,10,11,12,13,14]. However, the results of these studies are confusing rather than conclusive, and show strong racial and regional variations [11,13,15,16,17,18,19,20].

The Chinese population comprises 56 ethnic groups, of which Han is the largest (approximately 93% of the total population). The Han are descended from the Huaxia tribe who lived in the area of the Yellow River, and then migrated to the area of the Yangtze River. The Han have now spread throughout the country and live

in different regions of China. Many studies that investigated the association in the Chinese Han population between T2DM and SNPs in the adiponectin gene have been reported recently [16,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43]. Two SNPs in particular have been analyzed: rs2241766 (+45 T>G in exon 2) and rs1501299 (+276 G>T in intron 2). A series of association studies was carried out to investigate the relationship between these two SNPs and T2DM in the Han population in different regions of China. However, the results were still fairly contradictory, and showed regional variation. Therefore, a meta-analysis of the association of the adiponectin gene polymorphisms SNP+45 and SNP+276 with T2DM in the Chinese Han population is necessary in order to clarify the role of these SNPs in T2DM.

The aim of the current study was first to evaluate the association of SNP+276 with T2DM in the Han population in Yunnan Province, in the southwest of China. Then, we combined our data with those of 25 previous studies for a carefully designed meta-analysis to investigate the association of the SNP+45 and SNP+276 polymorphisms in the adiponectin gene with T2DM in the Chinese Han population. Our study will provide a more

thorough evaluation of the significance of the association of the SNP+45 and SNP+276 polymorphisms with T2DM in the Chinese Han population.

Results

1. Association study results

1.1 Clinical characteristics of the enrolled subjects. The clinical characteristics of the enrolled subjects are presented in Table S1. Anthropometric parameters (BMI, WC, and HC) were significantly higher in patients with T2DM than in NDM subjects. Although fasting insulin did not differ between the T2DM and NDM groups, the T2DM subjects had a significantly higher insulin resistance index.

1.2 Association of SNP+276 and T2DM. SNP+276 conformed to HWE in both the T2DM group and the NDM group ($P=0.72$ and $P=0.34$), respectively. The allele and genotype frequencies for SNP+276 are shown in Table S2. The allele frequencies for SNP+276 were 0.71 for G and 0.29 for T in the T2DM group. In the NDM group, the allele frequencies were 0.68 for G and 0.32 for T. The genotype frequencies for SNP+276 were 0.51 for GG, 0.40 for GT, and 0.09 for TT in the T2DM group. In the NDM group, the genotype frequencies were 0.45 for GG, 0.47 for GT, and 0.08 for TT. The genotype frequencies for SNP+276 showed no significant differences between the T2DM and NDM groups ($\chi^2=1.59$, $P=0.45$). After adjusting age and gender, the genotype frequencies for SNP+276 also showed no significant differences between the T2DM and NDM groups ($\chi^2=3.74$, $P=0.15$). In addition, the allele frequencies for SNP+276 showed no significant differences between the T2DM and NDM groups ($\chi^2=0.65$, $P=0.42$, OR = 0.87).

2. Meta-analysis result

2.1 Flow of included studies. The initial search strategy to identify association studies for T2DM and SNPs in the adiponectin gene yielded a total of 262 potentially relevant references among all the databases, 146 of which were overlapping. After subsequent screening, 26 studies were identified for recruitment in the light of the inclusion criteria.

2.2 Study characteristics. Table S3 and S4 show the 23 case-control studies for SNP+45, with a total of 4161 T2DM subjects and 3709 NDM subjects, and 11 case-control studies for SNP+276, with a total of 2533 T2DM subjects and 2212 NDM subjects, that were included in the analysis, respectively [16,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43]. All subjects were selected randomly without sex or age restriction. The diagnosis of T2DM followed the 1999 WHO Diabetes Criteria, except for one study that used the 1985 WHO criteria[23].

2.3 Association of SNP+45 and SNP+276 with T2DM. Fig. 1 and Fig. 2 show the ORs and 95% CI for the association of T2DM with SNP+45 and SNP+276, respectively, in individual studies. There was significant heterogeneity among the results of the individual studies, $P_{\text{heterogeneity}} < 0.01$, $I^2 = 84.6\%$ for SNP+45 and $P_{\text{heterogeneity}} < 0.01$, $I^2 = 76.9\%$ for SNP+276. Therefore, the random-effects model (I-V heterogeneity) was used to calculate the pooled ORs and 95% CI for both SNPs. Overall, there was a trend towards an increased risk of T2DM for the SNP+45G allele as compared with the SNP+45T allele (OR = 1.34, 95% CI = 1.11–1.62, $P < 0.01$). However, there was no trend towards an increased risk of T2DM for the SNP+276T allele as compared with the SNP+276G allele (OR = 0.90, 95% CI = 0.73–1.10, $P = 0.31$).

2.4 Publication bias. Begg's funnel plot and Egger's test were performed to determine whether the literature showed a publication bias. The Begg's funnel plots were symmetrical by visual inspection (Fig. 3 and Fig. 4), and neither the Begg's test nor the Egger's test suggested publication bias. The P-values for Egger's test were 0.07 (95% CI = -2.97 to 5.85) for SNP+45 and 0.60 (95% CI = -4.69 to 2.87) for SNP+276.

2.5 Sensitivity analysis. A sensitivity analysis was performed by omitting one study at a time and calculating the pooled ORs for the remaining studies. This analysis showed that none of the individual studies influenced the pooled ORs, which ranged from 1.29 (95% CI = 1.08–1.55) to 1.41 (95% CI = 1.19–1.69) for SNP+45, and 0.85 (95% CI = 0.76–0.96) to 0.97 (95% CI = 0.88–1.06) for SNP+276. The sensitivity analysis indicated that the results of the meta-analysis were reliable and stable.

Discussion

The adiponectin gene is located on human chromosome 3q27, where a region identified as a susceptibility locus for metabolic syndrome and T2DM has been reported, and is composed of three exons that span 17 kb[44,45,46,47]. Two common SNPs in the adiponectin gene (SNP+45 and SNP+276) were determined to be associated with T2DM in the Japanese population by Hara et al[11]. They observed that Japanese subjects with the SNP+45GG genotype or SNP+276GG genotype had a significantly increased risk of T2DM. In the current study, the associations of the SNP+276 alleles and genotypes with T2DM were assessed separately, and no significant association of SNP+276 with T2DM was found. These results were similar to some previous studies of the Chinese Han population[19,20,23,26,37], but contradicted other studies that showed there was a significant association of SNP+276 with T2DM [32,35]. The conflicting results indicated that a meta-analysis should be performed to determine whether these SNPs in the adiponectin gene were associated with T2DM in the Chinese Han population.

To the best of our knowledge, this is one of the largest systematic reviews of the literature that has used a meta-analysis to study the association between the SNP+45 and SNP+276 polymorphisms and T2DM in Chinese Han populations. The previous meta-analysis included eight papers for SNP+45 and four papers for SNP+276[48], whereas we combined our results with those of recently published studies, namely 23 papers for SNP+45 and 11 papers for SNP+276. As a result, we were able to conduct a comprehensive meta-analysis in which the number of studies was almost three times higher than in the previous analysis[48].

HWE is the principal law in population genetic studies. If a locus conforms with HWE, the samples are representative. In fifteen studies of SNP+45 and nine studies of SNP+276, the genotypes in both the T2DM and NDM groups conformed with HWE. Therefore, a further meta-analysis was performed in which only the studies that conformed with HWE were included. The further meta-analysis data showed that there was heterogeneity among the results of the individual studies, $P_{\text{heterogeneity}} < 0.01$, $I^2 = 76.9\%$ for SNP+45 and $P_{\text{heterogeneity}} < 0.01$, $I^2 = 71.3\%$ for SNP+276. The results from the application of the random-effect models revealed that subjects who carried the SNP+45G allele had a significantly increased risk of T2DM as compared with those who carried the SNP+45T allele (OR = 1.40; 95% CI, 1.16–1.68; $P < 0.01$). However, there was no trend towards an increased risk of T2DM for the SNP+276T allele as compared with the SNP+276G allele (OR = 0.93; 95% CI, 0.76–1.14; $P = 0.46$). These results were similar to those of the initial meta-analysis in which all the studies were included.

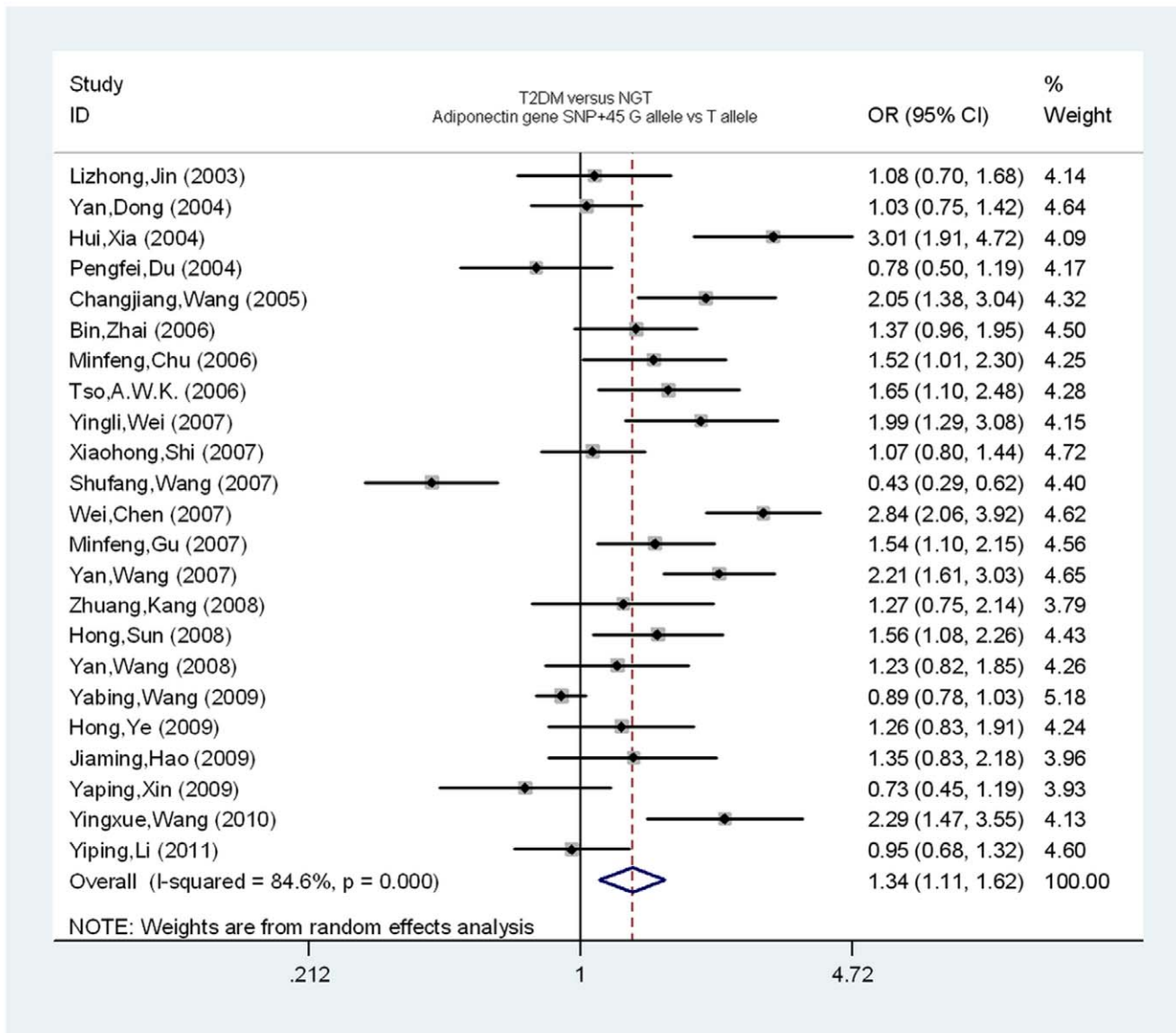


Figure 1. Individual and pooled ORs and 95% CI for SNP+45 (G vs.T) for all studies.
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Heterogeneity is a potential problem when interpreting the results of meta-analysis [49]. Our meta-analysis revealed significant between-study heterogeneity for SNP+45 ($P_{\text{heterogeneity}} < 0.01$, $I^2 = 84.6\%$) and SNP+276 ($P_{\text{heterogeneity}} < 0.01$, $I^2 = 76.9\%$). All of the subjects in the current meta-analysis study were Han Chinese but from different regions and the Han Chinese population is not a genetically homogenous group. Thus, this might explain the significant between-study heterogeneity. The differences in age and gender distributions among the included studies, and differences in sample content might also contribute to the heterogeneity.

In 2002, Hara *et al* first reported that the SNP45+GG genotype of the adiponectin gene was associated with T2DM in the Japanese population [11]. In 2005, Zacharova *et al* investigated the SNP+45 and SNP+276 polymorphisms of the adiponectin gene as predictors of the conversion from impaired glucose tolerance to T2DM in the STOP-NIDDM trial [50]. They observed that the SNP+45G allele was associated with a 1.8-

fold increased risk of T2DM (95% CI, 1.12–3.00; $P = 0.015$) in the placebo group [50]. As a consequence, they concluded that the SNP+45G allele is a predictor of conversion to T2DM [50]. Many studies on the Chinese population also observed an association between the SNP+45G allele and T2DM [20,21,33,38,39]. These results agreed with our meta-analysis data (OR = 1.34; 95% CI, 1.11–1.62; $P < 0.01$). Thus, we inferred that the SNP+45G allele might be a susceptibility allele for T2DM. However, the SNP+45 polymorphism, which is located within exon 2 of the adiponectin gene, does not alter the amino acid sequence of the adiponectin protein. Thus, rather than having a direct effect itself, SNP+45 might be in linkage disequilibrium with a polymorphism in one of the introns that destabilizes the pre-mRNA, results in reduced mRNA levels, and finally leads to pathophysiological effects [51]. Systematic screening of the intronic regions of the adiponectin gene to identify other SNPs should clarify why the SNP+45G allele is associated with T2DM in many studies and in our meta-analysis.

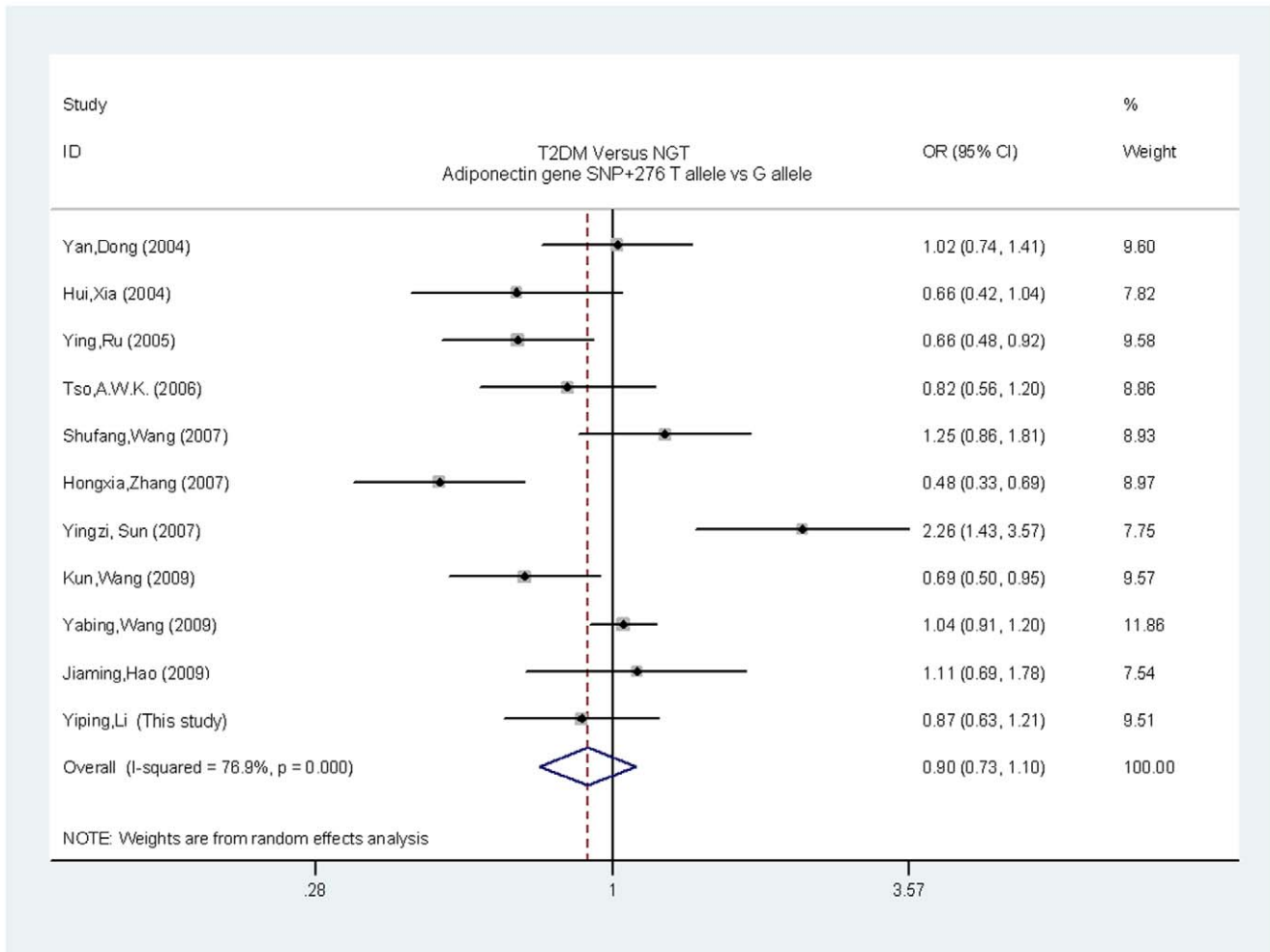


Figure 2. Individual and pooled ORs and 95% CI for SNP+276 (T vs.G) for all studies.
doi:10.1371/journal.pone.0019686.g002

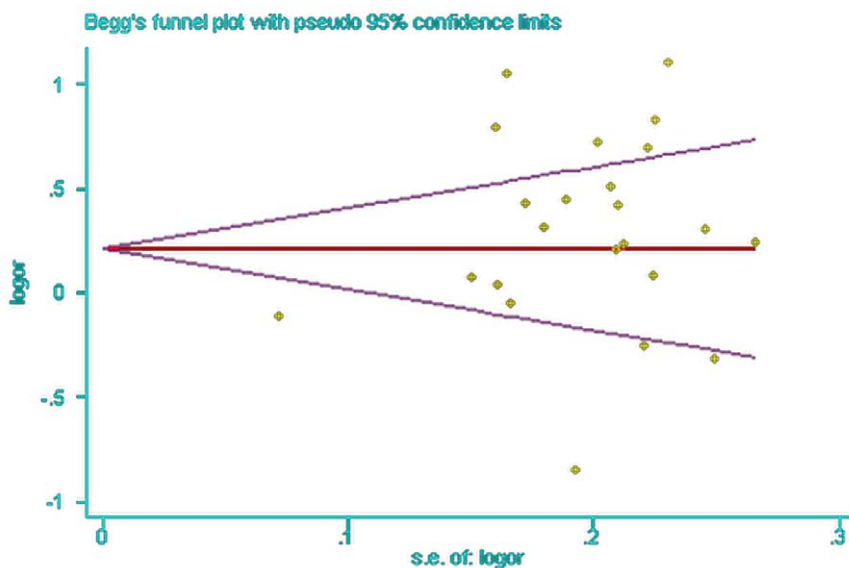


Figure 3. Begg's funnel plot analysis for the comparison of the SNP+45 alleles. P value of Begg's test was 0.79 (continuity corrected).
doi:10.1371/journal.pone.0019686.g003

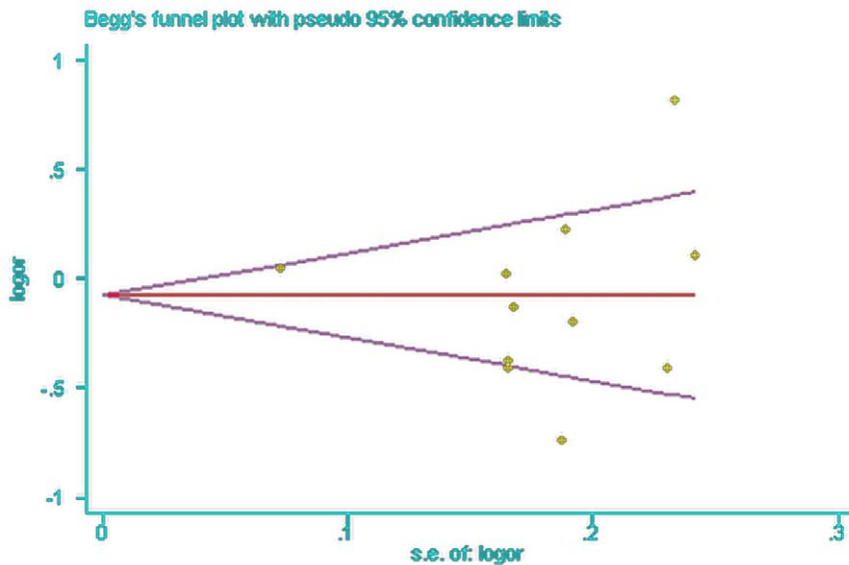


Figure 4. Begg's funnel plot analysis for the comparison of the SNP+276 alleles. P value of Begg's test was 0.76 (continuity corrected). doi:10.1371/journal.pone.0019686.g004

Hara et al. also reported that the SNP+276GG genotype of the adiponectin gene was associated with T2DM in the Japanese population[11]. However, we did not observe any association of SNP276 with T2DM in the current study. Many other studies also did not observe this association in the Chinese Han population[19,20,23,26,37]. In addition, the results of our meta-analysis showed no significant association between SNP+276 and T2DM (OR = 0.90; 95% CI, 0.73–1.10; P = 0.31). Possible explanations for the absence of an association with T2DM are: (a) the SNP+276 polymorphism in the adiponectin gene is not a candidate SNP for T2DM in the Chinese Han population; (b) the effect of SNP+276 might be masked by the summed effects of other unidentified genetic factors; (c) only 11 studies were included in our meta-analysis. Thus, a conclusive assessment of the possible association probably requires the inclusion of more studies and larger sample sizes. It was an interesting finding that the SNP+45 and SNP+276 are only 231 bp far away in adiponectin gene, however, only SNP+45 associated with T2DM in our meta-analysis. Wang et al. reported that SNP+45 just were partly in linkage disequilibrium with SNP+276 in Chinese Han[37]. Therefore, we assumed this could be possible one of causes of the divergence that only SNP+45 associated with T2DM in Han Chinese, but not SNP+276.

The results of our meta-analysis demonstrated that the SNP+45G allele might be a susceptibility allele for T2DM. However, we could not observe any association of SNP+276 with T2DM. As we know, T2DM is influenced by gene–environment interactions. In addition, many genetic factors, including the adiponectin gene, influence the occurrence of T2DM. Therefore, in order to understand the mechanisms underlying T2DM better, future research should be considered and carried out to explore the effects of gene–gene interactions, environmental factors, and individual genetic background.

Materials and Methods

1. Association study between SNP+276 and T2DM

1.1 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.

1.2 Subjects. The study included 202 patients (males = 121; females = 81) who were diagnosed with T2DM at the Second People's Hospital of Yunnan Province from December 2006 to September 2010. T2DM was confirmed using the criteria of the World Health Organization from 1999. Patients who were treated with insulin or an insulin secretagogue were excluded from the study. The nondiabetes group (NDM) included 143 subjects (males = 59; females = 84) 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 were also excluded from the study. All participants were ethnic Han by self report.

1.3 Clinic measurements. Weight, height, waist circumference (WC), and hip circumference (HC) were measured by trained personnel in duplicate and the results were averaged. WC was measured midway between the lower rib margin and the iliac crest. HC was measured at the level of the greater trochanter. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m²). Waist to hip ratio (WHR) was calculated as WC divided by HC.

1.4 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 using a HITACHI 7600-020 Automatic Analyzer. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were determined by enzymatic methods with a HITACHI 7600-020 Automatic Analyzer. Low-density lipoprotein cholesterol (LDL-C) was calculated by using the Friedewald formula. Glycosylated hemoglobin (HbA1c) was determined by immunoturbidimetry with a HITACHI 7600-020 Automatic Analyzer. Fasting serum insulin was measured by radioimmunoassay with a Gamma counter. Insulin resistance was assessed by homeostatic model assessment (HOMA; insulin resistance index = [fasting glucose (mmol/L)×fasting insulin (μU/ml)]/22.5).

1.5 Genotyping the SNP+276 polymorphisms in the adiponectin gene. Genomic DNA was extracted from

peripheral lymphocytes by a standard hydroxybenzene–chloroform method. SNP+276 (rs1501299) was genotyped by the polymerase chain reaction-based restriction fragment-length polymorphism (PCR-RFLP) method. The PCR product was 745 bp and was digested with BmsI into fragments of 523 bp and 222 bp. The digested products were subjected to electrophoresis through a 2% agarose gel, stained with ethidium bromide, and visualized under ultraviolet light. Some of the PCR products were characterized by direct sequencing (3100 Genetic Analyzer; Applied Biosystems, Tokyo, Japan) using a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) after purification with Sephadex™ G-50 (GE Healthcare, Piscataway, NJ, USA).

1.6 Statistical analysis for the population and case-control study. The allele and genotype frequencies for SNP+276 were calculated by the direct-counting method. Hardy–Weinberg equilibrium (HWE) was tested in both the cases and the controls (<http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>). A χ^2 test was used to determine differences in allele and genotype frequencies between T2DM subjects and NDM subjects. The association of SNPs with T2DM was assessed by logistic regression after adjusting for age and gender. A P value of less than 0.05 was considered statistically significant.

2. Meta-analysis Study

2.1 Search strategy. Our meta-analyses use the PRISMA statement as a guide. All of the studies included in the meta-analysis were studies of the association between the adiponectin SNPs and T2DM in Chinese populations. Sources included the MEDLINE, EMBASE, Chinese VIP, Chinese CNKI, and Chinese WanFang databases (up to February 2011). The search terms were as follows: ‘adiponectin’ OR ‘APM1’, ‘polymorphism’ AND ‘type 2 diabetes mellitus’, ‘China’ OR ‘Chinese’.

2.2 Selection. To be included in the meta-analysis, studies had to meet all the following criteria: (a) an unrelated case-control design, (b) all subjects were Han Chinese, (c) available genotype and allele numbers or frequencies, (d) published in any language. PCR-single stranded conformational polymorphism (PCR-SSCP) or PCR-RFLP analysis and DNA sequencing were used to examine the mutations in the adiponectin gene. If there were multiple publications from the same group, only the most recent study was included in the analysis.

2.3 Data extraction and study characteristics. The two authors who conducted the literature search (Yiping Li and Li Shi) also extracted the data from the studies independently. Any disagreement was adjudicated by consensus and by consulting two additional authors (Ying Zhang and Yufeng Yao). Author name, journal and year of publication, region of origin, diagnosis criteria for T2DM, size of case and control groups, and adiponectin SNP loci analyzed were collected. Sample sizes, genotype and allele numbers, and P values for HWE in the T2DM and NDM groups were summarized (Table S3 and Table S4).

References

- Abbasi F, Chu JW, Lamendola C, McLaughlin T, Hayden J, et al. (2004) Discrimination between obesity and insulin resistance in the relationship with adiponectin. *Diabetes* 53: 585–590.
- Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G (2003) Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor- α expression. *Diabetes* 52: 1779–1785.
- Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, et al. (2003) Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes* 52: 239–243.
- Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, et al. (2001) Hypoadiponectinemia in obesity and type 2 diabetes: close association with

2.4 Statistical meta-analysis. Hardy–Weinberg equilibrium (HWE) was tested for all studies included (<http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>). Then, we compared T2DM cases with controls by using the allele model (A/a) for each SNP. The odds ratios (ORs) and 95% confidence intervals (CI) were calculated to determine the differences in each SNP between the T2DM and NDM groups. The χ^2 -based Q statistic test was used to assess the between-study heterogeneity[52]. Heterogeneity was considered significant at a P value of <0.10. The inconsistency index I^2 was also calculated to evaluate the amount of variation that was caused by heterogeneity rather than by chance: higher values of the index indicate the existence of heterogeneity[53]. Data were combined using both fixed-effects (Mantel–Haenszel) and random-effects (I-V heterogeneity) models. The fixed-effects model (if $p>0.10$) or the random-effects model (if $p<0.10$) was used to pool the results. From the individual ORs, a pooled OR was estimated, whose statistical significance was determined using the Z-test. Sensitivity analysis was performed to assess the stability of these results. Potential publication bias was estimated by Begg’s funnel plot and Egger’s linear regression test. $P<0.05$ was considered to represent a statistically significant publication bias[54,55]. All P-values were two-sided. All meta-analysis was performed using Stata statistical software (STATA version SE-10.1; Stata Corporation, College Station, TX).

Supporting Information

Table S1 Clinical characteristics of the subjects enrolled in the present study. (DOCX)

Table S2 Comparison of genotypic and allelic distribution of SNP+45 and SNP+276 between type 2 diabetic and nondiabetic subjects. (DOCX)

Table S3 Characteristics of case-control studies included in a meta-analysis of the association between SNP+45 of adiponectin gene and T2DM. (DOCX)

Table S4 Characteristics of case-control studies included in a meta-analysis of the association between SNP+276 of adiponectin gene and T2DM. (DOCX)

Author Contributions

Conceived and designed the experiments: YL YZ YY. Performed the experiments: YL XL LS WT YX. Analyzed the data: YL LS YY MY. Contributed reagents/materials/analysis tools: YL XL LS WT YX YY MY. Wrote the paper: YL YZ YY.

insulin resistance and hyperinsulinemia. *The Journal of clinical endocrinology and metabolism* 86: 1930–1935.

- Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, et al. (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical and Biophysical Research Communications* 257: 79–83.
- Behre CJ, Gummesson A, Jernas M, Lystig TC, Fagerberg B, et al. (2007) Dissociation between adipose tissue expression and serum levels of adiponectin during and after diet-induced weight loss in obese subjects with and without the metabolic syndrome. *Metabolism: Clinical and Experimental* 56: 1022–1028.
- Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, et al. (2000) Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2

- diabetic patients. *Arteriosclerosis, Thrombosis, and Vascular Biology* 20: 1595–1599.
8. Fumeron F, Aubert R, Siddiq A, Betoulle D, Pean F, et al. (2004) Adiponectin gene polymorphisms and adiponectin levels are independently associated with the development of hyperglycemia during a 3-year period: the epidemiologic data on the insulin resistance syndrome prospective study. *Diabetes* 53: 1150–1157.
 9. Gibson F, Froguel P (2004) Genetics of the APM1 locus and its contribution to type 2 diabetes susceptibility in French Caucasians. *Diabetes* 53: 2977–2983.
 10. Gu HF, Abulaiti A, Ostenson CG, Humphreys K, Wahlestedt C, et al. (2004) Single nucleotide polymorphisms in the proximal promoter region of the adiponectin (APM1) gene are associated with type 2 diabetes in Swedish caucasians. *Diabetes* 53 Suppl 1: S31–35.
 11. Hara K, Boutin P, Mori Y, Tobe K, Dina C, et al. (2002) Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes* 51: 536–540.
 12. Populaire C, Mori Y, Dina C, Vasseur F, Vaxillaire M, et al. (2003) Does the -11377 promoter variant of APM1 gene contribute to the genetic risk for Type 2 diabetes mellitus in Japanese families? *Diabetologia* 46: 443–445.
 13. Vasseur F, Helbecque N, Dina C, Lobbens S, Delannoy V, et al. (2002) Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Human Molecular Genetics* 11: 2607–2614.
 14. Vasseur F, Helbecque N, Lobbens S, Vasseur-Delannoy V, Dina C, et al. (2005) Hypoadiponectinaemia and high risk of type 2 diabetes are associated with adiponectin-encoding (ACDC) gene promoter variants in morbid obesity: evidence for a role of ACDC in diabetes. *Diabetologia* 48: 892–899.
 15. He L, Liu P, Ye F, Li JN, Dong CP (2006) Association of SNPs in proximal promoter region of APM1 gene with serum adiponectin level and type 2 diabetes in Shaanxi Chinese. *Journal of the Fourth Military Medical University* 27: 1493–1495.
 16. Ru Y, Ma M, Ma T, Wang CJ, Wang YM, et al. (2005) Association of SNP276 in adiponectin gene with type 2 diabetes mellitus and insulin sensitivity. *Chinese Journal of Medical Genetics* 22: 698–701.
 17. Shi XH, Jin F, Wang L, Yang Z (2007) Association of SNPs -11377C/G in proximal promoter region of adiponectin gene with type 2 diabetes in Northern Chinese Han population. *Journal of Clinical Rehabilitative Tissue Engineering Research* 11: 6815–6818.
 18. Wang JY, Wang YB, Yu YC, Li Z, Teng XH, et al. (2007) Polymorphism of adiponectin gene in pedigree of type 2 diabetes mellitus. *Academic Journal of Second Military Medical University* 28: 143–147.
 19. Wang SF, Zhao JJ, Jiang Q, Gao L, Ma H (2007) The correlation between adiponectin gene polymorphism and type 2 diabetes. *Chinese Journal of Endocrinology and Metabolism* 23: 51–52.
 20. Xia H, Mo YZ, Bian RW, Shen J, Ma LJ (2004) Correlation between single nucleotide polymorphism of adiponectin gene and type 2 diabetes in Chinese. *Chinese Journal of Endocrinology and Metabolism* 20: 236–237.
 21. Chen W, Yi HZ, Ma XW (2007) Single nucleotide polymorphism of adiponectin gene 45 site in patients with type 2 diabetes in the south of Henan province. *Journal of Zhengzhou University (Medical Sciences)* 42: 1145–1147.
 22. Chu MF, Gou LX, Pan Q, Guo FJ, Sun MX, et al. (2006) Association of adiponectin gene polymorphism with type 2 diabetes mellitus and artery intima-media thickness. *Chinese Journal of Endocrinology and Metabolism* 22: 24–26.
 23. Dong Y, Li G, Luo TH, Wu G, Huang W, et al. (2004) Relationship between adiponectin gene polymorphisms and type 2 diabetes. *Academic Journal of Shanghai Second Medical University* 24: 1001–1003.
 24. Du PF, Xu M, Hong J, Gu WQ, Zhang YF, et al. (2004) Adiponectin gene polymorphism and its association with insulin resistance. *Chinese Journal of Diabetes* 12: 393–396.
 25. Gu MF, Wu WJ, Bu RF, Zhu SW, Xu L, et al. (2007) Studies on serum adiponectin level and SNP45 of adiponectin gene in patients with type 2 diabetes. *Journal of Jiangsu University (Medicine Edition)* 17: 498–502.
 26. Hao JM, Dian ZH, Liu JX (2009) Correlation between single nucleotide polymorphism of adiponectin gene and type 2 diabetes in Han population of Hainan. *Hainan Medical Journal* 20: 1–3.
 27. Jin LZ, Liu DM, Yu DM, Wang WL, Fan XP (2003) Study on association of Gly5Gly polymorphism in adiponectin gene with type 2 diabetes. *Journal of Tianjin Medical University* 9: 211–213.
 28. Kang Z, Sun CK, Zhao HZ, Sha YB, Yu DM, et al. (2008) Correlation between polymorphism of adiponectin gene and type 2 diabetes mellitus in Bai and Han population at Dali area. *Chinese Journal of Diabetes* 16: 718–720.
 29. Li YP, Zhang Y, Song DP, Yang Y, Yao YF, et al. (2011) Single nucleotide polymorphism haplotypes of adiponectin gene were associated with Type 2 diabetes of Han population. *Chinese Journal of Diabetes* 19: 101–104.
 30. Shi XH, Jin F, Sun L, Li H, Wang L, et al. (2007) Association of the polymorphism of SNP+45(T/G) in adiponectin gene with type 2 diabetes. *Journal of Clinical Rehabilitative Tissue Engineering Research* 11: 4941–4944.
 31. Sun H, Gong ZC, Yin JY, Liu HL, Liu YZ, et al. (2008) The association of adiponectin allele 45T/G and -11377C/G polymorphisms with Type 2 diabetes and rosiglitazone response in Chinese patients. *British Journal of Clinical Pharmacology* 65: 917–926.
 32. Sun YZ, Guo ZX (2007) An association study of adiponectin gene SNP276 and Type 2 Diabetes. *Shanxi Medicine Journal* 36: 661–663.
 33. Tso AW, Sham PC, Wat NM, Xu A, Cheung BM, et al. (2006) Polymorphisms of the gene encoding adiponectin and glycaemic outcome of Chinese subjects with impaired glucose tolerance: a 5-year follow-up study. *Diabetologia* 49: 1806–1815.
 34. Wang CJ, Wang YM, Ru Y, Hu HL, Chen MW, et al. (2005) Association of SNP45 in adiponectin gene with obesity and insulin resistance. *Chinese Journal of Diabetes* 13: 324–325.
 35. Wang K, Nie XL, Liu DM, De M (2009) The association of adiponectin gene polymorphism with insulin resistance and type 2 diabetes mellitus. *Journal of Tianjin Medical University* 15: 190–193.
 36. Wang Y, Wang T, Zhong HT (2008) An association research of adiponectin gene SNP45T/G polymorphism and Type 2 Diabetes Mellitus. *Progress in Modern Biomedicine* 8: 84–86.
 37. Wang Y, Zhang D, Liu Y, Yang Y, Zhao T, et al. (2009) Association study of the single nucleotide polymorphisms in adiponectin-associated genes with type 2 diabetes in Han Chinese. *J Genet Genomics* 36: 417–423.
 38. Wang YX, Zhao L, Yu SG, Liu CM (2010) correlation of adiponectin gene polymorphism and type 2 diabetes mellitus. *Shandong Medical Journal* 50: 1–2.
 39. Wei YL, Huo ZH, Zhao W (2007) The relationship of the adiponectin +45 nucleotide T/G polymorphism with insulin resistance, obesity and type 2 diabetes. *Chinese Journal of Diabetes* 15: 583–585.
 40. Xin YP, Zhang SH, Li QJ, Tian CG, Zhang DM, et al. (2009) Association between Adiponectin SNP45 and Type 2 Diabetes with cerebral infarction. *Chinese Journal of Practical Nervous Diseases* 12: 29–30.
 41. Ye H, Kang J (2009) Association of the polymorphism of SNP+45(T/G) in adiponectin gene with type 2 diabetes in Chinese Han population. *Pharmaceutical Care and Research* 9: 158–160.
 42. Zhai B, Ye L, Liu JW, Liu J (2006) Interaction of adiponectin and peroxisome proliferator activated receptor gamma 2 gene polymorphisms and their relationship with type 2 diabetes in population from Beijing communities. *Chinese journal of Clinical Rehabilitation* 10: 28–31.
 43. Zhang HX, Li YY, Zou CY, Li Q, Chen HY, et al. (2007) Relationship between polymorphism of adiponectin gene and type 2 diabetes with vascular diseases. *Shandong Medical Journal* 47: 1–2.
 44. Vionnet N, Hani EH, Dupont S, Gallina S, Francke S, et al. (2000) Genomewide search for type 2 diabetes-susceptibility genes in French whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2-diabetes locus on chromosome 1q21-q24. *American Journal of Human Genetics* 67: 1470–1480.
 45. Takahashi M, Arita Y, Yamagata K, Matsukawa Y, Okutomi K, et al. (2000) Genomic structure and mutations in adipose-specific gene, adiponectin. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity* 24: 861–868.
 46. Mori Y, Otabe S, Dina C, Yasuda K, Populaire C, et al. (2002) Genome-wide search for type 2 diabetes in Japanese affected sib-pairs confirms susceptibility genes on 3q, 15q, and 20q and identifies two new candidate Loci on 7p and 11p. *Diabetes* 51: 1247–1255.
 47. Kissebah AH, Sonnenberg GE, Myklebust J, Goldstein M, Broman K, et al. (2000) Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. *Proceedings of the National Academy of Sciences of the United States of America* 97: 14478–14483.
 48. Li S, Li L, Li K, Qi X, Hoekema D, et al. (2008) Association of adipose most abundant transcript 1 gene (apM1) with type 2 diabetes mellitus in a Chinese population: a meta-analysis of case-control studies. *Clinical Endocrinology* 68: 885–889.
 49. Nakaoka H, Inoue I (2009) Meta-analysis of genetic association studies: methodologies, between-study heterogeneity and winner's curse. *Journal of Human Genetics* 54: 615–623.
 50. Zacharova J, Chiasson JL, Laakso M (2005) The common polymorphisms (single nucleotide polymorphism [SNP] +45 and SNP +276) of the adiponectin gene predict the conversion from impaired glucose tolerance to type 2 diabetes: the STOP-NIDDM trial. *Diabetes* 54: 893–899.
 51. Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, et al. (2002) Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. *Diabetes* 51: 37–41.
 52. Lau J, Ioannidis JP, Schmid CH (1997) Quantitative synthesis in systematic reviews. *Annals of Internal Medicine* 127: 820–826.
 53. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. *BMJ* 327: 557–560.
 54. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50: 1088–1101.
 55. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315: 629–634.