Adiponectin rs16861194 polymorphism and diabetes risk in multi-ethnic population: a meta- analysis of case-control studies

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Abstract: Adiponectin rs16861194 has been implicated in risk for diabetes. However, the results from different studies remain controversial. The present meta-analysis of literatures was performed to clarify these association in multi-ethnic population. A comprehensive literature search was conducted to identify all case-control studies of adiponectin rs16861194 polymorphism and risk of diabetes. A total of 5 eligible studies, including 2726 diabetes cases and 2889 controls, were identified to the meta-analysis. The results in total population showed that the risk for diabetes was increased among the variant heterozygous genotype AG and the dominant model AG+GG, compared with the wild type AA (OR:1.28 ; 95% CI 1.12-1.45; *P*=0.0002 and OR:1.29; 95% CI 1.14-1.47; *P*=0.0001). However, no association were found between diabetes risk and the homozygote genotype GG. In the subgroup analyses by ethnicity, the OR for the variant homozygote GG was 1.74 (95% CI 1.04-2.91) for Chinese. But, there is a protective effect of the variant heterozygote genotype AG and the dominant model AG+GG for non-Chinese population. This meta-analysis has demonstrated that adiponectin rs16861194 polymorphism might have contributed to individual susceptibility to type 2 diabetes.

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1. Introduction

The incidence of diabetes is increasingly worldwide. It is estimated that 250 million people will have diabetes by the year 2020, the most of whom will have type 2 diabetes mellitus(H King et al.,1998). Therefore, prevention and treatment of type 2 diabetes is a global health priority (S Wild et al., 2004).

The gene coding for adiponectin, previously called “adipose most abundant gene transcript 1” (AMP1) or “adipocyte C1q and collagen domain-containing” (ACDC) (OMIM 605441), is officially designated as ADIPOQ by the Human Genome Organization. It is located on chromosome 3q27 including 3 exons and 2 introns and spanning 16 kb of genomic sequence. Adiponectin is an important adipocytokine that is secreted by adipocytes and plays a key role in the regulation of insulin sensitivity and glucose homeostasis(F Abbasi et al.,2004, PA Kern et al.,2003, O Tschritter et al.,2003, C Weyer et al.,2001). Serum adiponectin concentrations are highly heritable, and a number of genome-wide association studies (GWAS) have identified ADIPOQ, the gene encoding adiponectin, as the main locus contributing to variations in serum levels in European and Asian populations(SH Jee et al.,2010, IM Heid et al.,2010, H Ling et al.,2009, JB Richards et al., 2009). Adiponectin cellular signaling is mediated by two adiponectin receptors. These two receptors (ADIPOR1 and ADIPOR2), although generally not associated with serum adiponectin, have been implicated in insulin resistance and type 2 diabetes risk in genetic association studies, but also with inconsistent results(N Stefan et al.,2005, JT Kim et al.,2009, NA Crimmins and LJ Martin,2007, K Hara et al.,2005, SC Collins et al.,2007).

Cross-sectional studies in healthy and diabetic populations have provided further evidence for the association of single nucleotide polymorphisms (SNPs) in ADIPOQ with serum adiponectin concentrations(F Vasseur et al.,2002, IM Heid et al.,2006, MF Hivert et al.,2008, C Menzaghi et al.,2007, P Henneman et al.,2010). Many studies have reported that single nucleotide polymorphisms (SNPs) in the adiponectin gene are associated with type 2 diabetes in different populations(F Vasseur et al.,2002, F Fumeron et al.,2004, F Gibson and P Froguel,2004, HF Gu et al.,2004, K Hara et al.,2002, C Populaire et al.,2003, F Vasseur et al.,2005). However, the results of these studies are confusing rather than conclusive, and show strong racial and regional variations(F Vasseur et al.,2002, K Hara et al.,2002, L He et al.,2006, Y Ru et al.,2005, XH Shi et al.,2007, JY Wang et al.,2007, SF Wang et al.,2007, H Xia et al.,2004, M Yang et al.,2008, Y Wang et al.,2009, TX Sheng et al.,2009, N Mtiraoui et al.,2012).

ADIPOQ promoter −1500 to −1350 bp is a region rich of CpG where methylation and demethylation process occurs mainly. Methylation

and demethylation will lead to promoter SNPs which draw our attention. In promoter region there are many SNPs. Many molecular epidemiological studies have been conducted focusing on the association between polymorphisms in this region and the risk of type 2 diabetes since the initial study by Hara et al. in 2002(K Hara et al.,2002), who reported variant in ADIPOQ might play an important role in the pathogenesis of type 2 diabetes, but the results remain conflicting in following studies. Therefore, to summarize the published data, we conducted a meta-analysis from all eligible case-control studies to assess the association between the polymorphism in rs16861194 of ADIPOQ and the risk of type 2 diabetes.

2. Material and Methods

2.1Identification and Eligibility of Relevant Studies

Reported data from November 2002 to February 2012 on the association of diabetes risk with adiponectin rs16861194 polymorphism were identified through computer-based searches of the PubMed and ISI Web database by using the terms of "adiponectin", "polymorphism", "diabetes", "variant", "SNP" as well as their combinations.

The full text of the candidate articles were examined carefully to determine whether they accorded with the inclusion criteria for the meta-analysis. The inclusion criteria were as follows: (1) case-control studies were conducted to examine the associations of polymorphism rs1681194 in adiponectin gene with diabetes risk; (2) the genotype distribution of the polymorphism in cases and controls were described in detail and the polymorphism status were determined by using molecular biological methods; (3) the results were expressed as odds ratio (OR) and corresponding 95 percent confidence interval (95%CI); (4) the diagnosis of diabetes patients was confirmed pathologically and controls were confirmed as free from diabetes, and (c) written in English. The articles, in which the genotype of controls for a certain polymorphism was not consistent with Hardy-Weinberg equilibrium (HWE), were excluded from the analysis of this polymorphism.

2.2 Data Extraction

For each study, the following characteristics were collected: authors, journal, publication time, ethnicity, country, selection and characteristics of study population (sample size, sources of cases and controls), DNA source, genotyping results of cases and controls, crude odds ratio (OR) or adjusted OR (including adjusted factors), and method of genotyping. Furthermore, we examined whether matching had been used and if the genotyping assay had been validated.

2.3 Statistical Analysis

The analyses were conducted in Review Manager 4.2.8 (http://www.cc-ims.net/RevMan). The risks (ORs) of diabetes associated with the adiponectin gene polymorphisms were calculated directly from the data given in the eligible studies. We estimated the risks of the variant homozygotes, heterozygotes and combined variant genotypes (AA/GG, AA/AG, and AA/AG+GG for rs16861194) compared with the wild-type genotypes. Furthermore, studies were stratified according to ethnicity (Chinese and non-Chinese) and source of controls (hospital-based and population-based). We assessed the departure from the HWE for the control group in each study using Pearson's goodness-of-fit $\chi 2$ test with 1 degree of freedom. For each genetic group, we estimated the heterogeneity, and a random-effects (DerSimonian and Laird) model was selected to pool data if there is significant heterogeneity ($P<0.05$), otherwise, the fixed-effects model was used. If there were significant heterogeneity among included studies, the sources of heterogeneity would be explored using meta regression in Stata version 11.0 (http://www.stata.com). One-way sensitivity analyses were performed to assess the stability of the results, in which a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. The publication bias was diagnosed by using inverted funnel plots, Begg's test and the Egger's test by Stata 11.0. Statistical tests performed in the present analysis were considered significant whenever the corresponding null-hypothesis probability was $P<0.05$.

3. Results

3.1Characteristics of Eligible Studies

A total of 5 studies on the association of adiponectin rs16861194 polymorphism with diabetes risk were identified and screened for data retrieval. The main characteristics of these studies were listed in Table 1, including first author, published year, reference number, language, ethnicity, source of controls, assay, genotype distribution and HWE test of controls. All the 5 eligible articles were selected for this meta-analysis, including 2726 diabetes cases and 2889 controls for rs16861194. All these studies indicated that the distribution of genotypes in controls was consistent with Hardy-Weinberg equilibrium, except for 1 study(HF Gu et al.,2004). In the three studies, DNA was extracted from antecubital vein, and another two studies from peripheral blood. A classic sequence assay was used in four studies, and the only one study by PCR.

Table 1. Main characteristics of studies included in the meta-analysis

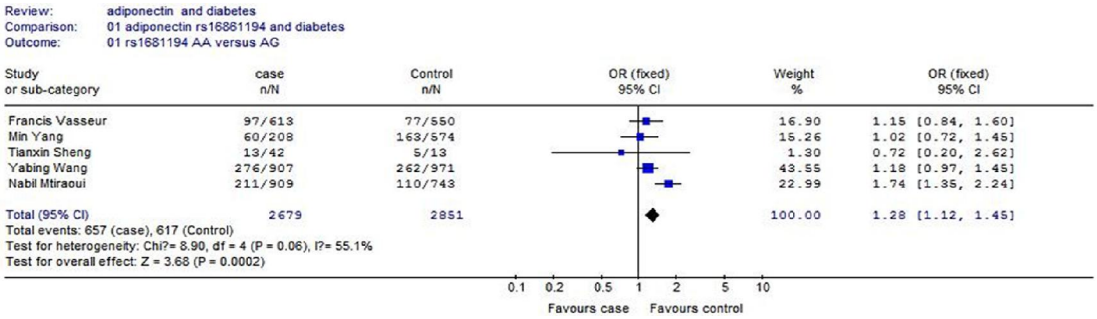
Study	Year	Language	Ethnicity	Source of control	Assay	Genotype distribution(case/control)				HWE(*P*)
						AA	AG	GG	Total	
Vasseur[16]	2002	English	French Caucasians	PB	Sequence	516/473	97/77	3/4	616/554	0.657
Gu[23]	2004	English	Swedish Caucasians	PB	PCR-DASH	79/416	22/70	2/8	103/494	0.016
Yang[33]	2008	English	Chinese	PB	Sequence	148/411	60/163	4/11	212/585	0.260
Wang[34]	2009	English	Chinese	PB	Sequence	631/709	276/262	32/18	939/989	0.269
Sheng[35]	2009	English	Chinese	HB	Sequence	29/8	13/5	-/-	42/13	0.391
Mtiraoui[36]	2012	English	Tunisian Arabs	HB	PCR-ASA	698/633	211/110	8/5	917/748	0.926

Table 2. Results of meta-analysis for adiponectin rs16861194 polymorphisms and diabetes risk

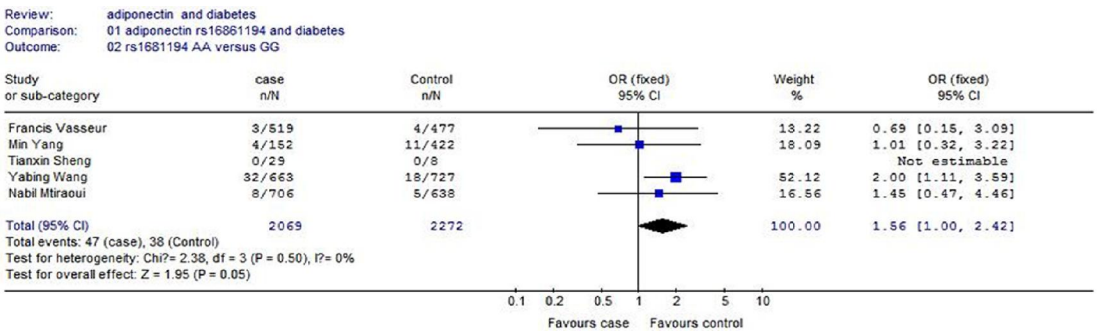
Groups	sample size(case/control)	AA/AG		AA/GG		AA/AG+GG	
		P	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)
Total	2726/2889	0.0002**	1.28(1.12, 1.45)	0.05	1.56(1.00, 2.42)	0.0001**	1.29(1.14, 1.47)
Chinese	1193/1587	0.16	1.13(0.95, 1.35)	0.03*	1.74(1.04, 2.91)	0.07	1.17(0.99, 1.38)
non-Chinese	1533/1302	0.0001**	1.49(1.22, 1.82)	0.81	1.11(0.46, 2.69)	0.0001**	1.47(1.21, 1.79)
PB	1767/2128	0.08	1.14(0.98, 1.33)	0.0001**	1.47(1.21, 1.79)	0.04*	1.17(1.01, 1.36)
HB	959/761	0.0001**	1.68(1.31, 2.16)	0.52	1.45(0.47, 4.46)	0.0001**	1.67(1.31, 2.14)

PB population based; HB hospital based; *P<0.05, **P<0.01

a



b



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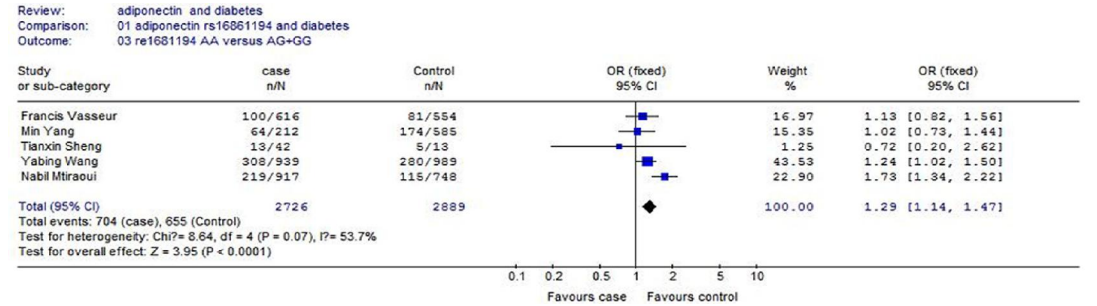
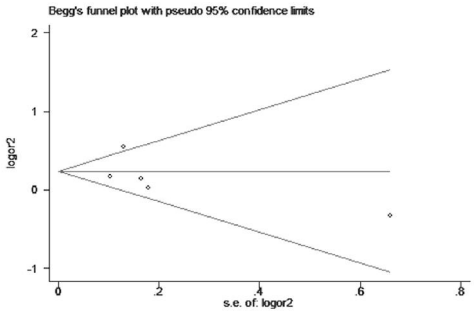


Figure 1. Forest plots of ORs with 95% CI for adiponectin rs16861194 polymorphism and risk for diabetes. The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. The summary OR is represented by the diamond, where the center of the diamond indicates the OR and the ends of the diamond correspond to the 95% CI. a AA vs AG; b AA vs GG; c AA vs AG+GG

a



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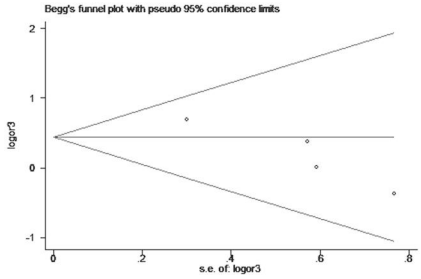

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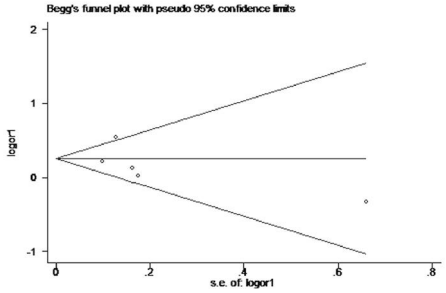

Figure 2. Funnel plots for adiponectin rs16861194 polymorphism and diabetes risk. a AA vs AG; b AA vs GG; c AA vs AG+GG

Table 3. Results of Egger's test and Begg's test

Comparison	Egger's test				Begg's test	
	t	*P*	95%*CI*		*Z*	*P*
AA/AG	-0.66	0.557	-6.782 4.455		0.24	0.806
AA/GG	-4.53	0.045	-3.986 -0.103		1.70	0.089
AA/AG+GG	-0.79	0.486	-6.663 4.008		1.22	0.221

3.2 Overall and Subgroup Meta-analysis Results

Figure 1 showed the association of diabetes risk with adiponectin rs16861194 polymorphism. The variant heterozygous genotype AG carriers have a significant increased risk of diabetes compared with those of wild type AA (AG vs. AA: ORfixed 1.28; 95% CI 1.12-1.45; P=0.06 for heterogeneity). Besides, the strong associations were found in dominant model (AG + GG vs. AA: ORfixed 1.29; 95% CI 1.14-1.47; P =0.07 for heterogeneity). However, the homozygous genotype GG did not show a significant increased risk of diabetes (AG vs. AA: ORfixed 1.29; 95% CI 1.14-1.47; P =0.50 for heterogeneity).

On the basis of the potential overestimation of the true effect of the polymorphism on the diabetes risk, we stratified these studies according to ethnicity and source of controls (Table 2). First, when it was stratified according to ethnicity, the OR for the variant homozygote GG of rs16861194 was 1.74 (95% CI 1.04-2.91) for Chinese. And for non-Chinese population the OR for the variant genotype AG and the dominant model AG+GG were 1.49 (95% CI 1.22-1.82) and 1,47 (95% CI 1.21-1.79), respectively. Besides, when it was stratified according to source of controls, we found a protective effect of GG genotype (OR: 1.47; 95% CI 1.21-1.79) and AG +GG genotype (OR: 1.17; 95% CI 1.01-1.36) for diabetes on the basis of population controls, while on the basis of hospital controls the OR for the variant genotype AG and the dominant model AG+GG were 1.68(95% CI 1.31- 2.16) and 1.67(95% CI 1.31-2.14), respectively.

3.3 Test of Heterogeneity

There was substantial heterogeneity among the 5 studies that included the adiponectin rs16861194 polymorphism (Figure 1). Subsequently, Stata11.0 was used to assess the source of heterogeneity, including controls source (from hospital or population), assay (sequence or non-sequence), matched controls (yes or not), publication year (before or after year of 2008) and Hardy-Weinberg equilibrium in controls (yes or no). It was detected that the systemic results were not affected by these characteristics ($P > 0.05$).

3.4 Publication Bias

Furthermore, there was no influence of publication bias in our study by using of Begg's test and Egger's test (Table 3), as indicated by the funnel plot (Figure 2).

4. Discussions

Type 2 diabetes is a complex disease. The pathogenesis of type 2 diabetes and the metabolic syndrome are not fully clarified, but the interaction between genetic factors and environmental triggers is important. Genetic association between the SNPs of candidate genes and type 2 diabetes may not be fully explained by a single population study. Adiponectin is a cytokine exclusively secreted by mature adipocytes, circulates at a high concentration(H Ling et al.,2009, Y Ru et al.,2005), promotes fatty acid oxidation and glucose uptake(JB Richards et al.,2009, N Stefan et al.,2005) and has strong anti-

inflammatory and anti-atherogenic effects(SC Collins et al.,2007, F Vasseur et al.,2002). It was reported that plasma adiponectin levels are decreased in type 2 diabetes patients and inversely associated with cardiovascular risk(NA Crimmins and LJ Martin,2007). rs16861194 of the adiponectin gene was the only SNP positively associated with type 2 diabetes in Han Chinese population, which is different from previous reports in Chinese(S Li et al.,2008, Y Wang et al.,2008) and other populations(SC Collins et al.,2007, N Siitonen et al.,2006, AW Tso et al.,2006, Y Liu et al.,2007). One of the explanation for the discrepancy might be ethnic difference. These findings promoted us to carry out a systematic meta-analysis to derive a more precise estimation of the association between adiponectin rs16861194 polymorphism and diabetes risk in multi-ethnic population.

In this meta-analysis, both the variant heterozygous genotype AG and the dominant model AG + GG carriers have a significant increased risk of diabetes compared with those of wild type AA. when it was stratified according to ethnicity, in Chinese population, the variant GG genotype was associated with diabetes. But there were strong associations of the AG and AG+GG genotypes with diabetes risk in the non-Chinese population. Therefore, ethnicity may be a major source of heterogeneity. When studies were stratified by controls source, the OR for the variant AG genotype was 1.68 (95% CI 1.31-2.16) for hospital-based controls while 1.14 (95% C I0.98-1.33) for population-based controls, and the OR for the variant GG genotype was 1.45 (95% CI 0.47-4.46) for hospital-based controls while 1.47 (95% CI 1.21-1.79) for population-based controls, which indicated that the allele distribution of the adiponectin rs16861194 between hospital controls and population controls were different.

Although we have put considerable effort and resources into testing possible association between adiponectin polymorphisms and diabetes risk, there are still some limitations inherited from the published studies. First, selection bias could have played a role because the genotype distribution of adiponectin polymorphism among control subjects disobeyed the law of Hardy-Weinberg equilibrium in 1 studies. Second, there was substantial between-heterogeneity among 5 studies in the analysis of adiponectin rs16861194 polymorphism. Possible sources of heterogeneity, such as sample size, controls source, matched controls and publication year did not demonstrate the evidence of any significant variation by meta-regression. It is possible that other limitations of recruited studies may partially contribute to the observed heterogeneity. Third, when we were collecting, the unpublished studies, index words, search area and language all could produce biases. Finally, confounding factors may impact on the conclusion of our study because of case-control studies. For instance, some studies used a healthy population as the reference group, whereas others selected hospital patients without organic endocrine diseases as the reference group, which may influence the meta-analysis results because the hospital controls may be more likely to develop to diabetes in the future.

In the present meta-analysis, we searched as many publications, which had been carried out in multi-ethnic population, as we could. The most of the literatures with full-text we searched are in English, and we believe that most of the related literature have been obtained and screened in our study. Furthermore, we performed test of heterogeneity and examined the sources of heterogeneity. Publication bias was not observed in the analysis of funnel plot, Begg's test and Egger's test. Therefore, the results of our meta-analysis could be considered as accurate and valid.

In conclusion, this meta-analysis has demonstrated that rs16861194 polymorphism of adiponectin gene is associated with an increased risk of diabetes. To further evaluate the effect of polymorphism sites of adiponectin, gene-gene interaction and gene-environment interaction on diabetes risk, a single study with large sample size is required to get conclusive results.

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