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Correlation Between Adiponectin Gene rs1501299 Polymorphism and Nonalcoholic Fatty Liver Disease Susceptibility: A Systematic Review and Meta-Analysis

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Background: Metabolic related nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver diseases around the world. A single nucleotide polymorphism (SNP) rs1501299 (+276G>T) in the adiponectin gene has been recently revealed to be responsible for susceptibility to NAFLD. This meta-analysis intended to assess the association risk of NAFLD and rs1501299 polymorphism.





Material/Methods: We conducted a literature search on PubMed, Embase, and Cochrane Library databases. All involved studies were selected based on our search criteria. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to quantify the strength of the association. Subgroup analysis considered the effects of ethnicity, subject scope, and source of control. Publication bias was assessed by Begg's tests.

Results: Eight qualified case-control studies with 1639 patients and 1426 controls demonstrated a significant correlation between rs1501299 polymorphism in adiponectin and NAFLD under the dominant model (OR=1.18, 95% CI=1.02–1.36), allelic contrast (OR=1.21, 95% CI=1.09–1.36), homozygote comparison (OR=1.63, 95% CI=1.26–2.01) and the recessive allele model (OR=1.58, 95% CI=1.23–2.02) with evident heterogeneity. No association was observed between the risk of NAFLD and the genotypic variants in heterozygote comparison (OR=1.11, 95% CI=0.95–1.29) without heterogeneity. Subgroup analysis suggested that the sample size could be the potential source of heterogeneity. Source of control was not the reason for between-study heterogeneity and further sensitivity analysis and publication bias revealed good consistency and symmetry in the pooling studies.

Conclusions: Results from our current meta-analysis gave insight into the correlation between rs1501299 polymorphism and the risk of NAFLD, indicating the variant of rs1501299 might be related to increased NAFLD susceptibility.

MeSH Keywords: **Adiponectin • Fatty Liver • Polymorphism, Single Nucleotide**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/912737>

 2530  3  5  46



Background

Nonalcoholic fatty liver disease (NAFLD) is the most prevailing cause of chronic liver disease worldwide. It is the hepatic manifestation of metabolic syndrome and is correlated with type 2 diabetes mellitus, high blood pressure, dyslipidemia, cardiovascular disease, obesity, and insulin resistance [1–3]. Its spectrum ranges from simple steatosis to complicated NAFLD, consisting of steatohepatitis, fibrosing steatohepatitis, and cirrhosis. The latter can even develop into hepatocellular carcinoma (HCC). According to the United States National Health and Nutrition Examination Survey (NHANES), the incidence of NAFLD among chronic liver disease cases grew from 47% to 75% between 1988 and 2008 [4].

Most researchers agree that its progress requires underlying steatosis followed by a “second hit” that induces inflammation, fibrosis, or necrosis [5]. The interplay of cytokines between oxidative stress and lipid peroxidation has been presumed to play an important role in NAFLD [6,7]. Studies indicate that both genetic and environmental factors are essential to the occurrence and development of NAFLD as its progression is a multifactorial and multistep process. Host genetic variants are associated with the susceptibility and pathophysiology of metabolic syndrome. Variants of some genes involved in innate immunity have been studied and identified as candidates for metabolic syndrome effectors, especially polymorphisms of adiponectin gene [8].

Adiponectin protein is considered to be an anti-inflammatory adipokine participated in modulating glucose levels and fatty acid breakdown. Reduction in levels of adiponectin which is produced by adipocytes has been reported in several studies in patients with insulin resistance, metabolic syndrome, and obesity as well as NAFLD [9–11]. One of the most common single nucleotide polymorphisms (SNPs) of adiponectin gene is rs1501299 (+276G>T) in the intronic region. This variant (rs1501299) is connected with low adiponectin level and it might be related to overweight and insulin resistance [12]. Thus, it is of great value to evaluate the association between different genotypes of +276 G>T polymorphism in the adiponectin gene with the development of NAFLD. In other words, rs1501299 is related to reduce adiponectin expression, which might result in increased body weight and insulin resistance reversely and therefore increase the risk of developing NAFLD [13,14].

Material and Methods

Methods of the analysis and inclusion criteria were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Search strategy

We conducted searches on PubMed, Embase, and Cochrane Library databases (the last retrieve was performed on September 30, 2017) assembling the following terms, “genetic polymorphism, single nucleotide polymorphism, gene mutation, genetic variants, rs1501299, +276G>T, G276T, nonalcoholic fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, NAFLD” to select all possibly correlative studies. Other potential eligible studies were also manually searched for meeting our criteria through the reference lists from retrieved articles. The qualification assessment for full-text studies was independently conducted by 2 reviewers (Jiaxing Liu and Hong Qiu) according to inclusion and exclusion criteria. All the authors were supposed to critically estimate the articles to judge of the inclusion or exclusion of a certain article when disagreements occurred.

Eligibility criteria

All the eligible studies were selected on the basis of the pre-defined inclusion criteria: a) evaluation of association between NAFLD and rs1501299 G/T polymorphism; b) case-control study; c) The allele frequency provided by articles ought to be sufficient for calculating genotypic odds ratio (OR) combined with corresponding 95% CI in both cases and controls. The major exclusion criteria of studies were: a) repeated records; b) review articles, editorial comments, case reports and animal studies; c) no information on genotype frequency.

Data extraction

Data extraction was conducted independently by 2 authors (Jiaxing Liu and Hong Qiu). We extracted the following elements from each qualified study 1): first author’s name, year of publication; 2) study type; 3) sample size of each group; 4) participants characteristics in cases and controls (ethnicity or geographic location of studied population, control source); 5) genotyping method; 6) genotype distributions and Hardy-Weinberg equilibrium test in controls.

Quality score assessment

The Newcastle-Ottawa Scale (NOS) [16] was applied to evaluate the methodological quality of involved studies mainly on 3 aspects: cases selection, comparison of populations as well as ascertainment of exposure to risks. The NOS fluctuates between zero (worst) and 9 stars (best) and NOS scores of studies ≥ 7 were suggested to show high-quality.

Statistical analysis

Firstly, Hardy-Weinberg equilibrium about the genotype frequencies of rs1501299 polymorphism in group of controls was

assessed using a chi-square goodness-of-fit test ($P > 0.05$) [17]. The combination of ORs and the corresponding 95% CIs was computed to estimate the correlation between rs1501299 polymorphism and NAFLD risk. Besides, the statistical significance of the ORs was calculated by using the Z-test. A chi-square-based Q-test was applied to assess heterogeneity among studies. The random-effect model (DerSimonian-Laird method) was used when a probability value of $P < 0.10$ [18]. If not, the fixed effect model (Mantel-Haenszel method) was adopted [19]. Generally, pooled effect of correlation between rs1501299 polymorphism and NAFLD susceptibility was assessed in 5 genetic models: allele model (T versus G), homozygote (co-dominant) model (TT versus GG), heterozygote (co-dominant) model (GT versus GG), dominant model (TT+GT versus GG) and recessive model (TT versus GG+GT). Stratified analyses were further conducted according to ethnicity (Asian and Caucasian), design (hospital-based and population-based) and sample size (less than 200 or more than 200 in case groups and control groups). Publication bias and funnel plot asymmetry were evaluated by using Begg's test and P values less than 0.05 were considered to be significant [20]. Sensitivity analysis was carried out as well to estimate the robustness of each included study through the leave-one-out approach. The current meta-analysis was done using STATA 12.0 (STATA Corp., College Station, TX, USA).

Results

Eligible studies

A total of 142 studies were identified by initial retrieval on the basis of our search strategy from the PubMed, Embase, and Cochrane Library databases, and 97 records were selected after removing duplicates. Among them, 64 irrelevant records were excluded by screening the titles and abstracts. This left 33 full manuscripts for detailed evaluation, of which 25 studies were further excluded for inappropriate article types, not case-control studies, or insufficient data. Thus, 8 eligible studies were involved in our meta-analysis [11,21–27]. The PRISMA flow diagram of the literature search and selection process is presented in Figure 1.

Baseline characteristics

A total of 3065 patients from the 8 articles were involved in the meta-analysis. Included studies were conducted in 3 countries and published between 2008 and 2017. Among the 8 eligible studies, 6 studies were undertaken in Asian and 2 studies were carried out in Caucasian populations. As for the source of controls, 4 control groups were hospital-based (HB) and 4 control groups were population-based (PB). In terms of sample size in case groups and control groups, there were more than 200 samples included in 3 studies while less than

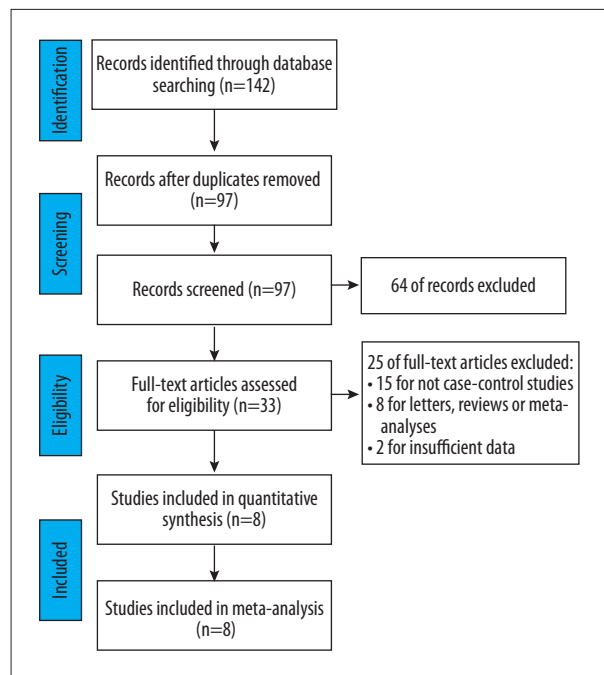


Figure 1. PRISMA flowchart of the selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

200 samples were involved in the other 5 studies. Detection methods included PCR-RFLP, TaqMan, Tetra-ARMS-PCR, and other PCR techniques. In addition, none of the genotype distributions among controls in individual studies were inconsistent with Hardy-Weinberg equilibrium. As for assessment of studies we included, the NOS of 6 included studies was ≥ 7 and on 2 of the included studies it was the NOS was 6. Characteristics of the included studies are detailed in Table 1. Finally, the minor allele frequencies (MAFs) in the case groups and control groups were 0.32 and 0.28 respectively, being in good agreement with the Global MAF reported in the SNP database.

Meta-analysis of association between rs1501299 and NAFLD

Table 2 summarizes the ORs with corresponding 95% CIs for the correlation between rs1501299 polymorphism in the adiponectin gene and NAFLD risk in different genetic models. In the pooled analysis of heterozygote comparison, no significant correlation was found between NAFLD susceptibility and the genotypic variants of rs1501299 T/G (OR=1.11, 95% CI=0.95–1.29, $P_{\text{heterogeneity}}=0.206$, $P=0.191$). However, pooling studies demonstrated a significant increased association between rs1501299 and NAFLD under other models: allelic contrast (OR=1.21, 95% CI=1.09–1.36, $P_{\text{heterogeneity}}=0.000$, $P=0.001$), homozygote comparison (OR=1.63, 95% CI=1.26–2.01, $P_{\text{heterogeneity}}=0.000$, $P=0.000$), the dominant allele model (OR=1.18, 95% CI=1.02–1.36, $P_{\text{heterogeneity}}=0.06$, $P=0.023$), and the recessive allele model

Table 1. Characteristics of involved studies on the association between Adiponectin gene rs1501299 polymorphism and NAFLD risk.

Author	Year	Ethnicity	Design	Subjects size	Case	Control	Case			Control			Method NOS	
							GG	GT	TT	GG	GT	TT		HWE
Wang	2008	Asian	HB	<200	248	160	117	111	20	74	73	13	0.39	PCR-CDGE 6
Tokushige	2009	Asian	PB	<200	118	115	67	47	4	59	47	9	0.93	PCR-SSP 7
Zhang	2016	Asian	HB	>200	302	310	161	120	21	184	112	14	0.83	PCR-RFLP 7
Mohseni	2017	Caucasian	PB	<200	75	76	33	32	10	39	28	9	0.27	DNA sequencing 8
Hashemi	2013	Caucasian	PB	<200	83	93	42	39	2	53	38	2	0.10	Tetra-ARMS-PCR 8
Li	2015	Asian	HB	>200	357	357	113	164	80	161	165	31	0.21	PCR-RFLP 7
Zhou	2010	Asian	PB	<200	106	106	68	29	9	50	39	17	0.06	PCR-RFLP 8
Hsieh	2015	Asian	HB	>200	350	209	175	126	49	113	79	17	0.55	TaqMan 6

PB – population-based; HB – hospital-based; PCR-CDGE – PCR-constant denaturant gel electrophoresis; PCR-SSP – PCR-sequence specific primer; PCR-RFLP – restriction fragment length polymorphism polymerase chain reaction; Tetra-ARMS-PCR – tetra-primer amplification refractory mutation system PCR; HWE – Hardy-Weinberg equilibrium of control group.

Table 2. The main results of subgroup analysis on Adiponectin gene rs1501299 polymorphism and NAFLD risk.

Variables	N	Case/Control	T-allele vs. G-allele			GT vs. GG			TT vs. GG			TT+GT vs. GG			TT vs. GT+GG		
			OR (95% CI)	P _h ^a	P ^b	OR (95% CI)	P _h	P	OR (95% CI)	P _h	P	OR (95% CI)	P _h	P	OR (95% CI)	P _h	P
Total	8	1639/1426	1.21 (1.09–1.36)	0.000	0.001	1.11 (0.95–1.29)	0.206	0.191	1.63 (1.26–2.10)	0.000	0.000	1.18 (1.02–1.36)	0.006	0.023	1.58 (1.23–2.02)	0.002	0.000
Source of control																	
HB	4	1257/1036	1.36 (1.20–1.55)	0.011	0.000	1.18 (0.98–1.40)	0.435	0.073	2.18 (1.61–2.94)	0.022	0.000	1.32 (1.11–1.56)	0.091	0.001	2.03 (1.52–2.70)	0.058	0.000
PB	4	382/390	0.85 (0.68–1.06)	0.037	0.153	0.93 (0.69–1.26)	0.151	0.651	0.62 (0.36–1.07)	0.242	0.085	0.87 (0.66–1.16)	0.058	0.341	0.65 (0.38–1.11)	0.457	0.116
Ethnicity																	
Asian	6	1481/1257	1.21 (1.08–1.36)	0.000	0.001	1.08 (0.92–1.27)	0.107	0.336	1.66 (1.27–2.17)	0.000	0.000	1.17 (1.00–1.36)	0.001	0.048	1.62 (1.25–2.10)	0.000	0.000
Caucasian	2	158/169	1.21 (0.86–1.71)	0.955	0.275	1.32 (0.84–2.08)	0.928	0.231	1.30 (0.53–3.22)	0.972	0.566	1.32 (0.85–2.03)	0.935	0.217	1.14 (0.48–2.71)	0.986	0.765
Subject scope																	
<200	5	630/550	0.89 (0.75–1.07)	0.061	0.214	0.94 (0.74–1.20)	0.256	0.635	0.72 (0.46–1.12)	0.282	0.146	0.90 (0.72–1.13)	0.106	0.377	0.75 (0.49–1.16)	0.495	0.195
>200	3	1009/876	1.46 (1.27–1.69)	0.061	0.000	1.23 (1.01–1.50)	0.443	0.039	2.53 (1.82–3.52)	0.105	0.000	1.41 (1.17–1.70)	0.166	0.000	2.30 (1.68–3.15)	0.203	0.000

OR – odds ratio; 95% CI – 95% confidence interval. ^a P value of Q-test for heterogeneity test; ^b P value of Z-test for statistical significance.

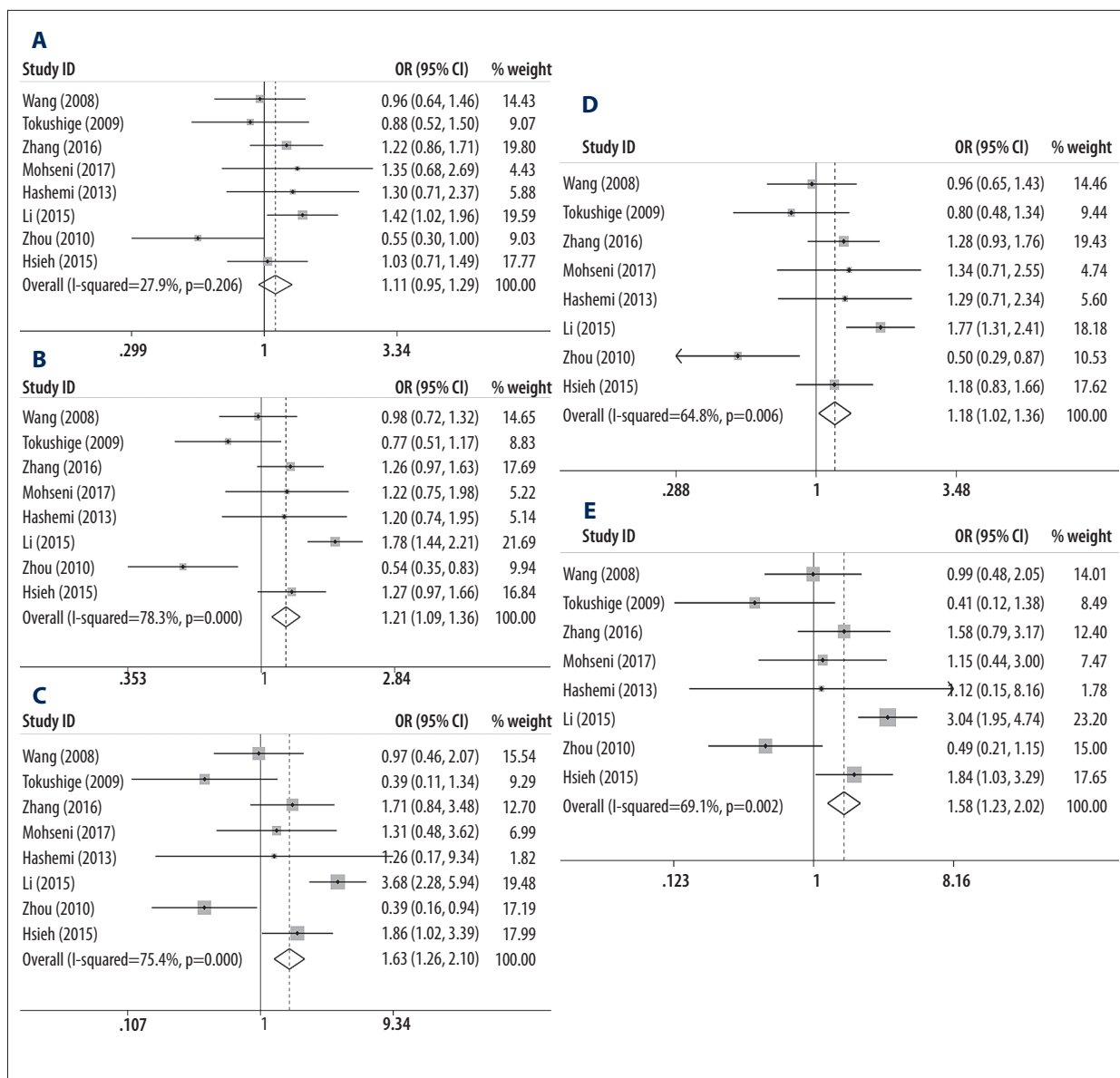


Figure 2. Forest plots of association between the susceptibility of NAFLD and (A) heterozygote model, (B) recessive allele model, (C) homozygote model, (D) dominant allele model, and (E) allelic model. NAFLD – nonalcoholic fatty liver disease.

(OR=1.58, 95% CI=1.23–2.02, $P_{\text{heterogeneity}}=0.002$, $P=0.000$) (Figure 2). To search for potential sources of heterogeneity in our studies, subgroup analyses were thus further performed.

For dominant inheritance model (Figure 3A–3C), in subgroup analysis by subject scope, heterogeneity nearly disappeared ($P_{\text{heterogeneity}} > 0.1$), suggesting that the sample size could be a potential source of heterogeneity and only when there were more than 200 participants in the 2 study groups, a clear susceptibility of NAFLD and rs1501299 polymorphism could be obtained. As for the design subgroup, a reduced heterogeneity was observed but no explicit conclusion could be given. Nevertheless, no obvious correlation between rs1501299

polymorphism and NAFLD risk was observed in the Caucasian study participants stratified by ethnicity without heterogeneity. A similar situation was also found in the other 3 correlated models (for example, the recessive comparison model (OR=1.30, 95% CI=0.53–3.22, $P_{\text{heterogeneity}}=0.972$, $P=0.566$) in Figure 3D. This suggested that subject scope was the main reason for between-study heterogeneity and the larger sample size was, the more obvious association between rs1501299 polymorphism and NAFLD risk could be observed.

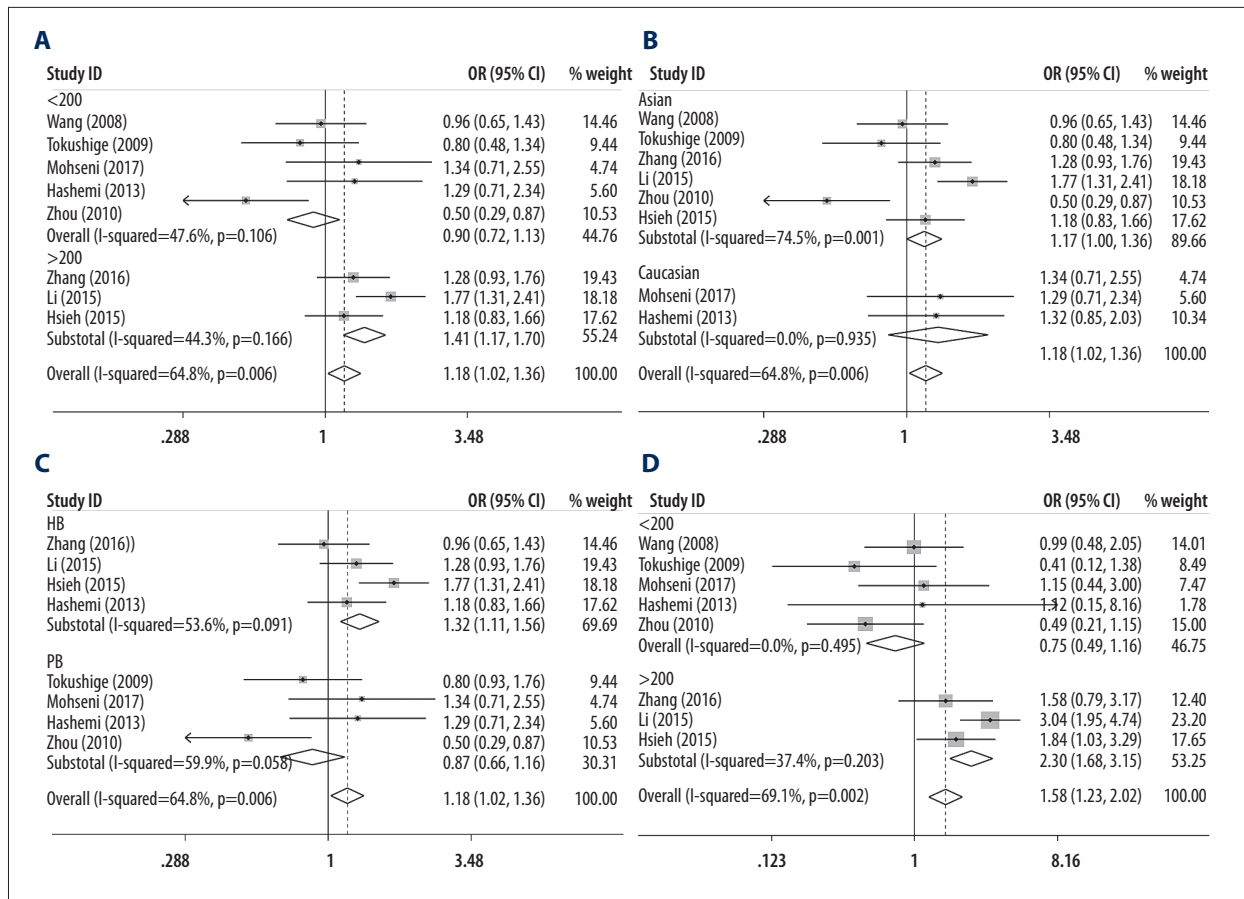


Figure 3. Forest plots of subgroup analysis on dominant model (A-C) and recessive model (D).

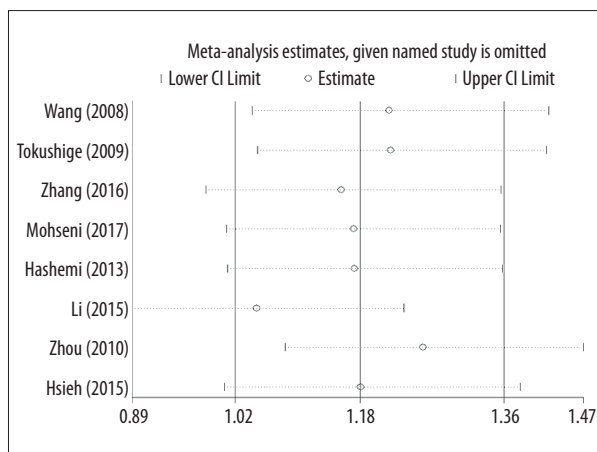


Figure 4. Sensitivity analysis of the dominant model.



Figure 5. Begg's funnel plot of dominant model.

Sensitivity study

A sensitivity study was performed to estimate the effects of each individual study on the pooled OR. The sensitivity analysis indicated that none of the solo study altered the pooled results significantly by excluding any involved study, confirming

that our results were credible and generalizable (Figure 4 is an example of the dominant model).

Publication bias

Begg's funnel plot was conducted to evaluate publication bias. As the dominant model shown in Figure 5, the shape of the

Table 3. Publication Bias of five genetic models.

Genetic model	P
Heterozygote model (GT vs. GG)	0.174
Homozygote model (TT vs. GG)	0.108
Dominant model (TT+GT vs. GG)	0.266
Recessive model (TT vs. GT+GG)	0.108
Allelic model (T vs. G)	0.108

P – P value of Begg's Test. * $P < 0.05$.

funnel plot showed good symmetry. Similar conclusion could be acquired in other inheritance models. The results of Begg's test in all comparison models were presented in Table 3.

Discussion

Adipokines, polypeptides expressed by adipocytes and/or adipose tissue-resident macrophages, which not only have a crucial role in energy homeostasis but also act as an endocrine organ. As a member of adipokines, adiponectin is a collagen-like protein hormone secreted by adipocytes. It can resist inflammation and serves as an insulin-sensitizing adipokine [28,29]. Apart from this, there are many other adipokines such as leptin, resistin and retinol binding protein-4. It seems that adipokine alterations, occurring during the expansion of adipose tissue, may contribute to the development of NAFLD [30]. Low serum adiponectin levels and high leptin and resistin levels have been observed in NAFLD patients in a series of articles [31–33]. Resistin rs1862513 as well as +299A/A genotype polymorphisms were found to influence genetic susceptibility to NAFLD [34,35]. In addition to that, leptin receptor Q223R A allele significantly reduced the risk of NAFLD [36]. With regard to adiponectin, it was reported that rs266729 and rs2241766 G alleles were closely associated with the progression of NAFLD [37]; rs822393 (–4522 C/T) polymorphism was correlated with increased risk of NAFLD as well [38]. There is no doubt that the study of adiponectin is a hot topic among these influencing factors.

Research has shown that the development of insulin resistance, type 2 diabetes mellitus, obesity, metabolic syndrome, and even osteoarthritis is linked with decreased plasma levels of adiponectin [39–41]. Whereas adiponectin deficiency might be critically involved in the pro-inflammatory state associated with obesity and related disorders. An imbalanced adipokine profile in obesity consecutively contributes to metabolic inflammation in NAFLD, which is associated with a substantial risk for developing HCC also in the non-cirrhotic stage of the disease. Recent relevant genome-wide association studies have reported the SNPs correlated with serum adiponectin [42]. The intron 2

synonymous +276 G/T (rs1501299) at the ADIPOQ locus is one of the hottest topic SNPs. But reports on this genetic substitution correlated with adiponectin level in Caucasian populations often have conflicting results [43,44]. Meanwhile, the relationship of this SNP with NAFLD is also contradictory. Considering these inconsistent results, meta-analysis is necessary to provide further explanation of these conflicts by analyzing the results of different studies focused on the same problem.

To evaluate the correlation between rs1501299 polymorphism and NAFLD risk, we reconstructed a meta-analysis [45] previously published and included additional publications, without eliminating any relevant studies in the previous meta-analysis. In the previous study, they included an inappropriate research performed by Al-Daghri et al. [46], which mainly concentrated on the rs1501299 polymorphism and type 2 diabetes mellitus risk, not susceptibility of NAFLD as we investigated. In addition, the previous meta-analysis focused on Asian populations and was almost 3 years prior to our study. Thus, our analysis was an important and necessary update to the literature. Our meta-analysis included 3065 study participants (1639 NAFLD patients and 1426 healthy controls) from 8 independent studies. The results demonstrated that rs1501299 polymorphism was significantly linked with the risk of NAFLD under homozygote, dominant, recessive and allelic models with heterogeneity across studies. No association was found between NAFLD risk and the heterozygote comparison. Subgroup analyses showed that sample size was one of the potential sources of heterogeneity for the 4 correlated genetic models and heterogeneities were almost eliminated by subject scope. When there were less than 200 people in the case studies and control studies, no correlation was found in any of the inheritance models, while an increased risk of NAFLD could be clearly observed in the opposing group. However, no evident correlation was shown in the studies with Caucasian participants, differing from the findings of 2 previous reviews on this topic [42,43]. One possible reason for this discrepancy may be the relatively small sample size involved in our meta-analysis. Additionally, in the subgroup study controls, no definite conclusion could be made. Meanwhile, the Begg's test and funnel plots demonstrated no publication bias, and the sensitivity analysis suggested that none of the individual studies affected the pooled OR of all the included studies. These data further enhanced the reliability and stability of the meta-analysis results.

Several limitations to this meta-analysis should be acknowledged. First, only 8 published articles with a total 3065 study participants were selected for the final meta-analysis. The number of participants was still relatively small and might therefore influence the detection power on the association between rs1501299 polymorphism in the adiponectin gene and the susceptibility to NAFLD. Thus, more studies with a larger sample size should be performed to test for a more representative

conclusion in the future. Secondly, 6 out of the 8 studies were conducted in Asian populations and only 2 studies were undertaken in Caucasian populations, and no studies were conducted in African populations. Therefore, further analysis should include more studies conducted in other races to improve the reliability of the statistical analysis. Last, the omission of the raw data such as family history of type 2 diabetes, insulin resistance, and stage of NAFLD from published articles may influence our final conclusions.

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Conclusions

In brief, our meta-analysis indicated that SNP rs1501299 in adiponectin gene may play a significant role in increasing risk of NAFLD. Nevertheless, we anticipate that further rigorous larger scale case-control studies should be performed to verify these conclusions. In addition, research investigating the potential interplays between gene and environment factors on the susceptibility of NAFLD are also important and necessary in the future. Despite some limitations, this meta-analysis still provides us with a new insight into adiponectin gene correlation with the occurrence and progression of NAFLD.

Conflict of interest

None.

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