Review Article
The association of PPARγ C1431T polymorphism with susceptibility to type 2 diabetes: a systemic review and meta-analysis

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Abstract: The association between peroxisome proliferators-activated receptor γ (PPARγ) C1431T polymorphism and Type 2 diabetes mellitus (T2DM) risk is inconclusive and contradictory. Therefore, a comprehensive meta-analysis was conducted to assess the association of PPARγ C1431T polymorphism with susceptibility to T2DM. We searched the PubMed and Web of Science to select eligible studies following included criteria. Finally we identified seven publications for the further analysis. Statistical analysis was performed by using the software of Revman 5.3. The results revealed that C1431T polymorphism was significantly associated with T2DM risk in 4 models (Codominant model CT vs CC: OR = 0.87, 95% CI = 0.76-0.99, P = 0.03; Codominant model TT vs CC: OR = 0.36, 95% CI = 0.21-0.63, P = 0.0003; Recessive model TT vs CT+CC: OR = 0.35, 95% CI = 0.25-0.49, P < 0.00001; and Allele model T vs C: OR = 0.78, 95% CI = 0.62-0.99, P = 0.04) except in dominant model: CT+TT vs CC. Furthermore, we found that the significantly decreased risk of T2DM in Caucasian was associated with the Codominant model TT vs CC, Recessive model TT vs CT+CC, dominant model: CT+TT vs CC; and Allele model T vs C. And no obvious publication bias was observed using the funnel plot. Overall, the current study suggests that PPARγ C1431T polymorphism may be associated with the risk of T2DM in Caucasian.

Keywords: PPARγ, C1431T, polymorphism, type 2 diabetes, meta-analysis

Introduction
Globally, it is estimated that about 382 million adults were diagnosed with diabetes in 2013, and this number is predicted to increase to 592 million by 2035 [1]. Type 2 diabetes mellitus (T2DM), which accounts for more than 90% of diabetes cases, has been revealed to have complex interactions with environmental and genetic factors [2, 3].

The gene of PPARγ, which encodes a nuclear transcription factor involved in the expression of hundreds of genes, is located on chromosome 3p25 [4-6]. Since 1997, more and more evidences indicated that both common and rare polymorphisms of the genes of PPARγ acted as critical roles in the regulation of glucose metabolism [7-10]. Screening of the PPARγ gene of patients with type 2 diabetes for mutations has led to the identification of two polymorphisms: A c to g substitution at nucleotide 39 in the exon unique to PPARγ which results in the replacement of proline 12 with alanine (P12A) and a c to t substitution at nucleotide 1431 (c1431t) which doesn’t cause an amino acid change [11, 12]. Although recent years the C1431T polymorphism in PPARγ has been widely studied with respect to T2DM, the results were still inconclusive and controversial. To the best of our knowledge, no one has performed a meta-analysis to investigate the association of this polymorphism with T2DM.

In this study, we collected all published case-control studies and prospective cohorts focused on the relationship between T2DM and PPARγ C1431T polymorphism. A meta-analysis
Meta-analysis of PPARγ C1431T polymorphism

was carried out and our aim was to clarify the controversial results.

Materials and methods

Search for study

A systematic search was performed by two investigators independently. Studies were mainly searched in PubMed and Web of Science from their inception to October 2016 with the following terms: ‘PPARγ’, ‘C1431T’, ‘polymorphism’, ‘Type 2 diabetes’. The search was limited to case-control studies. Reference lists from relevant articles were also examined to find additional publications. To avoid double counting or other errors, two investigators compared their results discreetly and disagreements were resolved by consensus or by a third investigator.

Selection of study

All the included studies met the following criteria: 1. case-control study and prospective cohorts; 2. evaluation of the association between PPARγ C1431T polymorphism and T2DM risks; 3. sufficient data for analysis including genotype frequency in both cases and controls; and 4. genotype frequency in the control group was in Hardy-Weinberg equilibrium (HWE). We excluded studies without eligible data for meta-analysis.

Data extraction

Two investigators who were blinded to each other abstracted the data in a traditionalized format and reached consensus on all items. The collected data included first author, publication year, country and available genotypes. Evaluation of evidence strength was carried out according to the modified Newcastle-Ottawa Scale [13] (Supplementary Table 1).

Statistical analysis

Statistical analysis was performed by using Revman 5.3 and STATA 14.0 software. X² tests and I² statistic were used to measure the study heterogeneity between trials. Both fixed- and random-effects models were applied where appropriate, with I² > 50% was considered representative of significant statistical heterogeneity and the random-effects models launched, otherwise, the calculations were performed with the fixed-effects model [14, 15]. Odds ratio (OR) with 95% confidence interval (95% CI) was used to evaluate the association between polymorphism and T2DM risk with the Codominant model: CT vs CC, Codominant model: TT vs CC, Dominant model: CT+TT vs CC, Recessive model: TT vs CT+CC and Allele model: T vs C. Sensitivity analysis was used to identify sources of significant heterogeneity by removing individual studies and analyzing the effect on the overall results. Publication bias was further assessed by Funnel plot and Begg's test [16, 17]. P value less than 0.05 was considered statistically significant in all statistics.

Results

Characteristics of the studies

Study flow diagram was shown in Figure 1. 17 studies of PPARγ C1431T polymorphism and T2DM risks were found in a primary literature search in the PubMed and Web of Science. After reviewing each publication, 10 articles were found inappropriate in the current meta-analysis given some of them were review articles, irrelevant to the current study or contained duplicated data. Seven studies with 3830
cases and 5693 controls shown in Table 1 were identified appropriate for the current meta-analysis [18-24]. The genotype distribution of control population was in agreement with Hardy-Weinberg equilibrium in all seven studies.

Quantitative synthesis

We analyzed the association between PPARγ C1431T polymorphism and T2DM risk within five genetic models as mentioned in the Method. The quantitative synthesis results were presented in Table 1. Interestingly, the pooled results revealed a significant association between C1431T polymorphism and T2DM risk in the codominant model (CT vs CC: OR = 0.87, 95% CI = 0.76-0.99, P = 0.03) and allele model (T vs C: OR = 0.78, 95% CI = 0.62-0.99, P = 0.04). Furthermore, drastically significant difference was found between the T2DM group and control group in codominant model (TT vs CC: OR = 0.36, 95% CI = 0.21-0.63, P = 0.0003) and recessive model (TT vs CT+CC: OR = 0.35, 95% CI = 0.25-0.49, P < 0.00001). In contrast, no statistically significant association was found in the dominant model (CT+TT vs CC).

Sensitivity analysis

In order to assess the stability of the results, sensitivity analysis was performed. The sensitivity analyses did not detect any individual study which affected the results using the exclusion method step by step (Supplementary Figure 1).
Meta-analysis of PPARγ C1431T polymorphism

Publication bias

The funnel plot was performed to estimate the publication bias. The shape of the funnel plots was symmetrical, suggesting that there was no evidence of publication bias for the PPARγ C1431T polymorphism (Figure 2). Begg’s test showed no evidence of publication bias (P = 0.293).

Discussion

PPARγ was the first gene reproducibly associated with T2DM. The association between the substitution of alanine by proline at codon 12 of PPARγ (Ala12) and the risk for T2DM has been widely studied since this polymorphism was first reported in 1997 [25]. In this meta-analysis seven studies including 3830 cases and 5693 controls were collected according to our inclusion criteria. As a result, C1431T polymorphism was found to be associated with T2DM risk in 4 models (Codominant model: CT vs CC, Codominant model: TT vs CC, Recessive model: TT vs CT+CC and Allele model: T vs C) except in dominant model: CT+TT vs CC. Stratified analysis of ethnicity showed that significant differences were found between the T2DM group and control group in codominant model (TT vs CC), recessive model (TT vs CT+CC), dominant model (CT+TT vs CC1) and allele model (T vs C) in Caucasian group. However, no difference was found in Asia group.

The association between the C1431T polymorphism and the risk of T2DM was firstly reported in 2001 and the researchers found that A12/c1431 haplotype was responsible for the T2DM risk [21]. Although not changing the coding sequence of PPARγ, the C1431T polymorphism has been associated with increased body weight and is in tight allelic disequilibrium with the Ala12 variant [26]. However, some researchers identified T allele could decrease weight and BMI and had a protection effect in T2DM [18]. In addition, it also reported that there was no association between C1431T and T2DM [22]. Our results revealed that T allele might lower the risk of T2DM mainly in Caucasian group. The controversial findings could be explained by the different genetic and environmental factors and additional studies will be required not only to detect its more prevalence rate in T2DM but also to investigate the possible biophysical mechanisms of C1431T polymorphism in coordination with other mutations.

Limitations in our analysis should also be considered. First, many other clinical factors such as age, sex or other mixed mutations in each study might lead to bias and haven’t been considered in the study. Second, we restricted our included studies published in English. Last, more subgroup analysis should be carried out but no details could be extracted from the original articles.

Disclosure of conflict of interest

None.

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References

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[23] Doney AS, Fischer B, Cecil JE, Boylan K, McGuigan FE, Ralston SH, Morris AD and Palmer CN. Association of the Pro12Ala and


**Supplementary Table 1.** Quality assessment of studies included in the systematic review according to the modified Newcastle-Ottawa Scale

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**Supplementary Figure 1.** Sensitive analysis of studies in the meta-analysis.