Correlation of the TCF7L2 (rs7903146) polymorphism with an enhanced risk of type 2 diabetes mellitus: a meta-analysis


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ABSTRACT. Increasing evidence has demonstrated that a transcription factor 7-like 2 (TCF7L2) polymorphism (rs7903146) is significantly associated with type 2 diabetes mellitus (T2DM); however, limited sample size and variance of ethnicity in the studies investigating this association have led to conflicting reports regarding its role. Therefore, a comprehensive meta-analysis was conducted to quantitatively assess the association between the TCF7L2 polymorphism (rs7903146) and T2DM including published case-control studies in global populations. We searched the PubMed, EMBase, CNKI, and Wanfang databases for publications that studied correlation between TCF7L2 polymorphism (rs7903146) and risk of T2DM. Thirty-six studies from 30 eligible papers were identified. After data extraction and reference quality assessment, summary odds ratio and 95% confidence intervals (95%CI)
of the TCF7L2 (rs7903146) polymorphism were calculated and combined using the fixed-effect model. Hardy-Weinberg equilibrium was evaluated to determine selection bias of the control subjects. Heterogeneity among studies was examined using the Q-test and the I² test. Publication bias in studies was assessed using Begg’s plots and the Egger test. The results showed that the rs7903146 T allele of the TCF7L2 gene was positively correlated with an enhanced risk of T2DM in the allelic, heterozygote, homozygote, dominant, and recessive models, with odds ratios of 1.35 (T vs C, 95%CI = 1.31-1.39), 1.32 (CT vs CC, 95%CI = 1.27-1.38), 1.74 (TT vs CC, 95%CI = 1.63-1.87), 1.40 (TT+CT vs CC, 95%CI = 1.35-1.46), and 1.59 (TT vs CT+CC, 95%CI = 1.49-1.69), respectively. No obvious publication bias was observed using the Egger linear test.

**Key words:** Meta-analysis; Polymorphism; Transcription factor 7-like 2; Type 2 diabetes

**INTRODUCTION**

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by hyperglycemia caused by progressive insulin deficiency with insulin resistance and is a large health burden worldwide (Sun et al., 2015). The incidence of T2DM is increasing significantly, with 90 million individuals with diabetes in China in 2011, and shows no signs of alleviation. Individuals with T2DM often suffer serious systematic complications, including nephropathy, retinopathy, neuropathy, and accelerated cardiovascular disease progression (Grant et al., 2006). Therefore, diabetes and its complications impose economic pressure on individuals, families, and society, and it is imperative that the detailed mechanisms of diabetes genesis are elucidated and the high-risk populations are identified.

Although the mechanism of T2DM is not completely understood, genetic variants play a critical role in the pathophysiology and etiology of the disease (Risérus et al., 2009; Wu, 2015). The transcription factor 7-like 2 (TCF7L2) gene, which is located on chromosome 10q25.3, encodes a high mobility group box-containing transcription factor that plays a central role in the Wnt pathway and in the regulation of beta-cell function (Wagner et al., 2014). TCF7L2 is considered a major susceptibility gene of T2DM (Grant et al., 2006; Pagán et al., 2014). The TCF7L2 protein is associated with blood glucose homeostasis. Increasing evidence suggests that TCF7L2 polymorphisms were associated with T2DM in different ethnic populations and that it is one of the most significant gene loci for T2DM susceptibility (Bodhini et al., 2007; Xia et al., 2015). Among the several single nucleotide polymorphisms of TCF7L2, variant rs7903146 (IVS3C/T) showed the strongest correlation with the risk of T2DM in previous studies (Grant et al., 2006; Saxena et al., 2006; Cauchi and Froguel, 2008). Therefore, studies of TCF7L2 genetic polymorphisms will increase the understanding of the mechanism of T2DM and facilitate the screening for individuals at a relatively high risk of T2DM (Cauchi and Froguel, 2008). However, previous studies show conflicting results and clear variations based on ethnicity and regions (Miyake et al., 2008; Ren et al., 2008; Yu et al., 2010). Given their limited sample sizes, the previous studies were underpowered for evaluating the association of the TCF7L2 (rs7903146, IVS3C/T) polymorphism with the susceptibility to...
TCF7L2 polymorphism and risk of T2DM

T2DM, and thus combined data regarding this single nucleotide polymorphism can be used to assess the global impact of the TCF7L2 polymorphisms on T2DM.

Therefore, we performed this comprehensive meta-analysis to investigate the TCF7L2 (rs7903146, IVS3C/T) polymorphism in previous case-control studies and to assess the association between this polymorphism and T2DM. The results of previous studies were combined to evaluate the strength of this association.

MATERIAL AND METHODS

Identification and eligibility of relevant studies

We searched the PubMed, EMBase, CNKI, and Wanfang databases for publications that studied the correlation between the TCF7L2 polymorphism (rs7903146) and the risk of T2DM from January 2006, when the relationship between TCF7L2 and T2DM was first reported (Grant et al., 2006) to April 30, 2014. The combination of MeSH terms and key words, including “transcription factor 7-like 2”, “transcription factor 7-like 2 polymorphism”, “TCF7L2”, “TCF7L2 gene polymorphism”, “diabetes”, “type 2 diabetes”, “diabetes 2”, “type 2 diabetes mellitus”, “T2DM”, and “T2D”, was used in our search strategy. In addition, the references of all retrieved publications were screened for additional studies, and then the “Related Articles” option of PubMed was reviewed for potentially relevant publications. The search was conducted independently by two investigators. We selected publications if they met the following inclusion criteria: 1) the publication studied the association between the TCF7L2 polymorphism (rs7903146, IVS3C/T) and T2DM; 2) there were sufficient data for each allele and genotype to recalculate the odds ratio (OR) and 95% confidence interval (95%CI); 3) the publication used a population-based design; and 4) the control group of the study met Hardy-Weinberg equilibrium (HWE) (P > 0.05). Studies were excluded based on the following criteria: 1) studies without control subjects; 2) studies including overlapping data; 3) studies that were reviews or meta-analysis; and 4) studies where the average age of cases and controls were less than 25 years (in an attempt to obviate patients with type 1 diabetes). Patients with T2DM were diagnosed and confirmed based on the World Health Organization criteria in 1999 and if they were taking anti-diabetic treatments (Alberti and Zimmet, 1998). Normoglycemic subjects were defined as the control group and had plasma glucose levels lower than 7.8 mM and fasting glucose levels lower than 6.1 mM in the 2-h oral glucose tolerance test.

Data collection

Two experienced investigators independently conducted the data extraction. Discrepancies were resolved through discussion. The following detailed information was collected from each publication: name of the first author and the publication year, region, design, ethnicity, number of cases and controls, genotyping method, genotype frequencies, and P value of HWE in control subjects. We recalculated the P value of the HWE test according to the reported genotype frequencies if the studies did not show HWE. To enhance the statistical power, we performed meta-analysis for the TCF7L2 polymorphism (rs7903146) with reported data extracted from more than 10 independent studies.
Statistical analysis

The statistical STATA 12.0 software was used to conduct the meta-analysis based on genotype frequencies. The P value of HWE for control subjects was evaluated by utilizing the chi-squared test. There was no deviation from HWE if the P value >0.05. The pooled ORs and 95% CIs were used to measure the strength of the association of the TCF7L2 polymorphism (rs7903146, IVS3C/T) with the risk of T2DM in all genetic models. Heterogeneity among studies was examined using the Q-test and the I² test. According to Cochrane reviewer’s handbook, the heterogeneity among studies with I² < 50% and P > 0.05 were accepted (Ling et al., 2004). There was no obvious heterogeneity among studies, so the fixed-effect model was used to perform meta-analysis (Mantel and Haenszel, 1959). Otherwise, a random-effect model was used to calculate the pooled OR and 95% CI (Midgette et al., 1994). Subgroup analyses were conducted by ethnicity (Asian or Caucasians) for each model. Begg’s funnel plot and the Egger linear test were used to evaluate publication bias. A symmetric plot or a P value of the Egger test more than 0.05 indicated no obvious publication bias (Harbord et al., 2006). The stability and reliability of the meta-analysis were assessed using sensitivity analysis by omitting one study at a time, and thus the impact of each study on the overall summary results was evaluated.

RESULTS

Study characteristics

We first identified 352 potentially relevant publications using the search strategy. After excluding the studies that did not present useful data related to the meta-analysis or did not meet the inclusion criteria, 36 case-control studies from 33 eligible papers were obtained, including 26,498 case and 37,282 control subjects. The search strategy is shown as a flow chart in Figure 1. The detailed characteristics of the studies, such as the first author’s name, year of publication, ethnicity, country, genotyping method, design, total numbers, and case and control subjects are presented in Table 1. Eight studies used hospital-based controls, whereas the remaining studies used population-based controls. Blood samples were collected for genotyping. The scores of quality assessment for each included publication were more than 26 (moderate-high quality) (da Costa et al., 2011). The P value of HWE for control groups and genotype frequencies of the TCF7L2 gene polymorphism (rs7903146, IVS3C/T) were recalculated and extracted from the eligible studies and are presented in Table 2. All included studies were in HWE (P > 0.05).

Quantitative analysis

Thirty-three eligible studies including 26,498 type 2 diabetic subjects and 37,282 control subjects were evaluated for the association between the TCF7L2 rs7903146 polymorphism and T2DM. The comprehensive results for these 33 studies are shown in Table 2. We observed that the TCF7L2 rs7903146 T allele was significantly correlated with an enhanced susceptibility to T2DM under the allelic (Figure 2), heterozygous (Figure 3), homozygous (Figure 4), dominant (Figure 5), and recessive (Figure 6) models. Since there was no heterogeneity among studies, the fixed-effect model was used for analysis.
Figure 1. Flow chart of included and excluded studies.

Table 1. Characteristics of studies included in the meta-analysis.

<table>
<thead>
<tr>
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<th>Control</th>
<th>Genotyping</th>
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The pooled OR for T2DM risk was 1.35 for allelic comparison (T vs C, 95%CI = 1.31-1.39, $P = 0.000$, $I^2 = 22.1\%$, $P_{\text{heterogeneity}} = 0.121$), 1.32 for heterozygous comparison (CT vs CC, 95%CI = 1.27-1.38, $P = 0.000$, $I^2 = 43.5\%$, $P_{\text{heterogeneity}} = 0.003$), 1.74 for homozygous comparison (CC vs CT+CC, 95%CI = 1.49-1.69, $P = 0.000$, $I^2 = 0.59$) for dominant comparison (TT+CT vs CC, 95%CI = 1.35-1.46, $P = 0.000$, $I^2 = 15.3\%$, $P_{\text{heterogeneity}} = 0.213$), 1.40 for recessive comparison (TT vs CT+CC, 95%CI = 1.49-1.69, $P = 0.000$, $I^2 = 19.8\%$, $P_{\text{heterogeneity}} = 0.150$). Since no obvious heterogeneity among studies was detected, the fixed-effect model was used to calculate the pooled OR.

**Publication bias diagnostics**

In order to evaluate the publication bias of the included studies, Beggar’s funnel plot and the Egger linear test were used. As demonstrated in Figure 7A for the heterozygous model (CT vs CC, $z = 0.40$, $P = 0.693$), Figure 7B for the homozygous model (TT vs CC, $z = 0.89$, $P = 0.376$), Figure 7C for the dominant model (TT+CT vs CC, $z = -0.01$, $P = 1.000$), and Figure 7D for the recessive model (TT vs CT+CC, $z = 1.10$, $P = 0.270$), the funnel plots showed no significant asymmetry in all genetic models.
Figure 2. Forest plot showing association between the TCF7L2 rs7903146 polymorphism and T2DM risk under allelic model (T vs C).

Figure 3. Forest plot showing association between the TCF7L2 rs7903146 polymorphism and T2DM risk under heterozygous model (CT vs CC).
Figure 4. Forest plot showing association between the TCF7L2 rs7903146 polymorphism and T2DM risk under homozygous model (TT vs CC).

Figure 5. Forest plot showing association between the TCF7L2 rs7903146 polymorphism and T2DM risk under dominant model (TT+CT vs CC).
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**Figure 6.** Forest plot showing the association between TCF7L2 rs7903146 polymorphism and T2DM risk under recessive model (TT vs CT+CC).

Furthermore, the Egger test revealed significant evidence of symmetry (P = 0.983 for CT vs CC, P = 0.278 for TT vs CC, P = 0.520 for TT+CT vs CC, and P = 0.310 for TT vs CT+CC).

**Figure 7.** Begg’s funnel plot for publication bias test. **A.** Heterozygous model (CT vs CC); **B.** homozygous model (TT vs CC); **C.** dominant model (TT+CT vs CC); and **D.** recessive model (TT vs CT+CC).
Sensitivity analysis

To assess the value of individual studies, we conducted sensitivity analysis by omitting one at a time and then calculated the combined OR for the selected studies. No studies deviated from the combined results of the heterozygous model (CT vs CC), homozygous model (TT vs CC), dominant model (TT+CT vs CC), and recessive model (TT vs CT+CC) (data not shown), suggesting that the results of our meta-analysis were robust and reliable.

DISCUSSION

Despite increasing evidence that the TCF7L2 gene is associated with an increased T2DM risk in ethnic groups worldwide (Hayashi et al., 2007; Miyake et al., 2008; Palizban et al., 2012; Uma Jyothi et al., 2013; Wang et al., 2013), some studies presented the opposite conclusion (Chang et al., 2007; Ng et al., 2007; Zheng et al., 2012a). No consistent results have been reported because of the limited sample size and ethnicity heterogeneity in the studies. Based on our comprehensive meta-analysis, the TCF7L2 rs7903146 polymorphism was associated with an enhanced susceptibility to T2DM in the genetic models tested.

However, the exact mechanisms by which TCF7L2 increases the risk of T2DM remain unclear. Loos et al. (2007) demonstrated that TCF7L2 polymorphisms increase the risk of T2DM by impairing β-cell function and modulating proinsulin levels in a British Europid population. TCF7L2 encodes a basic helix-loop-helix transcription factor 4 (TCF-4), which acts as a nuclear receptor for the Wnt/β-catenin pathway (Smith, 2007), and can preferentially bind to Wnt-responsive elements in genes induced by β-catenin (Gougelet et al., 2014). It is well known that the β-catenin/TCF-4 complex participates in various biological events. Particularly, the complex has been found to have a critical role in pancreatic and islet development (Mulholland et al., 2005; Papadopoulou and Edlund, 2005), and thus contributes to T2DM initiation and progression. In addition, Wnt signaling may utilize β-catenin/TCF-4 to mediate the expression of many target genes such as tumor necrosis factor-α, interleukin-1β, fibroblast growth factor, and vascular endothelial growth factor (Zhang et al., 2009). Moreover, high levels of tumor necrosis factor-α were correlated with impaired glucose tolerance, defective glucose regulation, and glycated hemoglobin, as well as hyperglycemia and whole-body insulin resistance in T2DM (Daniele et al., 2014; Ellekilde et al., 2014). Individuals with T2DM have significantly increased levels of interleukin-1β compared with healthy individuals (Atieh et al., 2014). A previous study (Yang et al., 2010) demonstrated that the vascular endothelial growth factor polymorphism (rs2010963) was a key risk factor for coronary artery disease susceptibility in T2DM patients.

The results of our meta-analysis were based on both Asian and Caucasian subjects, including 26,498 T2DM patients and 37,282 control subjects, and demonstrated that the rs7903146 polymorphism was associated with an elevated risk for T2DM under the allelic, heterozygous, homozygous, dominant, and recessive models, which agrees with the original findings. This is the most comprehensive and systematic meta-analysis that has used worldwide populations to explore the association between the TCF7L2 rs7903146 polymorphism and T2DM. Publication bias testing and sensitivity analysis were conducted systematically to validate the reliability and robustness of the meta-analysis. However, potential limitations must be recognized. T2DM is a complex disease resulting from the combined effect of genetic variants and environmental predisposing factors (Brunetti et al., 2014; Chang et al., 2014; Li...
et al., 2014; Wang et al., 2014; Picos-Cárdenas et al., 2015), which were not systematically assessed in our meta-analysis. Therefore, to increase the power of our conclusions, additional well-designed studies including larger sample sizes are required to reveal the association between genetic variants and T2DM.

Conflicts of interests

The authors declare no conflict of interest.

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