Review Article

Quantitative assessment of the influence of TNF-α -308G/A polymorphism on gestational diabetes mellitus risk

Lin-Zhen Wu, Zhu-Qing Liu, Yun-Jun Lin, Jing Qian

Department of Obstetrics and Gynecology, Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine, Hangzhou 310006, China

Received February 9, 2018; Accepted October 9, 2018; Epub June 15, 2019; Published June 30, 2019

Abstract: Tumor necrosis factor-α (TNF-α) has been reported to be associated with gestational diabetes mellitus (GDM), but results from previous studies are conflicting. Thus, a meta-analysis was performed to clarify the effects of this polymorphism on GDM risk. Web of Science, Embase, PubMed and CNKI databases were retrieved to determine the eligible TNF-α -308G>A polymorphism studies and the susceptibility of the GDM risk. Finally, a total of 7 articles with 465 cases and 589 controls fulfilled the inclusion criteria. The pooled odds ratio (OR) with 95% confidence interval (95% CI) was calculated to examine the associations. Meta-analysis results showed that the TNF-α -308G>A polymorphism is associated with a significantly increased risk of GDM (AA vs GG: OR = 5.17, 95% CI 2.78-9.61; GA vs GG: OR = 1.73, 95% CI 1.22-2.45; the dominant model: OR = 2.21, 95% CI 1.37-3.56; the recessive model: OR = 4.26, 95% CI 2.34-7.78). In the subgroup analysis according to the ethnicity, we found that the TNF-α -308G>A polymorphism was associated with GDM risk in Asians, but not in other ethnic groups. The present article suggested that the TNF-α -308G>A polymorphism is associated with a significantly increased risk of GDM, especially in Asians.

Keywords: TNF gene, genetic variant, gestational diabetes mellitus

Introduction

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications [1]. The prevalence of GDM, with a rising trend globally, varies by area and ethnic population. In the past decade, the incidence of GDM is about 1-3% of all pregnancies in western countries [2], and 5-10% among Asian pregnancies [3]. GDM has short and long-term adverse consequences for women and their offspring, including susceptibility to metabolic syndrome and type 2 diabetes mellitus [4]. Although the precise pathophysiological mechanisms of GDM are unclear, it is generally believed that GDM and type 2 diabetes mellitus (T2DM) share the same underlying pathological mechanisms, including insulin resistance and beta cell dysfunction leading to metabolic changes [5]. Furthermore, several studies have revealed that susceptible genes are involved in T2DM and probably also contribute to the genetic aetiology of GDM.

Insulin resistance has been associated with abnormal secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 and decreased production of anti-inflammatory mediators such as IL-4 and IL-10 [6]. TNF-α is an inflammatory cytokine produced by macrophages, which can induce cellular growth, death, and regeneration. The TNF-α gene is located in the major histocompatibility complex III region on chromosome 6p21.3. Genetic screening of the TNF-α gene has revealed that the -238G/A (rs361525) and -308G/A (rs1800629) polymorphisms in the promoter region of TNF-α, have been related to high TNF-α production [7]. TNF-α -308G/A is a G to A transition at nucleotide position 308 in the promoter region of this gene.

A number of studies have reported the association between GDM risk and TNF-α -308G/A polymorphisms, but the results are controversial. A single case-control study may not have enough statistical power to comprehensively
TNF-α polymorphism and gestational diabetes mellitus

demonstrate this complex relationship because the sample size involved is relatively small. Meta-analysis is a helpful method to analyze complicated data from case-control studies that are somewhat limited by small sample sizes and may represent lower statistical power [8]. The purpose of this meta-analysis was to investigate the association between the TNF-α -308G>A polymorphism and GDM risk through conducting a meta-analysis of all relevant articles published to date.

**Methods**

**Literature search**

A systematic document retrieval was performed of the Web of Science, Embase, PubMed and CNKI databases from their inception to 2017 without language restrictions. We used the following keywords: “tumor necrosis factor” or “-308G/A” or “rs1800629” and “gestational diabetes mellitus”. All relevant reports identified were included without language restriction. In addition, the references of all the selected articles were manually and independently searched by two researchers. If more than one article was published in the same population, we selected the most complete and updated publication for this analysis.

**Inclusion and exclusion criteria**

The publications that we have chosen for our research had to meet the following criteria: 1) case-control studies that included GDM patients and healthy controls; 2) studies that evaluated the relationship of TNF-α -308G>A polymorphism with GDM risk; 3) all cases were diagnosed as having GDM; 4) studies that included sufficient data for analysis. We excluded articles that met the following criteria: 1) review papers and animal studies; 2) studies that included a lack of data; and 3) articles that did not present the target alleles.

**Data extraction**

Two investigators independently extracted genetic data from the relevant databases according to the selection criteria. All disagreements in the extracted data were resolved via a senior investigator. The following information was extracted from the publications: first author’s surname, publication date, ethnicity, diagnostic criteria of participants, genotyping method, mean age of case and control, mean BMI of case and control, frequency of genotypes, $p$ value for Hardy-Weinberg Equilibrium (HWE) test.

**Quality evaluation**

The quality of the included articles was assessed according to the Newcastle-Ottawa Quality Assessment (NOS) scale [9]. The system was divided into three domains with the maximum score of 9 points: 4 points for the selection of the study groups, 2 points for the comparability of the groups, and 3 points for the ascertainment of either the exposure or outcome of interest for the case-control studies. Seven stars are considered the cut-off to distinguish “high-quality research” from “low-quality research”.

Figure 1. Detailed process of study selection.
## Table 1. Characteristics of the included studies for meta-analysis

<table>
<thead>
<tr>
<th>Study included</th>
<th>Year</th>
<th>Area</th>
<th>Race</th>
<th>Diagnostic criteria</th>
<th>Control group</th>
<th>Published language</th>
<th>Mean age of case/control</th>
<th>Mean BMI of case/control</th>
<th>Cases/Controls</th>
<th>Genotype distribution</th>
<th>HWE test</th>
<th>Quality scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang</td>
<td>2005</td>
<td>China</td>
<td>Asian</td>
<td>OGGT confirmed</td>
<td>Normal glucose tolerant</td>
<td>Chinese</td>
<td>30.0/28.0</td>
<td>22.7/31.4</td>
<td>35/35</td>
<td>GG/GA/AA</td>
<td>0.00</td>
<td>5</td>
</tr>
<tr>
<td>Yang</td>
<td>2005</td>
<td>China</td>
<td>Asian</td>
<td>OGGT confirmed</td>
<td>Normal glucose tolerant</td>
<td>Chinese</td>
<td>29.0/27.0</td>
<td>21.1/20.8</td>
<td>110/159</td>
<td>GG/GA/AA</td>
<td>0.50</td>
<td>6</td>
</tr>
<tr>
<td>Zhang</td>
<td>2008</td>
<td>China</td>
<td>Asian</td>
<td>OGGT confirmed</td>
<td>Normal glucose tolerant</td>
<td>Chinese</td>
<td>30.1/28.5</td>
<td>NA/NA</td>
<td>30/30</td>
<td>GG/GA/AA</td>
<td>0.22</td>
<td>5</td>
</tr>
<tr>
<td>Montazeri</td>
<td>2010</td>
<td>Malaysia</td>
<td>Asian</td>
<td>OGGT confirmed</td>
<td>Normal glucose tolerant</td>
<td>English</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>110/102</td>
<td>GG/GA/AA</td>
<td>0.00</td>
<td>5</td>
</tr>
<tr>
<td>Guevoghlanian-Silva</td>
<td>2012</td>
<td>Brazil</td>
<td>Mixed</td>
<td>GDM patients</td>
<td>Non-diabetic participants</td>
<td>English</td>
<td>31.3/29.1</td>
<td>28.9/23.2</td>
<td>79/169</td>
<td>GG/GA/AA</td>
<td>0.19</td>
<td>5</td>
</tr>
<tr>
<td>Guzmán-Flores</td>
<td>2013</td>
<td>Mexico</td>
<td>Mixed</td>
<td>OGGT confirmed</td>
<td>Normal glucose tolerant</td>
<td>English</td>
<td>33.0/25.6</td>
<td>29.6/24.5</td>
<td>51/44</td>
<td>GG/GA/AA</td>
<td>0.70</td>
<td>4</td>
</tr>
<tr>
<td>Chen</td>
<td>2016</td>
<td>China</td>
<td>Asian</td>
<td>OGGT confirmed</td>
<td>Normal glucose tolerant</td>
<td>Chinese</td>
<td>28.7/29.8</td>
<td>27.3/24.2</td>
<td>50/50</td>
<td>GG/GA/AA</td>
<td>0.86</td>
<td>6</td>
</tr>
</tbody>
</table>

HWE, Hardy-Weinberg equilibrium.
Statistical analysis

We used the $X^2$ test to assess the HWE of the control group for each study, and $P < 0.05$ was considered significant disequilibrium [10]. The per-allele OR and 95% CIs were calculated for a homozygote comparison (AA vs GG), a heterozygote comparison (GA vs GG), a dominant model

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>AA versus GG</th>
<th>GA versus GG</th>
<th>Dominant model</th>
<th>Recessive model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
<td>6.84 (3.33-14.09)</td>
<td>2.03 (1.31-3.14)</td>
<td>2.71 (1.83-4.01)</td>
<td>2.33 (2.68-10.59)</td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
<td>1.41 (0.32-6.14)</td>
<td>1.30 (0.73-2.32)</td>
<td>1.32 (0.76-2.31)</td>
<td>1.34 (0.31-5.79)</td>
</tr>
<tr>
<td>HWE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>6.99 (3.03-16.14)</td>
<td>1.82 (1.25-2.65)</td>
<td>2.21 (1.55-3.15)</td>
<td>5.84 (2.54-13.42)</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>3.43 (1.33-8.80)</td>
<td>1.35 (0.27-6.60)</td>
<td>1.85 (0.36-9.49)</td>
<td>2.83 (1.16-6.90)</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; $P^*$ value of Q test for assessing heterogeneity, *Number of comparisons.
TNF-α polymorphism and gestational diabetes mellitus

Meta-analysis estimates, given named study is omitted

<table>
<thead>
<tr>
<th>Study</th>
<th>Lower CI Limit</th>
<th>Estimate</th>
<th>Upper CI Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al 2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montazeri et al 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guevoghlian-Silva et al 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guzman-Flores et al 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al 2016</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Sensitivity analysis of the relationship between the TNF-α -308G>A polymorphism and GDM risk.

Results

Eligible studies

The search identified 55 relevant studies, seven of these were case-control studies that met our inclusion criteria and were included in this meta-analysis [14-20]. The flow chart of study selection is shown in Figure 1. Among the 7 case-control studies, there were 5 studies about Asians, and 2 studies about mixed ethnicities. The genotype distributions in the controls of all studies were in agreement with HWE except for two studies [14, 17]. All included studies were of low quality as the quality score assessment of each one was less than or equal to 6 points. The baseline characteristics of the included articles are summarized in Table 1.

Meta-analysis results

The main results of this meta-analysis are presented in Table 2. In pooled analysis using data from all 7 studies, meta-analysis results showed that the TNF-α -308G>A polymorphism is associated with a significantly increased risk of GDM (see Figure 2: AA versus GG: OR = 5.17, 95% CI = 2.78-9.61; GA versus GG: OR = 1.73, 95% CI = 1.22-2.45; Dominant model: OR = 2.21, 95% CI = 1.37-3.56; Recessive model: OR = 4.26, 95% CI = 2.34-7.78). We then performed stratified analysis to investigate the effect of ethnicity and HWE of control. As for ethnicity, increased cancer risk was found in Asians (AA versus GG: OR = 6.84, 95% CI = 3.33-14.09; GA versus GG: OR = 2.03, 95% CI = 1.31-3.14; Dominant model: OR = 2.71, 95% CI = 1.83-4.01; Recessive model: OR = 2.33, 95% CI = 2.68-10.59).
Sensitivity analysis was performed by omission of non-HWE studies and the final result was not altered, indicating the final conclusion of meta-analysis had statistical significance (Table 2). In addition, sensitivity analysis was performed and the results showed that no individual study affected the pooled OR (Figure 3), because no substantial change was found.

**Publication bias**

The potential publication bias was evaluated via funnel plot and Egger’s test. No publication bias was found on visual inspection of the funnel plot (Figure 4). And Egger’s test suggested that no publication bias was present in any of the comparison models (P>0.05).

**Discussion**

GDM is a global public health problem and the incidence rate is increasing yearly. Insulin resistance induced by pregnancy is rapidly reversed upon delivery [21] and is thought to be secondary to both greater maternal adiposity and other hormones, including human placental lactogen, progesterone, leptin, cortisol, prolactin, human chorionic gonadotropin, and TNF-α as well as other inflammatory mediators that are produced by placental and other tissues [22]. Additionally, evidence is accumulating that susceptibility to GDM has a genetic component [23]. We conducted a meta-analysis to investigate the potential association between the -308G>A polymorphism in TNF-α, a genetic variant of a known T2DM loci, and GDM risk [24].

Our meta-analysis, of 7 articles including 465 cases and 589 controls from different ethnic origins, provided us a much higher possibility to reach the reasonably strong conclusion. As far as we know, this is the first meta-analysis performed to investigate the relationship of the TNF-α -308G>A polymorphism with GDM. The results indicated a significant association between this polymorphism and GDM risk, with no evidence of between-study heterogeneity. In the subgroup analysis by ethnicity, a significant association between the TNF-α -308G>A polymorphism and GDM was found in Asians, but not in the mixed population.

The mechanism of how TNF-α -308G>A polymorphism relates to GDM risk remains unclear. Several studies have shown that TNF-α plays a key role in the pathogenesis of insulin resistance [25, 26]. And the TNF-α -308G>A polymorphism increases TNF-α levels and insulin resistance in women with GDM [19, 27, 28]. In addition, evidence suggest that the TNF-α -308G>A and -238G/A polymorphisms synergistically increased the risk of GDM [19]. Interaction between other risk factors and this polymorphism in relation to GDM need to be further studied.

Several limitations should be addressed. Firstly, there are few relevant articles and the sample size was not large. Furthermore, all included studies were low-quality studies according to NOS Scale. Secondly, because of the lack of original data, our results were based on unadjusted estimates of ORs without adjustment for individual’s age, sex and environment factors (the mother’s healthy lifestyle or the exposures to other risk factors). Thirdly, we only chose articles from the Web of Science, Embase, PubMed and CNKI databases, and might have missed studies in other languages.

Our meta-analysis suggests that the TNF-α -308G>A polymorphism is associated with GDM susceptibility, especially in Asians. Further well-designed articles with larger sample sizes, and more environmental factors are needed to validate our findings.

**Disclosure of conflict of interest**

None.

**Address correspondence** to: Lin-Zhen Wu, Department of Obstetrics and Gynecology, Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine, No. 261, Huansha Road, Hangzhou 310006, Zhejiang, China. Tel: +86 0571 8791-4773; E-mail: linzhenwu08@sina.com

**References**


