GCK rs1799884 Polymorphism and Gestational Diabetes Mellitus: A System Review and Meta-Analysis

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Abstract

Background: The correlation among Glucokinase (GCK) rs1799884 polymorphism and the risk of gestational diabetes mellitus (GDM) remains controversial, as previous studies have reported inconsistent findings. The potential relationship among the GDM risk and GCK rs1799884 polymorphism was examined by a meta-analysis. Methods: In order to find relevant studies for our investigation, we performed an extensive search across multiple databases, such as Ovid, PubMed, China National Knowledge Infrastructure, and Web of Science. Afterward, the link among the GDM risk and GCK rs1799884 polymorphism was evaluated by employing either random-effects models or fixed-effects to compute 95% confidence intervals (CIs) and pooled odds ratios (ORs). Results: This meta-analysis comprised a total of 11 studies. The findings revealed that the GCK rs1799884 polymorphism was linked to a decreased risk of GDM across all examined models. The pooled analysis demonstrated a substantial link, with the corresponding 95% CIs and the following ORs: Allele contrast: 0.80 (0.73–0.88), recessive model 0.81 (0.76–0.88), homozygote 0.60, (0.49–0.73), heterozygote 0.84, (0.78–0.91), dominant model 0.59, (0.48–0.72). Conclusions: The GCK rs1799884 variant, according to the current meta-analysis, may act as a genetic biomarker of GDM. The investigation was registered on PROSPERO (https://www.crd.york.ac.uk/prospero/) under registration number CRD42023492185.

Keywords: gestational diabetes mellitus; GCK; polymorphisms; meta-analysis

1. Introduction

Gestational diabetes mellitus (GDM) is characterised by hyperglycemia and glucose intolerance during pregnancy [1]. It is projected that about 14% of pregnant women worldwide are glucose intolerant [2]. GDM is associated with adverse pregnancy outcomes and foetal chronic metabolic diseases. The mechanism as well as the aetiology of GDM is yet to be fully known. Nevertheless, published evidences suggests that GDM is a clinical illness caused by environmental and genetic determinants [3,4]. For GDM, genetic susceptibility is an important risk factor [5].

Glucokinase (GCK) is a crucial enzyme in glycolysis due to its ability to promote glucose metabolism and regulate insulin release [6]. At present, a large number of studies have demonstrated that GCK gene mutations are associated with abnormal glucose metabolism [7–9]. Weedon et al. [10] reported a significant correlation between the GCK rs1799884 polymorphism and fasting blood glucose levels in the general population. A study by Holmkvist et al. [8] found that GCK gene β cell-specific promoter mutation-30G >A (rs1799884) increased the risk of type 2 diabetes.

Numerous investigations conducted over the previous 20 years have assessed the possible correlation among the GCK rs1799884 polymorphism and the risk of GDM in various national races; nonetheless, the ultimate outcomes have been non-uniform and ambiguous [11–15]. Consequently, the correlation among the GDM risk and GCK rs1799884 mutation was examined by a meta-analysis utilising existing case-control studies.

2. Materials and Methods

2.1 Publication Search

All articles on the association between GDM risk and GCK rs1799884 polymorphism were extracted from Ovid, Pubmed, CNKI, and Web of Science using the keywords such as “GCK rs1799884”, “polymorphism” and “GDM”, and the latest search was updated on 10 December 2022. This study was previously registered with PROSPERO (CRD42023492185) and followed PRISMA guidelines (Supplementary Material).

2.2 Inclusion and Exclusion Criteria

Regardless of sample size, all studies needed to meet the following requirements to be considered: (i) to assess the association GCK rs1799884 polymorphism and the risk of GDM, (ii) for case-control research, and (iii) to have sufficient data to obtain a 95% confidence interval (95% CI) for the odds ratio (OR). Studies that fit within this scope...
Fig. 1. Study selection and literature search process utilised for a meta-analysis of GDM and GCK rs1799884 genetic polymorphism. GCK, Glucokinase; GDM, gestational diabetes mellitus.

have not been included: (i) abstracts, reviews, overviews, or editorials, (ii) studies with insufficient data.

2.3 Data Extraction

According to the inclusion criteria mentioned above, two reviewers (Y. Hu and A. Wang) have independently extracted the information from all eligible and qualified publications. After consulting with the arbitrators, the discrepancies were resolved (K. Yi).

The next available information was captured from all eligible publications: first author’s last name, date of publication, participants’ country, case- and control-sample size, races, genotyping methods, and minor allele frequencies (MAF). The ethnic groupings have been categorised as Asian, Caucasian, or African.

We used the Cochran Q statistic and the I^2 in order to verify and confirm the heterogeneity analysis. A p-value of >0.10 for the Q statistic suggests a shortage of between-
Fig. 2. GDM risk and GCK rs1799884 polymorphism forest plots of ORs with 95% CIs. (A–E) displays the allelic, homozygous, heterozygous, dominant model, and recessive models, respectively. OR, odd ratio; CI, confidence interval.

study heterogeneity [16]. To quantify ORs, we selected a fixed-effect model (Mantel-Haenszel method) [17]; and the random-effect model (DerSimonian and Laird method) was chosen to aggregate ORs [18].

Publishing bias was explored by visual examination of funnel diagrams using Egger’s power-weighted regression method and Begg’s hierarchy correlation method (p value < 0.05 was deemed statistically meaningful) [19,20]. STATA software, version 13.0 (STATACorp., College Station, TX, USA) was employed to process the statistical analyses.

2.4 Trial Sequential Analysis

We used trial sequential analysis (TSA) to assess the required information size (RIS) and the reliability of the results. The RIS was calculated based on a 5% risk of type I error (α = 5%), 80% power of the study (β = 20%), and a two-sided boundary was performed. TSA was carried out utilizing TSA software (version 0.9.5.10 beta, Copenhagen, Denmark).

3. Result

3.1 Characteristics of Studies

After conducting a meticulous literature retrieval, we eventually limited our scope to 42 publications that might merit in-depth confirmation. After further eliminating 29 articles based on their headings and abstracts, we searched the 13 articles’ full text. Finally, we went ahead and removed 1 article because it focused on a literature review [21], and another because it had nothing to do with GCK rs1799884 polymorphism [22]. A total of twelve case-control studies, derived from eleven publications, were identified for inclusion in this meta-analysis. These studies investigated the potential relationship between GDM risk and GCK rs1799884 polymorphism [11–15,23–28]. The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guiding principle were followed in the selection of these studies [29]. The documentation searching and research selection proceedings are shown in Fig. 1.

Table 1 (Ref. [11–15,23–28]) presents the unique attributes of the chosen studies. Seven studies included participants of Caucasian descent, four studies involved individuals of Asian descent, and one study encompassed people of African descent. Researches were conducted in Brazil, China, Poland, Russia, Sweden, Thailand, the UK, and the USA.

3.2 Quantitative Synthesis

Twelve case-control studies were included, comprising 11,129 controls and 5907 patients. The meta-analysis outcomes are displayed in Table 2. Fig. 2 shows the forest diagrams for assessing the correlation among the GDM risk and GCK rs1799884 polymorphism.

Overall, our analysis revealed that, in all of the models we tested, the GCK rs1799884 polymorphism was significantly associated with a reduced risk of gestational diabetes mellitus. Specifically, the homozygote model (GG vs. AA) yielded an OR of 0.60 and a 95% CI of 0.49–0.73; the allele contrast model (G vs. A) yielded an odds ratio (OR) of 0.80.
Table 1. Features of studies encompassed within the meta-analysis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Sample</th>
<th>Genotyping Methods</th>
<th>MAF in Controls</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al. [11]</td>
<td>1994</td>
<td>USA</td>
<td>African</td>
<td>94/99</td>
<td>PCR-SSCP</td>
<td>0.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Zaidi et al. [23]</td>
<td>1997</td>
<td>UK</td>
<td>Caucasian</td>
<td>47/92</td>
<td>PCR-SSCP</td>
<td>0.27</td>
<td>0.08</td>
</tr>
<tr>
<td>Shaat et al. [12]</td>
<td>2006</td>
<td>Sweden</td>
<td>Caucasian</td>
<td>642/1229</td>
<td>Taqman</td>
<td>0.15</td>
<td>0.50</td>
</tr>
<tr>
<td>Freathy et al. [13]</td>
<td>2010</td>
<td>UK</td>
<td>Caucasian</td>
<td>614/3811</td>
<td>Taqman</td>
<td>0.18</td>
<td>0.91</td>
</tr>
<tr>
<td>Santis et al. [24]</td>
<td>2010</td>
<td>Thailand</td>
<td>Asian</td>
<td>384/1706</td>
<td>Illumina</td>
<td>0.10</td>
<td>0.61</td>
</tr>
<tr>
<td>Li et al. [25]</td>
<td>2011</td>
<td>China</td>
<td>Asian</td>
<td>1023/907</td>
<td>PCR-RFLP</td>
<td>0.21</td>
<td>0.55</td>
</tr>
<tr>
<td>Han et al. [26]</td>
<td>2015</td>
<td>China</td>
<td>Asian</td>
<td>948/975</td>
<td>PCR-RFLP</td>
<td>0.10</td>
<td>0.98</td>
</tr>
<tr>
<td>Popova et al. [14]</td>
<td>2017</td>
<td>Russia</td>
<td>Caucasian</td>
<td>278/179</td>
<td>PCR-RFLP</td>
<td>0.10</td>
<td>0.12</td>
</tr>
<tr>
<td>Tarnowski et al. [27]</td>
<td>2017</td>
<td>Poland</td>
<td>Caucasian</td>
<td>204/207</td>
<td>Taqman</td>
<td>0.11</td>
<td>0.87</td>
</tr>
<tr>
<td>Popova et al. [28]</td>
<td>2021</td>
<td>Russia</td>
<td>Caucasian</td>
<td>688/454</td>
<td>PCR-RFLP</td>
<td>0.13</td>
<td>0.14</td>
</tr>
<tr>
<td>She et al. [15]</td>
<td>2022</td>
<td>China</td>
<td>Asian</td>
<td>835/870</td>
<td>Taqman</td>
<td>0.19</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Abbreviations: PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP, polymerase chain reaction–single strand conformation polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table 2. Quantitative analyses of the GCK rs1799884 polymorphism on the GDM risk.

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>Variables</th>
<th>Sample size</th>
<th>Allele contrast</th>
<th>Homozygote</th>
<th>Heterozygote</th>
<th>Dominant Model</th>
<th>Recessive Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N°</td>
<td>Case/control</td>
<td>OR (95% CI)</td>
<td>p value b</td>
<td>OR (95% CI)</td>
<td>p value b</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>5907/11129</td>
<td>0.80 (0.73, 0.88)</td>
<td>0.051</td>
<td>0.60 (0.49, 0.73)</td>
<td>0.314</td>
<td>0.69 (0.56, 0.85)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>7</td>
<td>2623/6572</td>
<td>0.77 (0.70, 0.86)</td>
<td>0.337</td>
<td>0.49 (0.38, 0.65)</td>
<td>0.668</td>
<td>0.59 (0.45, 0.79)</td>
</tr>
<tr>
<td>Asia</td>
<td>4</td>
<td>3190/4458</td>
<td>0.83 (0.70, 0.99)</td>
<td>0.015</td>
<td>0.74 (0.55, 0.99)</td>
<td>0.321</td>
<td>0.81 (0.61, 1.09)</td>
</tr>
<tr>
<td>African</td>
<td>1</td>
<td>94/99</td>
<td>0.79 (0.48, 1.28)</td>
<td>NA c</td>
<td>0.44 (0.08, 2.52)</td>
<td>NA c</td>
<td>0.54 (0.09, 3.16)</td>
</tr>
</tbody>
</table>

aNumber of comparisons.
b p value of Q-test for heterogeneity test. Random-effects model was used when p value for heterogeneity test <0.10; otherwise, fixed-effects model was used.
c NA, not available.
and a 95% confidence interval (CI) of 0.73–0.88; the dominant model (GG + GA vs. AA) yielded an OR of 0.59 and a 95% CI of 0.48–0.72; the heterozygote model (GA vs. AA) yielded an OR of 0.84 and a 95% CI of 0.78–0.91; and the recessive model (GG vs. GA + AA) yielded an OR of 0.81 and a 95% CI of 0.76–0.88.

3.3 Heterogeneity Analysis

The evaluations of the dominant model and allele model revealed significant heterogeneity (dominant model, $p_{\text{heterogeneity}} = 0.069$; allele model, $p_{\text{heterogeneity}} = 0.051$). The Galbraith plot analysis was employed to probe the heterogeneity sources in different researches. We observed that there were two studies that led to heterogeneity in the GCK rs1799884 polymorphism [14,25] (Fig. 3). When the outlier researches were removed, heterogeneity declined sharply (allele contrast, $p_{\text{heterogeneity}} = 0.948$; dominant model, $p_{\text{heterogeneity}} = 0.558$).

3.4 Cumulative and Sensitivity Analyses

The outcomes are stable, as shown by the sensitivity analyses (Fig. 4) and cumulative meta-analysis (Fig. 5).

3.5 Publication Bias

Egger’s and Begg’s tests were used to determine whether publishing bias existed in the literature. No asymmetric trends was exhibited by Begg’s funnel-plot curves (Fig. 6). Besides, the statistical outcomes showed no bias in publication. Both tests yielded the following outcomes: [homozygote 0.75 and 0.47, allele contrast 0.45 and 0.20, dominant model 0.75 and 0.66, heterozygote 0.37 and 0.29, recessive model 0.37 and 0.24].

3.6 Trial Sequential Analysis

TSA was employed to investigate the relationship among GCK rs1799884 and GDM risk. The outcomes revealed that while the cumulative Z value (Z-curve) did not surpass the TSA boundary value, it did cross the TSA boundary, implying that the cumulative amount of information might not have attained the RIS (Fig. 7). This suggests that the conventional meta-analysis might offer a false positive result, and it would be necessary to do additional research to verify the correlation.

4. Discussion

Based on 12 case-controlled investigations, the meta-analysis showed that GCK rs1799884 polymorphism significantly decreased GDM incidence. When we conducted subgroup analysis on the basis of ethnicity, a significantly decreased GDM risk was found among Caucasian descent in all models. We also found a considerably lower GDM risk among Asian descent in all models except dominant model (OR, 0.76; 95% CI, 0.57–1.00).
The findings of the GCK rs1799884 polymorphism are partially consistent with the previous research. In a meta-analysis based on seven investigations, Han et al. [26] found a substantial correlation among GCK rs1799884 and the susceptibility to GDM among individuals of Caucasian descent in all models. However, they did not observe a significant association between GCK rs1799884 and GDM among individuals of Asian descent in the homozy-
Fig. 6. Begg’s funnel plot for publication bias test. (A–E) displays the allelic, homozygous, heterozygous, dominant model, and recessive models, respectively.

Fig. 7. Trial sequential analyses for GDM risk and GCK rs1799884 polymorphism. (A–E) exhibits the allelic, homozygous, heterozygous, dominant model, and recessive models, respectively.

gote comparison and recessive model [26]. One possible explanation for the discrepancy is that the relatively small number of samples in previous research (two Asian studies with 1332 cases and 2681 controls) may result in poor reliability results. The current meta-analysis included four case-controlled studies of Asian ethnicity, comprising 4458 controls and 3190 patients.
In a meta-analysis, the extent of heterogeneity is important as non-homogeneous studies can lead to misleading outcomes. We assessed the significance of heterogeneity using $I^2$ statistics and Q-test, and observed significant heterogeneity in the allele contrast as well as the dominant model. Plotting Galbraith diagrams to determine the origins of heterogeneity showed that two studies were the main contributors. After excluding these two studies, the heterogeneity decreased substantially, and the overall finding remained unchanged.

The possibility of publication bias brought on by studies that are only partially reported is a crucial factor to take into account in a meta-analysis. The funnel plot curves and statistical data in our meta-analysis, which included Egger’s and Begg’s tests to evaluate publication bias, showed no indication of publication bias.

The present investigation has several shortcomings: (i) Because of these studies’ restrictive sample number and the limited studies encompassed, the outcomes were inadequate to statistically examine the actual associations; (ii) This research was based on unadjusted OR estimations, since not all incorporated experiments offered adjustable ORs. ORs may have been modulated by various elements, including smoking, ethnicity, or age, even if they were offered; (iii) There was a marked heterogeneity among studies in recessive model and allele contrast.

5. Conclusions

In summary, as suggested by our meta-analysis, the GCK rs1799884 variant may be useful as a genetic biomarker for GDM. However, more carefully designed investigations conducted across multiple centres are necessary to validate and strengthen our findings.

Availability of Data and Materials

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Author Contributions

KY conceived and designed the meta-analysis. YH and AW performed the literature search. AW analyzed the data. YH wrote the paper. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5105108.

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