Meta-Analysis of the Relationship between Common Type 2 Diabetes Risk Gene Variants with Gestational Diabetes Mellitus

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Abstract

Background: A number of case-control studies were conducted to investigate the association of common type 2 diabetes (T2D) risk gene polymorphisms with gestational diabetes mellitus (GDM). However, these studies have yielded contradictory results. We therefore performed a meta-analysis to derive a more precise estimation of the association between these polymorphisms and GDM, hence achieve a better understanding to the relationship between T2D and GDM.

Methods: PubMed, EMBASE, ISI web of science and the Chinese National Knowledge Infrastructure databases were systematically searched to identify relevant studies. Data were abstracted independently by two reviewers. A meta-analysis was performed to examine the association between 9 polymorphisms from 8 genes and susceptibility to GDM. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Heterogeneity among articles and their publication bias were also tested.

Results: We identified 22 eligible studies including a total of 10,336 GDM cases and 17,445 controls. We found 8 genetic polymorphisms were significantly associated with GDM in a random-effects meta-analysis. These polymorphisms were in or near the following genes: TCF7L2 (rs7903146), MTNR1B (rs10830963), IGF2BP2 (rs4402960), KCNJ11 (rs5219), CDKAL1 (rs7754840), KCNQ1 (rs2237892 and rs2237895) and GCK (rs4607517); while no association was found for PPARG with GDM risk. Similar results were also observed under dominant genetic model for these polymorphisms.

Conclusions: This meta-analysis found 8 genetic variants associated with GDM. The relative contribution and relevance of the identified genes in the pathogenesis of GDM should be the focus of future studies.

Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first detected during pregnancy [1]. It is characterized by impaired insulin secretion and action [2,3]. Gestational diabetes complicates about 1–3% of all pregnancies in the western world [4], whereas 5–10% among Asian women [5]. Although its exact etiology is unknown, accumulating evidence recognizes GDM as a quintessential multifactorial disease in which environmental triggers interact with genetic variants [6]. Given the fact that women with a history of GDM are at an increased risk of developing type 2 diabetes (T2D) later in their lives [7] and women with a family history of diabetes may be predisposed to an increased risk of GDM [8], it is plausible to hypothesize that GMD may share the same risk factors and genetic susceptibilities with T2D. However, knowledge regarding the genetics of GDM is very limited so far [9].

Recently, spectacular advance was made in identifying susceptible genes involved in T2D through genome-wide association strategy (GWAS) [10,11]. Consequently, a number of novel genetic variants (PPARG, KCNJ11, IGF2BP2, KCNQ1, TCF7L2, CDKAL1, and MTNR1B) were shown to increase the risk of T2D in reproducible studies. Therefore, several studies have examined the association of these newly identified loci using a candidate gene approach for GDM. It has been reported that the pathophysiological changes of GDM are similar to those observed in T2D, which is characterized by peripheral insulin resistance accompanied by an insulin secretory defect [12,13]. Functional studies showed that these new diabetogenic genes took part in many steps of the process, for instance, impaired β-cell function (CDKAL1, IGF2BP2, KCNQ1, KCNJ11, MTNR1B), insulin resistance (PPARG, TCF7L2), and abnormal utilization of glucose (GCK) [14–23].

Genetic association studies can be problematic to reproduce due to inadequate statistical power, multiple hypothesis testing, population stratification, publication bias, and phenotypic hetero-
geneity. Considering the lack of sufficient evidence about the effect of candidate genes of T2D on GDM and the conflicting results reported, we therefore performed a meta-analysis to assess the association between the most commonly studied polymorphisms in the PPARG, CDKAL1, KCNJ11, IGF2BP2, TCFT2L2, KCNJ11, MTNR1B, GCK genes and GDM risk.

Materials and Methods

Literature search strategy

Genetic association studies polymorphism and GDM risk published up to April, 2012 were identified through systematic searches in PubMed, EMBASE, ISI Web of Science and the Chinese National Knowledge Infrastructure (CNKI) databases. No language restrictions were applied. The search strategy consisted of multiple queries combining: 'gestational diabetes mellitus' and 'variations' or 'polymorphisms'. In addition, the names of specific genes and polymorphisms were combined with the topic 'gestational diabetes mellitus'. All reference lists from the main reports and relevant reviews were hand searched for additional eligible studies.

Eligible studies and data extraction

Eligible studies had to meet all the following criteria: (1) original papers containing independent data, (2) identification of gestational diabetes mellitus cases was confirmed pathologically, (3) case-control or cohort studies and (4) genotype distribution information in cases and controls or odds ratio (OR) with its 95% confidence interval (CI) and P-value. The major reasons for exclusion of studies were (1) overlapping data; (2) case-only studies, family based studies, and review articles.

Data extraction was performed independently by two reviewers. Review reports from the two were than compared to identify any inconsistency, and differences were resolved by further discussion among all authors. For each included study, the following information was extracted from each report according to a fixed protocol: first author’s surname, publication year, definition and numbers of cases and controls, frequency of genotypes, Hardy–Weinberg equilibrium status, source of controls, mean age of cases and controls, body mass index (BMI), ethnicity, and genotyping method.

Statistical methods

The strength of association between the genetic polymorphism and GDM was assessed by calculating odds ratio (OR) with 95% confidence interval (CI). For single nucleotide polymorphisms (SNPs), the frequency of the risk allele was compared between diabetic cases and non-diabetic controls. Additional pooled estimates were also given with corresponding results under dominant genetic model.

Cochran’s chi-square-based Q statistic test was performed in order to assess possible heterogeneity between the individual studies and thus to ensure that each group of studies was suitable for meta-analysis [24]. ORs were pooled according to a method of DerSimonian and Laird that takes into account the variation between studies, and 95% CI were constructed using Woolf’s method [25,26]. The Z test was used to determine the significance of the pooled OR. Pre-specified stratified analyses were performed to explain heterogeneity or investigate whether the reported association was present in a subgroup. Stratified analysis was performed for ethnicity (Caucasian vs East Asian origin).

Funnel plots was used to provide diagnosis of the potential publication bias. Egger’s regression test was also conducted to identify small study effects [27]. Chi-square test was used to check if there was significant deviation from Hardy–Weinberg equilibrium (HWE) among the control subjects in each study. All statistical analyses were carried out with the Stata software version 10.0 (Stata Corporation, College Station, TX). The type I error rate was set at 0.05. All the p-values were for two-sided analysis.

Results

Characteristics of studies

In all, we included 22 studies in this meta-analysis, with a total of 10,336 cases and 17,445 controls concerning 9 genetic variants in or near 8 genes. The detailed characteristics of the studies included were shown in Table 1. The study selection process is shown in Figure 1. These polymorphisms were found to occur in frequencies consistent with Hardy–Weinberg equilibrium in the control populations of the vast majority of the published studies. Details of analyses of all assessed genetic variants are provided in Table 2.

Genetic variants involved in β-cell function

Six genetic variants in five genes thought to be related to β-cell function were reproducibly associated with GDM. rs402960 of IGF2BP2 was associated with GDM (OR = 1.21, 95% CI = 1.08–1.36, P = 0.001; Supplementary figure 1) in four studies (n = 8,732), also in the subgroup among East Asian diabetes mellitus patients (OR = 1.24, 95% CI = 1.07–1.44, P = 0.004). The rs10039063 in MTNR1B were studied in five studies concerning diabetic patients form East Asian population. The overall OR of the G allele for GDM was 1.34 (95% CI = 1.18–1.52, P < 10⁻⁵; Supplementary figure 2). CDKAL1 rs7754040 polymorphism was studied in four studies and was associated with GDM in the meta-analysis (OR = 1.43, 95% CI = 1.20–1.71, P < 10⁻⁵; Supplementary figure 3). All four studies contained diabetic patients of East Asian descent. For KCNJ11 rs52219, our meta-analyses gave an overall OR of 1.15 (95% CI = 1.06–1.24, P = 0.0004; Supplementary figure 4) without statistically significant between-study heterogeneity. Significantly increased GDM risks were also found for Caucasian and East Asian populations when stratified by ethnicity. Significantly increased GDM risks were found for rs2237892 and rs2237895 of KCNJ11 with per-allele OR of 1.20 (95% CI = 1.09–1.31, P = 10⁻⁴; Supplementary figure 5) and 1.20 (95% CI = 1.09–1.31, P = 0.0001; Supplementary figure 6) respectively. In addition, statistically significant results were also observed for these polymorphisms under dominant genetic model. After adjusting for multiple testing using Bonferroni correction, all significant associations for these polymorphisms under the allelic comparison and dominant genetic model remained.

Genetic variants involved in insulin resistance

A variant in PPARG, rs1801282, was the most studied polymorphism in GDM, with 11 data sets resulting in a pooled odds ratio of 1.01 (95% CI = 0.96–1.06, P = 0.80, Supplementary figure 7). Subsidiary analyses of ethnicity yielded a per-allele OR for East Asians of 1.02 (95% CI: 0.93–1.11, P = 0.70) and for Caucasians of 1.00 (95% CI: 0.94–1.06, P = 0.98). Similar results were also detected under dominant genetic model.

rs7903146 of TCFT2L2, which is an important component in Wnt signaling pathway involved in development of the pancreas and islets, was associated with GDM (C allele: OR = 1.51, 95% CI = 1.39–1.65, P < 10⁻⁵; Supplementary figure 8; dominant model: OR = 1.69, 95% CI = 1.51–1.89, P < 10⁻⁵). Stratification by ethnicity indicated that the polymorphism was significantly associated with GDM for East Asians and Caucasians in all genetic
models. After Bonferroni correction, significant associations still maintained for the polymorphism.

Genetic variants involved in glucose utilization

rs4607517 of GCK, which is first rate-limiting step in the glycolysis pathway, was significantly associated with GDM in the meta-analysis (OR = 1.12, 95% CI = 1.02–1.23, \( P = 0.01 \), Supplementary figure 9). Similar results were also found using dominant genetic model with OR of 1.15 (95% CI = 1.01–1.30, \( P = 0.04 \)). However, for GCK rs4607517 association was no longer statistically significant using dominant genetic model after Bonferroni correction.

Publication bias

Begger's funnel plot and Egger's test were used to identify the potential publication biases of the literature, the shapes of the funnel plots appeared to be symmetrical (Supplementary figure 10–18) for polymorphisms in PPARG, TCF7L2, MTNR1B, IGF2BP2, KCNJ11, CDKAL1, KCNQ1 and GCK, suggesting that there was no obvious publication bias. Egger's test was used to provide further statistical evidence; similarly, the results showed no significant publication bias in this meta-analysis for these polymorphisms (\( P > 0.05 \) for all polymorphisms).

Discussion

Large sample and unbiased epidemiological studies of predisposition genes polymorphisms could provide insight into the in vivo relationship between candidate genes and complex diseases. In this meta-analysis, 8 genetic variants were found to be associated with increased GDM susceptibility. Genetic studies of several T2D associated variants in relation to GDM has been performed previously, but this is the first complete overview assessing for these genetic variants that are reproducibly associated with the presence of GDM. This information could lead to improved insight into underlying pathogenetic mechanisms and the relationship between GDM and T2D. These results support a role for the following in the pathogenesis of GDM: impaired β-cell function, insulin resistance and abnormal utilization of glucose. During pregnancy, women are faced with increased adiposity and increased insulin resistance. The insulin resistance that develops
Table 1. Characteristics of the studies included in the meta-analysis.

| Study          | Year | Ethnicity   | Case Description | Control Description | No. of case/control | Genotyping method       | Age of case/control | BMI of case/control |
|----------------|------|-------------|------------------|---------------------|---------------------|-------------------------|---------------------|---------------------|
| Kwak [28]      | 2012 | Korean      | OGTT confirmed   | Normal fasting glucose | 1399/2025          | Affymetrix array, TaqMan | 32.1/62.5           | 242/24.4            |
| Kim [29]       | 2011 | Korean      | OGTT confirmed   | Normal glucose tolerant | 908/966            | TaqMan                  | 32.2/32.2           | 233/21.4            |
| Deng [30]      | 2011 | Chinese     | GDM patients     | Non-diabetic participants | 87/91             | Sequencing              | 31.8/29.7           | 23.6/21.5           |
| Heude [31]     | 2011 | French      | OGTT confirmed   | Normal glucose tolerant | 109/1571          | TaqMan                  | NA/NA               | NA/NA               |
| Wang [32]      | 2011 | Chinese     | OGTT confirmed   | Normal glucose tolerant | 705/1029          | TaqMan                  | 32.0/30.0           | 21.7/21.5           |
| Pappa [33]     | 2011 | Greek       | GDM per IGDW criteria | Normal glucose tolerant | 148/107         | RFLP                    | 32.5/26.7           | 26.0/24.3           |
| Papadopoulou [34] | 2011 | Swede      | OGTT confirmed   | Normal glucose tolerant | 803/1110          | TaqMan                  | NA/NA               | NA/NA               |
| Shin [35]      | 2010 | Korean      | OGTT confirmed   | Healthy              | 930/628           | TaqMan                  | 32.2/NA             | 23.3/NA             |
| Cheng [36]     | 2010 | Chinese     | OGTT confirmed   | Normal glucose tolerant | 55/173           | RFLP                    | 27.0/29.6           | NA/NA               |
| Kwak [37]      | 2010 | Korean      | OGTT confirmed   | Normal fasting glucose | 869/532           | TaqMan                  | 27.9/64.7           | 23.1/23.3           |
| Santos [38]    | 2010 | Euro-Brazilian | GDM per ADA criteria | Healthy         | 150/600           | RFLP                    | 31.7/24.9           | 33.5/24.8           |
| Zhou [39]      | 2009 | Chinese     | OGTT confirmed   | Normal glucose tolerant | 520/916          | RFLP                    | 32.5/30.7           | 21.4/21.4           |
| Cho [40]       | 2009 | Korean      | OGTT confirmed   | Normal fasting glucose | 868/632          | TaqMan                  | 32.0/64.7           | 23.1/23.3           |
| Zhu [41]       | 2009 | Chinese     | GDM patients     | Non-diabetic participants | 179/180         | RFLP                    | 28.1/27.4           | 24.6/23.4           |
| Lauenborg [14] | 2008 | Dane        | OGTT confirmed   | Normal glucose tolerant | 276/2383         | TaqMan                  | 43.1/45.2           | 28.9/25.0           |
| Shaat [42]     | 2007 | Swede       | OGTT confirmed   | Non-diabetic participants | 637/1232        | TaqMan                  | 32.3/30.5           | NA/NA               |
| Tok [43]       | 2006 | Turkish     | OGTT confirmed   | Normal glucose tolerant | 100/62           | RFLP                    | 33.5/31.6           | 26.6/23.0           |
| Shaat [44]     | 2006 | Swede       | OGTT confirmed   | Non-diabetic participants | 641/1229        | RFLP                    | NA/NA               | NA/NA               |
| Shaat [45]     | 2005 | Swede       | OGTT confirmed   | Normal glucose tolerant | 588/1180        | TaqMan                  | 32.2/30.5           | NA/NA               |
| Shaat [46]     | 2004 | Swede       | OGTT confirmed   | Normal glucose tolerant | 500/550         | RFLP                    | 32.3/NA             | 30.1/NA             |
| Chiu [47]      | 1994 | American    | OGTT confirmed   | Non-diabetic participants | 174/99          | SSCP                    | 28.3/22.1           | 33.9/22.5           |
| Unpublished data | /    | Chinese     | OGTT confirmed   | Normal glucose tolerant | 50/50           | RFLP                    | 30.5/28.8           | 31.0/27.9           |

OGTT: Oral Glucose Tolerance Test, IGDW: International Gestational Diabetes Workshop, ADA: American Diabetes Association, NA: Not Available.

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Those who have limited function of human placental lactogen, estrogen, and prolactin [48–50]. During pregnancy is explained in part by the increased production of b-cell insulin secretory function similar to T2D [9]. After parturition, nearly one-half of these women progress to T2D within 5 years [51–53]. Therefore, GDM is often regarded as a herald of type 2 diabetes in later life. Functional studies remain to be performed to establish the precise roles of these variants and pathways.

The identification of GDM susceptibility variants can lead to novel biological insights and improved measures of individual etiological processes, as indicated previously [54]. Individual etiological processes could allow preventive and therapeutic interventions in complex disease to be tailored to individuals on the basis of their genetic profiles. From prediction studies with the T2D related gene polymorphisms and GDM susceptibility. In interpreting the results, some limitations of this meta-analysis should be addressed. Publication bias is a concern in all meta-analyses even though the use of a statistical test did not show it. Negative studies are less likely to be published, potentially leading to an overestimation of effects. Moreover, non-significant genetic associations might have been underreported in published articles. Therefore, the effect estimates of the present study should be interpreted with caution, especially in cases where associations were based on small numbers of studies and/or small sample numbers. Second, in the subgroup analysis by ethnicity, the numbers. The identification of GDM susceptibility variants can lead to novel biological insights and improved measures of individual etiological processes, as indicated previously [54]. Individual etiological processes could allow preventive and therapeutic interventions in complex disease to be tailored to individuals on the basis of their genetic profiles.

Table 2. Results of the pooled data analyses for the 9 studied polymorphisms and gestational diabetes mellitus risk.

| Variants per gene | Risk allele | Total/subgroup | No. of data sets | No. of case/control | Risk allele | Dominant model |
|-------------------|-------------|----------------|-----------------|--------------------|-------------|---------------|
|                   |             |                |                 |                    | OR (95%CI)  | P(Z) P(Q)     | OR (95%CI)  | P(Z) P(Q)     |
| PPARG rs1801282   | C           | Total          | 11              | 2908/6940          | 1.01 (0.96–1.06) | 0.80 1.00 | 1.14 (0.68–1.91) | 0.63 0.45 |
|                   |             | Caucasian      | 5               | 1559/5721          | 1.00 (0.94–1.06) | 0.98 0.99 | 1.01 (0.58–1.76) | 0.98 0.44 |
|                   |             | East Asian     | 4               | 1149/1035          | 1.02 (0.93–1.11) | 0.70 0.99 | 2.43 (0.38–15.43) | 0.35 0.27 |
| TCF7L2 rs7903146  | T           | Total          | 6               | 3148/6550          | 1.51 (1.39–1.65) | <10^-3 0.77 | 1.69 (1.51–1.89) | <10^-5 0.51 |
|                   |             | Caucasian      | 4               | 1812/4681          | 1.51 (1.38–1.65) | <10^-3 0.48 | 1.71 (1.49–1.96) | <10^-5 0.28 |
|                   |             | East Asian     | 2               | 1336/1869          | 1.55 (1.16–2.09) | 0.004 0.90 | 1.56 (1.24–2.22) | 0.001 0.75 |
| MTNR1B rs10830963 | G           | Total          | 5               | 3094/4111          | 1.34 (1.18–1.52) | <10^-3 0.02 | 1.46 (1.25–1.72) | <10^-5 0.11 |
| IGFBP2 rs4402960  | T           | Total          | 4               | 2304/5228          | 1.21 (1.08–1.36) | 0.001 0.09 | 1.25 (1.07–1.49) | 0.003 0.06 |
|                   |             | East Asian     | 3               | 2030/2894          | 1.24 (1.07–1.44) | 0.004 0.07 | 1.27 (1.12–1.43) | 0.0002 0.81 |
| KCNJ11 rs5219     | T           | Total          | 5               | 2305/5569          | 1.15 (1.06–1.24) | 0.0004 0.99 | 1.25 (1.10–1.42) | 0.001 0.88 |
|                   |             | Caucasian      | 3               | 991/3698           | 1.17 (1.05–1.30) | 0.005 0.98 | 1.25 (1.07–1.46) | 0.006 0.72 |
|                   |             | East Asian     | 2               | 1314/1871          | 1.13 (1.02–1.26) | 0.03 0.93 | 1.11 (1.03–1.20) | 0.02 0.29 |
| CDKL1 rs7754840   | C           | Total          | 4               | 2959/3675          | 1.43 (1.20–1.71) | <10^-4 0.0003 | 1.51 (1.33–1.82) | <10^-4 0.008 |
| KCNQ1 rs2237892   | C           | Total          | 3               | 2285/2168          | 1.20 (1.09–1.31) | <10^-4 0.70 | 1.42 (1.18–1.71) | 0.0002 0.97 |
| KCNQ1 rs2237895   | C           | Total          | 3               | 2286/2168          | 1.20 (1.09–1.31) | 0.0001 0.75 | 1.31 (1.16–1.48) | <10^-4 0.54 |
| GCK rs4607517     | A           | Total          | 5               | 2135/4193          | 1.12 (1.02–1.23) | 0.01 0.41 | 1.15 (1.01–1.30) | 0.04 0.43 |

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Novel biological insights may lead to development of new therapeutic targets, biomarkers and opportunities for disease prevention. Hypothesis-free approaches, such as GWAS, are most promising in this respect. At present, it seems wise to focus on assessing the relevance of previously detected genetic variants. As common SNPs associated with GDM and detected by GWAS may represent rare genetic variants with large effects, sequencing the regions surrounding highly significant and replicated genomic regions to detect rare variants appears to be reasonable. Follow-up in vitro and in vivo studies could then assess the functional relevance of these variants in GDM.

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Our meta-analysis identified 8 genetic variants associated with GDM. As studies among other populations are currently limited, further studies including a wider spectrum of subjects should be carried to investigate the role of those variants in other populations, which should lead to better, comprehensive understanding of the association between the genetic polymorphism and GDM. For future studies, gene–gene and gene–environment interactions should also be considered.

Supporting Information

Figure S1 Meta-analysis of the association between IGF2BP2 rs4402960 polymorphism and the risk for gestational diabetes mellitus.
(TIF)

Figure S2 Meta-analysis of the association between MTNR1B rs10830963 polymorphism and the risk for gestational diabetes mellitus.
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Figure S3 Meta-analysis of the association between CDKAL1 rs7754840 polymorphism and the risk for gestational diabetes mellitus.
(TIF)

Figure S4 Meta-analysis of the association between KCNJ11 rs5219 polymorphism and the risk for gestational diabetes mellitus.
(TIF)

Figure S5 Meta-analysis of the association between KCNQ1 rs2237892 polymorphism and the risk for gestational diabetes mellitus.
(TIF)

Figure S6 Meta-analysis of the association between KCNQ1 rs2237895 polymorphism and the risk for gestational diabetes mellitus.
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Figure S7 Meta-analysis of the association between PPARG rs1801282 polymorphism and the risk for gestational diabetes mellitus.
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Figure S8 Meta-analysis of the association between TCF7L2 rs7903146 polymorphism and the risk for gestational diabetes mellitus.
(TIFF)

Figure S9 Meta-analysis of the association between GCK rs4607517 polymorphism and the risk for gestational diabetes mellitus.
(TIF)

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