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Association of the glucokinase gene promoter polymorphism -30G > A (rs1799884) with gestational diabetes mellitus susceptibility: a case–control study and meta-analysis

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Abstract
Purpose Several studies have examined the association between glucokinase (GCK)-30G > A polymorphism and gestational diabetes mellitus (GDM). However, the results are still controversial. We performed the case–control study to investigate whether GCK-30G > A polymorphism correlates with the susceptibility of GDM in Chinese populations, and then conducted a meta-analysis by combining the previous studies.
Methods We recruited 948 GDM patients and 975 controls from May 2011 to August 2013. All the subjects were genotyped using the PCR-based invader assay. The differences of allelic frequencies and genotype distributions between GDM patients and controls were investigated in case–control study. A systematic search of all relevant studies was conducted. The observational studies that were related to an association between the glucokinase (GCK)-30G > A polymorphism and GDM were identified. The association between the glucokinase (GCK)-30G > A polymorphism and GDM susceptibility was assessed using genetic models.
Results The case–control study showed that GCK-30G > A polymorphism was associated with the susceptibility of GDM in a Chinese population. Furthermore, other six previously reported studies were included to perform meta-analysis. The meta-analysis showed that GCK-30G > A polymorphism was associated with GDM in Caucasian and Asian.
Conclusions This study suggested that GCK-30G > A polymorphism may be associated with the susceptibility of GDM in a Chinese population. The further meta-analysis provides additional evidence supporting the above result that the risk allele of the GCK-30G > A polymorphism may increase GDM risk.

Keywords Gestational diabetes mellitus · Single nucleotide polymorphism · Gene · Genetic factors · Glucokinase

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder during pregnancy, and is defined as glucose intolerance with onset or first recognition during pregnancy [1]. The prevalence of GDM varies in different ethnic populations. GDM affects about 1–3 % of all pregnancies in the western world but 5–10 % of Asian women [2, 3]. The frequency has increased in several populations during the last decade [4, 5]. Impaired beta cell function and insulin resistance characterize pregnancy complicated by GDM [6]. However, when insulin secretion is adjusted for the degree of insulin resistance, women with GDM have a severe reduction in beta cell function compared with normal pregnant women [7]. This beta cell dysfunction seems to persist in women with a history of GDM post-partum [6, 8].

In spite of much investigation, the causes of the development and progression of GDM have not been fully elucidated, and several evidence suggests that multiple genetic and environmental factors, as well as the interaction between these factors, determine the phenotype [9, 10]. Low et al. [11] reported that adiponectin SNP45TG is

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associated with GDM. Beltcheva et al. [12] showed that adiponectin promoter polymorphism rs266729 is associated with GDM.

Glucokinase (GCK), encoded by the GCK gene on chromosome 7p. GCK is a sensor and a key regulatory enzyme in the pancreatic beta cell, thus playing an important role in glucose homeostasis [13]. Because of its role in the regulation of insulin secretion, the GCK gene is an attractive candidate gene for both GDM and T2DM risk.

More than 600 mutations in the GCK gene have been described. Among these, the -30G > A (rs1799884) polymorphism in the GCK promoter region was found associated with T2DM [14], GDM [15] and obesity [16], although other studies failed to confirm these associations [14, 17]. The variant G to A at position -30 might lead to a decrease in GCK activity and to an increase in the threshold for glucose-stimulated insulin secretion [18]. Because this variant is located within a highly conserved region of the GCK promoter, it might alter transcriptional regulation of the gene [13]. If this variant reduced the transcription of the GCK gene, the cellular activity of GCK would likely decrease and lead to impaired glucose sensing, insulin secretion of beta cells and eventually diabetes [19].

Although several studies have investigated the role of the GCK-30G > A polymorphism in the development of GDM among various populations, results are still conflicting. To confirm the association between the GCK-30G > A polymorphism and GDM, we performed a case–control study for the association of rs1799884 with GDM in Chinese population, and then conducted a meta-analysis to derive a relatively comprehensive picture of the relationship between the GCK-30G > A polymorphism and the risk of GDM.

Materials and methods

Subjects

A total of 1,923 subjects were studied. All pregnant women were recruited from Obstetrics Department, Tianjin Central Hospital of Gynecology Obstetrics, Tianjin Medical University between May 2011 and August 2013. The present study was approved by the ethics committee of Tianjin Central Hospital of Gynecology Obstetrics, and all participants gave written, informed consent.

Eligible pregnant women underwent a 75-g OGTT at 24–32 weeks' gestation (as close to 28 weeks as possible). Fasting, 1-h, and 2-h glucose levels were measured. Height, weight, and blood pressure were also measured using standardized procedures and calibrated equipment. A sample for random plasma glucose was collected at 34–37 weeks' gestation as a safety measure to identify cases with hyperglycemia above a predefined threshold. Gestational age was determined as previously described. Demographic and lifestyle characteristics and age were collected via questionnaire. Race/ethnicity was self-identified. Participants and authors remained blinded to glucose values unless fasting plasma glucose was >5.8 mmol/l, 2-h OGTT plasma glucose was >11.1 mmol/l, random plasma glucose was >8.9 mmol/l, or any plasma glucose value was >2.5 mmol/l.

Genotyping

We selected the rs1799884 (GCK) single nucleotide polymorphisms (SNPs) for association analysis. Genomic DNA was extracted from peripheral blood leukocytes using genomic DNA isolation kits (Promega, Madison, WI) according to the manufacturer's instructions. The primers, probes and reaction conditions were available upon request. SNPs were genotyped by the PCR-based invader assay (Third Wave Technologies) using ABI 7900 (Applied Biosystems, Foster City, CA, WI) [20]. Genotyping was done by laboratory personnel blinded to subject status. Of the samples, 10 % were tested twice to validate the genotyping results with 100 % reproducibility. Two authors independently reviewed the genotyping results, data entry, and statistical analysis.

Meta-analysis

Candidate studies had to meet the following criteria: (1) all patients meeting the diagnostic criteria for GDM, (2) case–control study focused on the relationship between the GCK-30G > A polymorphism and GDM, and (3) sufficient original data for calculating odds ratios (ORs) with corresponding 95 % confidence intervals (CIs). The major reasons for excluding studies were design other than a case–control study, duplicate publications, and no available data reported.

Two of the authors independently extracted the following data from each full-text report using a standard data extraction form. The data extracted from the studies included the title, authors, year of publication, study design, number of cases or controls, ethnicity, genotyping method, genotype distribution, and frequency of allele of the rs1799884 polymorphism in cases or controls.

Statistical analysis

Standard χ^2 analysis was used to examine differences of allelic frequencies and genotype distributions between GDM patients and controls in case–control study. Hardy–Weinberg equilibrium was tested by a goodness-of-fit χ^2 test.

Meta-analysis was performed with STATA 12.0 (Statacorp, college station, Tex). The association between the GCK-30G > A polymorphism and GDM susceptibility was assessed under the following genetic models, which were treated as a dichotomous variable: (a) A-allele versus G-allele for allele level comparison; (b) AA + AG versus GG for a dominant model of the A-allele; (c) AA versus AG + GG for a recessive model of the T-allele, and (d) AA versus GG for the extreme genotype. Statistical heterogeneity was assessed using Q statistics. A fixed-effects (inverse variance) model was used when the effects were assumed to be homogenous ($P > 0.05$). $P < 0.05$ implied statistical heterogeneity, and a random effects model was used in those circumstances. Two-sided P values less than 0.05 were considered statistically significant.

Results

A total of 1,923 subjects (948 cases and 975 controls) were successfully genotyped and subjected to statistical analysis. The distributions of the alleles and genotypes for rs1799884 are presented in Table 1. Genotype frequencies of GDM group and the control group were conformed to the Hardy–Weinberg equilibrium ($P = 0.59$ and 0.60, respectively).

Case–control association study

In accordance with the genome-wide association study (GWAS), the risk allele (A-allele) lead to a higher risk for GDM in Chinese population (Table 1). A-allele of the -30G > A polymorphism was significantly associated with increased risk of GDM.

Meta-analysis

A total of 45 titles and abstracts were preliminarily reviewed, of which 5 of the published literature [15, 21–24] eventually satisfied the eligibility criteria (Fig. 1). All of the included studies investigated the relation between the rs1799884 polymorphism and GDM. Of these, one study contained data on two different groups [23]. We, therefore, performed meta-analysis between the previous studies [15, 21–24] and our case–control study. Ultimately, 6 studies (7 comparisons) investigated the relationship between -30G > A and GDM risk with a total of 2,959 GDM cases and 8,535 healthy controls. Characteristics of the studies that were included in the meta-analysis are presented in Table 2. First, we compared the allele frequency difference in GDM patients and controls. A significant relationship was observed between the A-allele and GDM susceptibility in all subjects (OR = 1.28, 95 % CI 1.17–1.39, $P < 0.001$). After stratification by ethnicity, subgroup analysis indicated that the A-allele frequency was significantly associated with GDM in Caucasian (OR = 1.24, 95 % CI 1.11–1.38, $P < 0.001$), and Asian (OR = 1.37, 95 % CI 1.18–1.60, $P < 0.001$), but not in African populations (OR = 1.12, 95 % CI 0.72–1.73, $P = 0.618$) (Fig. 2; Table 3). Summary ORs (95 % CI) and stratified analysis by ethnicity with various genetic models (AA vs. GG, AA + GA vs. GG, AA vs. GG + GA) are shown in Table 3.

Discussion

Gestational diabetes mellitus shares many risk factors with T2DM, and up to 50 % of women with GDM develop T2DM within 10 years after pregnancy [2]. However, the pathogenetic mechanisms of GDM is still unclear. GCK is the key glucose phosphorylation enzyme responsible for the first rate-limiting step in the glycolysis pathway and regulates glucose-stimulated insulin secretion from pancreatic beta cells and glucose metabolism in the liver [25]. Inactivating GCK mutations lead to maturity-onset diabetes of the young and neonatal diabetes [26], whereas activating GCK mutations cause persistent hyperinsulinemia and hypoglycemia [27, 28]. Therefore, GCK gene seems to play a key role in glucose homeostasis and is a determinant of diabetes risk in several populations. Although several case–control studies have evaluated the role of the GCK-30G > A polymorphism in the development of GDM among various populations, the results still remain controversial.

Table 1 Allele and genotype frequencies of GCK-30G > A in GDM in a Chinese population

	Genotype (%)			*P*	Allele (%)		*P*	OR (95 % CI)
	AA	AG	GG		A	G		
GDM group	17	226	705		260	1,636		
Control group	10	178	787	<0.001	198	1,752	<0.001	1.41 (1.16–1.71)

OR odds ratio, *CI* confidence interval

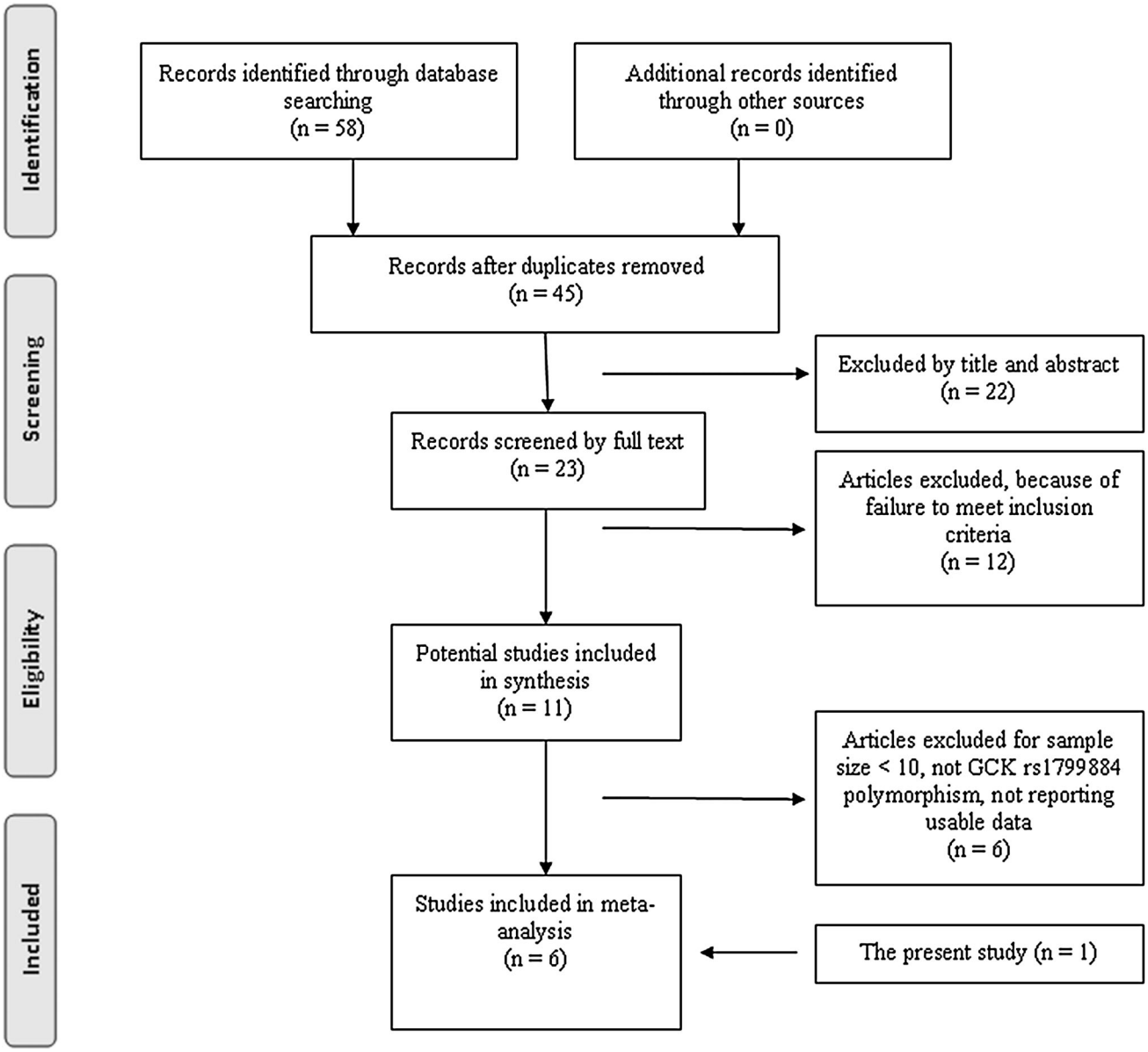

Fig. 1 Flow chart of study selection for meta-analysis

Genome-wide association study is a powerful method for the detecting genetic contributions to polygenic diseases, and has been increasingly used to study genetic predisposition in GDM. However, this method may produce spurious association [29, 30]. Therefore, replications of the associations in different ethnic groups and studies with large sample sizes are important to confirm the results of GWAS [31]. In the present study, we identified that GCK-30G > A polymorphism was associated with GDM susceptibility. The total number of GDM patients of the current study was more than that of previous studies, which provided more powerful evidence to support that rs1799884 may account for disease pre-disposition of GDM. Our study confirmed the earlier finding of positive association in Thailand population [23]. Moreover, the results of meta-analysis implicated that GCK-30G > A was associated with increased GDM susceptibility in the overall population. The present case–control study provides a more comprehensive summary of the currently available evidence on the association between the GCK-30G > A polymorphism and the risk of GDM.

Association studies are a useful tool to identify genetic factors conferring susceptibility to diseases [32]. However, the original association studies are not powerful enough to detect the genetic effects underlying the genetic susceptibility to develop diseases. This disadvantage has resulted in the reporting of inconsistent findings in the literature. The reasons for inconsistent results include the following items:

Table 2 Characteristics of included studies

Author	Country	Ethnicity	GDM group		Control group		Diagnostic criteria	Detection method
			Sample size	Age ($M \pm SD$)	Sample size	Age ($M \pm SD$)		
Chiu et al. [24]	USA	African	174	28.2 ± 5.8	99	22.1 ± 4.6	WHO	PCR-SSCP
Zaidi et al. [27]	UK	Caucasian	47	31.0 ± 5.5	45	30.2 ± 5.0	WHO	PCR-SSCP
Shaat et al. [15]	Sweden	Caucasian	642	NA	1,229	NA	DPSG-EASD	PCR–RFLP
Freathy et al. [23]	UK	Caucasian	614	NA	3,881	NA	IADPSG	Illumina
Freathy et al. [23]	Thailand	Asian	384	NA	1,706	NA	IADPSG	Illumina
Santos et al. [22]	Brazil	Caucasian	150	31.9 ± 6.2	600	25.2 ± 6.5	ADA	PCR–RFLP
Present study 2014	China	Asian	948	27.5 ± 5.6	975	24.1 ± 4.9	ADA	PCR–RFLP

ADA American Diabetes Association, *DPSG-EASD* Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes, *GDM* gestational diabetes mellitus, *IADPSG* new International Association of Diabetes and Pregnancy Study Groups, *NA* not available, *PCR–RFLP* polymerase chain reaction restriction fragment-length polymorphism, *PCR-SSCP* polymerase chain reaction–single strand conformation polymorphism, *SD* standard deviation, *WHO* World Health Organization

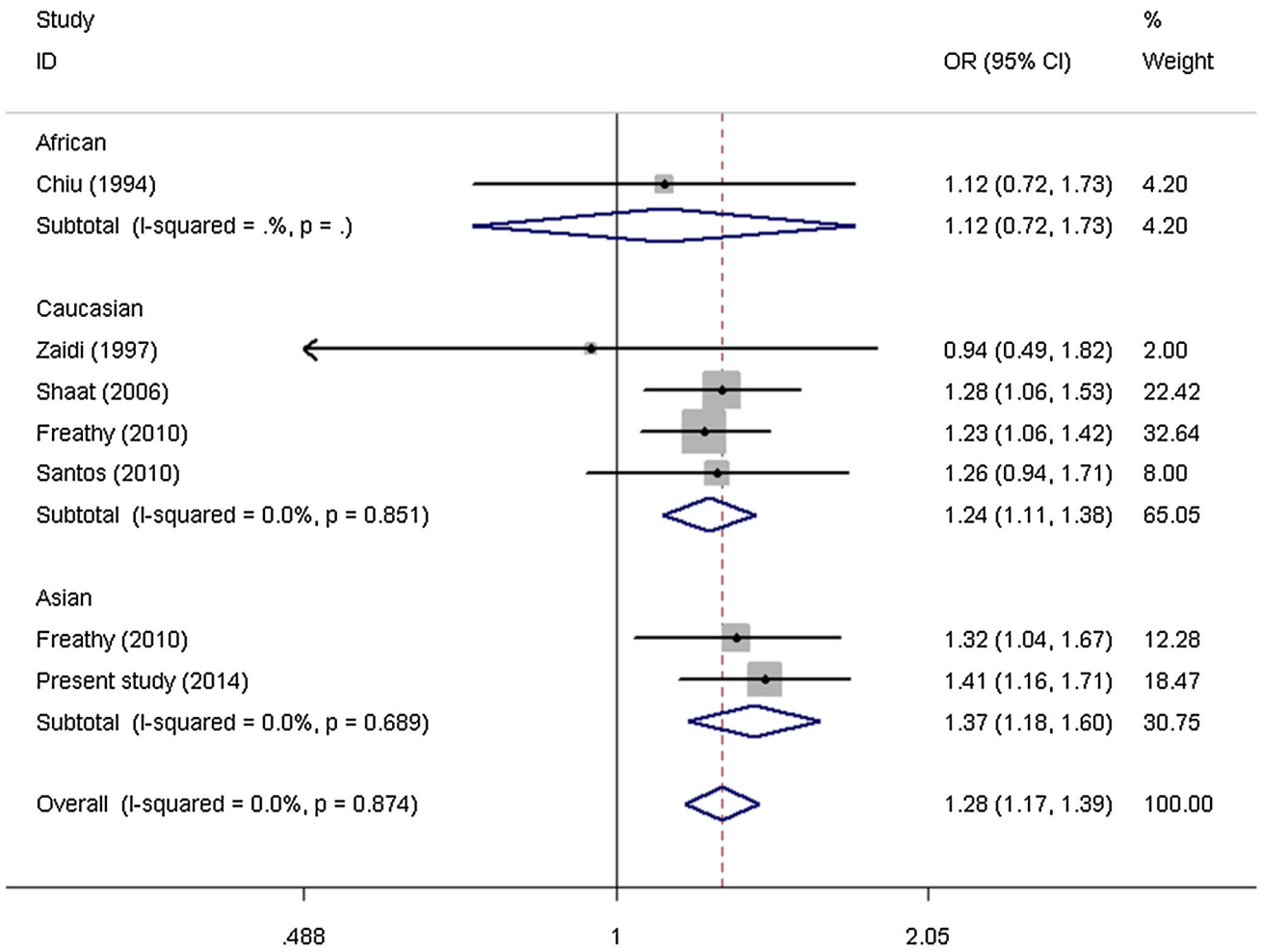

Fig. 2 Forest plots of the association between the glucokinase (GCK)-30G > A polymorphism and risk of GDM in allele comparison

limited sample size, poorly designed studies, false-positive studies, and different ethnicities. A meta-analysis method may permit the estimation of population-wide effects and the identification of sources of variability of genetic risk factors [33]. Therefore, we combined the genetic data from the included studies and present case–control study to

Table 3 Meta-analysis of the association between the GCK-30G > A polymorphisms and GDM

Comparison	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95 % CI	*P* value	Q test	*P* value	I^2
A-allele versus G-allele	Overall	7	1.28	1.17–1.39	<0.001	2.45	0.87	0.0 %
	Asian	2	1.37	1.18–1.60	<0.001	0.16	0.69	0.0 %
	African	1	1.12	0.72–1.73	0.618	NA	NA	NA
	Caucasian	4	1.24	1.11–1.38	<0.001	0.79	0.85	0.0 %
AA versus GA + GG	Overall	7	1.65	1.27–2.15	<0.001	2.05	0.92	0.0 %
	Asian	2	1.48	0.81–2.71	0.198	0.51	0.47	0.0 %
	African	1	1.43	0.27–7.54	0.670	NA	NA	NA
	Caucasian	4	1.71	1.27–2.30	<0.001	1.34	0.72	0.0 %
AA + AG versus GG	Overall	7	1.29	1.17–1.42	<0.001	3.29	0.77	0.0 %
	Asian	2	1.42	1.20–1.68	<0.001	0.06	0.81	0.0 %
	African	1	1.12	0.67–1.87	0.657	NA	NA	NA
	Caucasian	4	1.23	1.09–1.39	0.001	1.12	0.77	74.6 %
AA vs GG	Overall	7	1.75	1.34–2.28	<0.001	1.74	0.94	0.0 %
	Asian	2	1.60	0.88–2.92	0.127	0.52	0.47	0.0 %
	African	1	1.49	0.28–7.89	0.642	NA	NA	NA
	Caucasian	4	1.80	1.33–2.44	<0.001	1.05	0.79	0.0 %

OR odds ratio, *NA* not report, *CI* confidence interval, *GDM* gestational diabetes mellitus

evaluate the association of the rs1799884 polymorphism of the GCK gene to GDM with the help of a meta-analysis approach. Although seven comparisons were included in the present study, the study design of the original studies would be a limiting factor that exerts positive bias on the results. Genetic heterogeneity in the form of differences in the A-allele frequency of the rs1799884 polymorphism and the presence of admixture within the study populations could also be a source of heterogeneity influencing the conclusion of the present meta-analysis. Another potential explanation for the differences in the A-allele frequency is genotyping error, caused by different genotyping methods. To a certain degree, this could contribute to the variation in the A-allele frequency that we observed across the studies. Despite stratification by ethnicity, heterogeneity could not be absolutely omitted.

In the present study, stratification analyses were conducted to evaluate heterogeneity between studies. In the stratified analysis by ethnicity, a significant association was found in Caucasians and Asians for the polymorphism under most genetic models. However, no significant result was detected among Africans. The following items may account for such difference. (1) Different populations usually have different linkage disequilibrium patterns. The GCK-30G > A polymorphism may be in close linkage with different nearby causal variants in different populations. (2) The distribution of the A-allele varies extensively between different races. Further studies are still required to validate ethnic differences in the effect of this polymorphism on GDM. (3) Other clinical heterogeneity such as age, body mass index, years from onset, and disease severity may also explain the difference. Because only one study of Africans was included in the present meta-analysis. The exact conclusions of the meta-analysis in the African populations were doubtful due to the limited number of included studies.

Although stratification analyses were conducted, clinical heterogeneity cannot be resolved completely. Some degree of clinical heterogeneity was induced by the different genotyping method, severity of GDM, medical co-morbidities, nutritional status of patients and diagnostic criteria for GDM. Heterogeneity may also have been caused by different study design. Because of limited information got from original studies, heterogeneity cannot be completely resolved. Accordingly, although the results of the meta-analysis should be considered appropriate, methodological quality defects and clinical heterogeneity should be considered when interpreting the findings.

The limitations of this meta-analysis mainly include the following items: (1) The efficacy of the statistics may be further improved by including more studies in the future. The statistical power may be lower after subgroup analysis. Only one included study conducted in Africa cannot provide stable evidence. Further studies are still required in the future. (2) In the current meta-analysis, we only included published the English-language association studies of GCK-30G > A polymorphism and GDM. Thus, language bias may be an issue in the present study because it is exclusively based on the English-language reports. In addition, we may have missed some grey studies, including

negative results or unpublished studies. Our reasons for the reluctance to include grey literature included the absence of peer review of such unpublished literature. Meta-analysis of unpublished data from interested sources is a controversial issue. (3) Genetic association studies have generated some confusion over the years. Although a meta-analysis can be useful for obtaining a sufficient sample size, controversies may not be resolved without suitable genetic models and standardized genotyping. (4) Although a meta-analysis can extract several similar studies to increase the statistical power, heterogeneity among studies can introduce some bias. Stratification by ethnicity may help to improve homogeneity among studies, but it may also influence statistical power. (5) Only published studies were included, and as a result, publication bias may have occurred.

Conclusions

This study suggested that GCK-30G > A polymorphism was associated with the susceptibility of GDM in a Chinese population. The further meta-analysis provides additional evidence supporting the above result that the risk allele of the GCK-30G > A polymorphism may increase GDM risk. Due to the limited data currently available for Africans and Asians, further studies with large sample sizes are required.

Conflict of interest Each author certifies that he or she has no commercial associations that might pose a conflict of interest related to the submitted article.

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