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# Association of *CDKAL1* gene polymorphisms variations with gestational diabetes mellitus risk in women: A case-control study and meta-analysis

Watson Ray Gyan[1,2,3], Hengli Zhang[1,2,3], Taotao Shao[1,2], Taili Yang[3], Yue Wei[3], Mianqin Li[4*], Xiaoqun Che[5,6*], Qiaoli Zeng[1,2,3] and Runmin Guo[1,2*]

## Abstract

**Background** Gestational diabetes mellitus (GDM) has seen a significant rise and has become a growing concern worldwide, especially in Asian populations. Genetic factors, such as variations in the CDKAL1 gene, have been linked to its development. However, existing research on this connection is limited and inconclusive, highlighting the need for further investigation. This study aims to explore the association between CDKAL1 gene polymorphisms and GDM risk in a Chinese population using a comprehensive case-control study and meta-analysis.

**Methods** The SNPscan™ genotyping assay was used to genotype rs7754840 and rs7756992, in 502 control participants and 500 GDM patients. ANOVA, T-test, chi-square test, logistic regression, and other statistical tests were used to determine the differences in genotypes and alleles and their associations to the risk of GDM. Additionally, a meta-analysis of existing studies on CDKAL1 polymorphisms and GDM was performed to provide a broader context and resolve inconsistencies in the literature.

**Results** The GDM group had a significantly older average mean age and higher blood pressure, and fasting plasma glucose levels than the control group ($P < 0.05$). CDKAL1 rs7754840 showed significant associations under codominant homozygous model (CC vs. GG: OR = 1.748; 95% CI: 1.178–2.593; $P = 0.006$). After adjusting, these results indicated an association between CDKAL1 rs7754840 and increased risk of GDM in the codominant model (OR = 1.715; 95% CI: 1.133–2.595; $P = 0.011$). However, further analysis revealed no significant associations under all genetic models for CDKAL1 rs7756992. The study found that individuals under 30 with the rs7754840 CC genotype had higher fasting glucose and postprandial glucose levels ($P < 0.05$) compared to those with the GG genotype. Figure 3 A demonstrated a modest association between the CDKAL1 and GDM susceptibility (OR 1.16, 95% CI 1.104–1.29, $P = 0.0258$).

*Correspondence:
Mianqin Li
260278907@qq.com
Xiaoqun Che
xiaoqche@126.com
Runmin Guo
runmin.guo@gdmu.edu.cn

Full list of author information is available at the end of the article

**Conclusion** Individuals with the CDKAL1 rs7754840 polymorphism was associated to an increased risk of GDM, whereas rs7756992 did not show significant association with GDM risk. These results provide a theoretical foundation for GDM testing to mitigate its associated complications by enhancing our ability to predict, prevent and manage GDM. Ultimately improving outcomes for both mothers and their children. This research contributes to the growing evidence of genetic predisposition to GDM and highlights the importance of CDKAL1 as a potential genetic marker for GDM risk assessment.

**Keywords** Case-control study, CDKAL1 gene, Genetic association, Genetic risk factors, Gestational diabetes mellitus (GDM), Single nucleotide polymorphisms (SNP)

## Introduction

Gestational diabetes mellitus (GDM) is a type of diabetes that occurs by glucose intolerance that occurs during pregnancy. This condition presents significant health risks for both the mother and the baby. The global incidence of GDM is on the rise, particularly in Asian populations, including China and Japan. The development of GDM is influenced by a combination of genetic, environmental, and lifestyle factors [1]. Among the genetic factors contributing to GDM, single nucleotide polymorphisms (SNPs) in various genes, such as the CDKAL1 gene, have been identified as playing a role in the pathogenesis of the condition [2]. The dysfunction of β-cells, insulin resistance, and abnormal glucose utilization are primary causes of diabetes mellitus including GDM, although the complete understanding of its pathogenesis remains elusive [3–6]. In a study conducted on mice, the knockout of CDKAL1 (CDKAL1−/−) resulted in a reduction of mature insulin production in response to hyperglycemic conditions in pancreatic β-cells [7]. The prevalence of GDM has increased by approximately 30% in several countries in recent years, making it a major global health concern [8, 9]. Both genetic predisposition and environmental factors contribute to the onset of GDM, with specific genetic variants, including SNPs and other polymorphisms in different genes, being associated with the occurrence of the condition.

The CDKAL1 gene, is found on chromosome 6p22.3, it makes a protein involved in the modification of tRNA and is crucial for proper insulin secretion [10, 11]. Several genetic variations within the CDKAL1 gene, specifically SNPs, have been identified as contributing factors to type 2 diabetes (T2DM) [2]. More recent research has linked these same genetic variations to GDM [2]. Although many studies have investigated the connection between CDKAL1 polymorphisms and GDM, the exact nature of this relationship remains a subject of ongoing research, findings have been inconsistent. Some studies report a significant association, while others do not, suggesting the presence of population-specific genetic effects and potential interactions with environmental factors.

Previous studies have indicated that specific SNPs within intron 5 of the CDKAL1 gene are linked to the development of T2DM and GDM [2, 12–14]. Nevertheless, recent research by [15] did not find a relation between CDKAL1 and T2DM. A comprehensive analysis of existing literature reveals a lack of consistent evidence regarding the relationship between CDKAL1 polymorphisms and GDM. Past studies have produced conflicting results, potentially due to variations in research methodologies, sample sizes, ethnic backgrounds, and diagnostic criteria for GDM. This inconsistency highlights the necessity for well-designed studies with robust methodologies, and meta-analysis to clarify the genetic factors contributing to GDM.

This research aims to address these inconsistencies by conducting a comprehensive case-control study and meta-analysis to investigate the association between CDKAL1 gene polymorphisms and GDM risk in a Chinese Han population. By focusing on a well-defined ethnic group, this study seeks to clarify the role of CDKAL1 SNPs in GDM susceptibility and contribute to a more nuanced understanding of genetic risk factors for GDM.

This research aims to thoroughly examine the association between variations in the CDKAL1 gene and GDM among individuals of Chinese descent, using a comprehensive case-control study and meta-analysis. By addressing the limitations and contradictions of previous research, this study aims to enhance our understanding of the genetic factors contributing to GDM, ultimately informing better risk assessment, prevention, and management strategies for this increasingly prevalent condition and adds up to the current information in the area.

## Materials and methods

### The subject of study

For the research study, 1002 participants were enrolled, comprising 500 patients diagnosed with gestational diabetes mellitus (GDM) and 502 pregnant women diagnosed without GDM serving as control. The eligibility requirements were strict: individuals had to be ethnicity of Han Chinese, be at least eighteen years old, have voluntary written informed consent, have no history of complications in pregnancy, finally not using any glucose-lowering medications during pregnancy Fig. 1. The study was conducted from August 2021 to January 2022 at the Guangdong Medical University, Obstetrics Clinic at Shunde Maternal and Child Health Hospital.

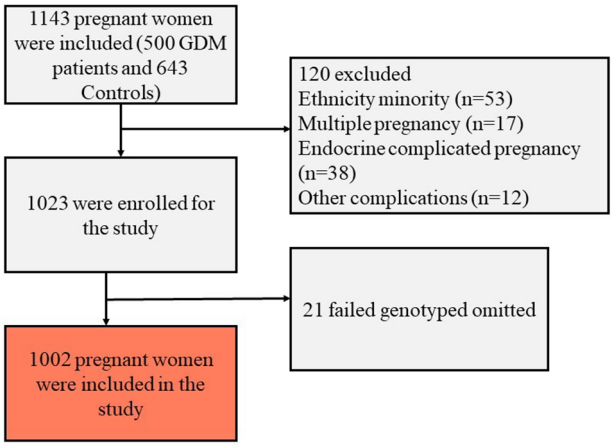


**Fig. 1** . Subject selection for the study was focused on Gestational Diabetes Mellitus (GDM)

Data collection occurred during the gestational period of 24–28 weeks, where all participants went through a routine 75 g of oral glucose tolerance test (OGTT). The diagnosis of GDM followed the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, which include fasting blood glucose (FBG) ≥ 5.1 mmol/L, 1-hour postprandial glucose (PG) ≥ 10.0 mmol/L, or 2-hour PG ≥ 8.5 mmol/L. Participants who met one or more of these criteria were diagnosed with GDM, whereas those in the control group did not exceed these thresholds. The research got approval from the Ethics Committee and adhered to the Declaration of Helsinki principles.

### Collection of vital clinical data

A comprehensive patient history was obtained by conducting individual interviews to gather demographic and clinical information for both the patients and control groups. This included details such as height, parity (primipara or multipara), age, pregestational weight, race, color, and blood pressure, along with other clinical vitals. These assessments were conducted during the 24–28 gestational weeks. The collected data was then utilized to calculate the (pre-BMI, Kg/$m^2$) pregestational body mass index = pregestational weight (kg) / height ($m)^2$. To determine the obesity status according to Chinese standards, the following criteria were employed: went through (< 18.5 Kg/$m^2$), normal (18.5–24.9 Kg/$m^2$), overweight (25-29.9 Kg/$m^2$), and obese (≥ 29 kg/$m^2$). This classification method was adopted based on the research conducted by [16].

### Single nucleotide polymorphism (SNP) genotyping

A methodical approach was used for genotyping and tag single-nucleotide polymorphism (SNP) selection. The SNPinfo, NCBI-dbSNP, and HapMap databases were utilized to analyze potential single nucleotide polymorphisms (SNPs) within the CDKAL1 gene. The HapMap project in 2002 focused on SNP with a MAF of at least 5% to identify high-frequency variants with significant effects and explore the relationship between rare mutations and diseases within the population. Through a genome-wide association study (GWAS) of Type 2 Diabetes Mellitus (T2DM) and MAF greater than 0.05 in the Asian population, along with a comprehensive review of relevant literature by [1, 17, 18] two candidate SNPs (rs7754840 and rs7756992) potentially associated with GDM risk were identified. During recruitment, two milliliters of fasting peripheral venous blood were collected in an EDTA anticoagulant tube. The samples were then processed, put in a small tube EP 1.5 mL and kept in a freezer at -80 °C until further analysis. Using a linkage disequilibrium criterion of $r^2 \geq 0.8$, SNPs of the CDKAL1 gene between 30 kb upstream and 30 kb downstream were chosen from the HapMap Phase III JPT + CHB database [19]. The QIAamp DNA Blood Kit from Qiagen, Germany was used to extract genomic DNA from blood cells, and Genesky Technologies Inc., Shanghai, China's SNPscan technique was used for genotyping. In order to ensure quality control, 5% of the samples were randomly selected and genotyped twice.

### Statistical analysis

SPSS 20.0 software was used to analyse the data. A *P*-value below 0.05 indicated a statistically significant. The independent sample t-test or $\chi^2$ test was utilized to evaluate disparities in genotypic distribution of candidate SNPs, allele frequency, and demographic factors between the GDM and control groups. The data was categorized and presented as frequency (n) and percentage (%), while quantitative data was presented as mean ± SD ($\bar{x} \pm$ SD). The Hardy-Weinberg equilibrium was checked in the control subject using the Pearson's chi-squared test. A value of *P* greater than 0.05 was used as a threshold to determine if the equilibrium was present. The ones that that didn't follow the normal distribution was also analysed with nonparametric tests. Through the utilization of multivariate logistic regression analysis, we assessed the comprehensive association between genotypes and GDM across various six genetic models including codominant heterozygous, recessive, overdominant, codominant homozygous, allele, and dominant. One-way analysis of variance (ANOVA) with dunnett-t method and post-hoc LSD tests was used to examine the associations between SNP variants and variables like glucose levels, neonatal weight, and maternal glucose (MG) concentrations. In order to evaluate the linkage disequilibrium (LD) between SNPs in the GIP gene, we utilized the online software SHesis available at (http://analysis.bio-x.cn/myAnalysis.php). Variables with skewed distributions were $\log^{10}$-transformed. To account for potential factors that

**Table 1** Fundamental and stratification characteristics of individuals of the study

| Variables | Healthy control (502) | GDM cases (500) | t/x2 | *P* |
|---|---|---|---|---|
| Age, year (mean ± SD) | 29 ± 4.0 | 31 ± 4.0 | -8.56 | < 0.001 |
| pre-BMI, kg/m$^2$ | 20.53 ± 2.58 | 21.51 ± 3.10 | -5.42 | < 0.001 |
| FPG, mmol/L | 4.50 ± 0.31 | 4.82 ± 0.64 | -9.65 | < 0.001 |
| 1 h-PG, mmol/L | 7.66 ± 1.27 | 10.17 ± 1.60 | -26.32 | < 0.001 |
| 2 h-PG, mmol/L | 6.69 ± 0.99 | 8.91 ± 1.60 | -25.85 | < 0.001 |
| SBP, mmHg | 114 ± 10 | 117 ± 11 | -3.53 | < 0.001 |
| DBP, mmHg | 68 ± 7.0 | 70 ± 8.0 | -3.23 | 0.001 |
| **Age Category** | | | | |
| Age, year | | | | |
| < 30 | 26 ± 3.0 | 27 ± 2.0 | -3.64 | < 0.001 |
| ≥ 30 | 33 ± 2.0 | 34 ± 3.0 | -3.14 | 0.002 |
| **pre-BMI, Category (kg/m$^2$)** | | | | |
| < 18.5 | 17.60 ± 1.50 | 17.45 ± 0.84 | 0.75 | 0.45 |
| 18.5 ≤ BMI < 24 | 20.67 ± 1.41 | 20.96 ± 1.49 | -2.63 | 0.009 |
| ≥ 24 | 25.83 ± 3.31 | 26.16 ± 2.84 | -0.60 | 0.548 |
| **Parity (n)** | | | 8.88 | 0.003 |
| Primipara | 258(51.4) | 210(42.1) | | |
| Multipara | 244(48.7) | 290(58.0) | | |

Data are presented as mean ± SD. Diastolic blood pressure = DBP, systolic blood pressure = SBP, fasting plasma glucose = FPG, 1-hour postprandial glucose = 1 h-PG, and 2-hour postprandial glucose = 2 h-PG

could influence the results, logistic regression was used. It helped adjust for the potential confounders. Odds ratios and their 95% confidence intervals were calculated to determine the risk of GDM. Calculations of the frequency distribution did not include haplotypes whose frequency was less than 0.03. To create statistical graphs, GraphPad Prism version 5.01 software was utilized. (GraphPad Software Inc., San Diego, CA, USA), and pre-BMI and age-based subgroup analyses were carried out.

### Meta-analysis

This meta-analysis exclusively included articles written and published in the English language. A wide-ranging literature search was done utilizing Google Scholar, Medline, PubMed databases, and NCBI to gather information on the combination of the genetic variants rs7754840 and rs7756992, in relation to GDM, type 2 diabetes mellitus (T2DM). The meta-analysis examined the association of two genetic variants with the T2DM and GDM. The included studies were case-control and cohort designs. Only studies that provided enough raw data for further analysis and discussion were considered. Research that did not follow the proper diagnostic criteria or had data that did not follow the expected pattern of genetic variation (Hardy-Weinberg equilibrium) were omitted. Data extraction was performed by four authors, and meta-analyses were conducted using fixed and random effect models to analyze six genetic models, examining on the extent diversity of heterogeneity. To examine publication bias, we utilised Egger's and Begg's tests in the meta-analyses, which were conducted using STATA version 16.0. This study aimed to provide a thorough analysis of the genetic variants rs7754840 and rs7756992 in relation to T2DM, and GDM, utilizing a systematic approach to gather and analyze relevant literature.

**Table 2** Single nucleotide polymorphisms results and the HWE analysis in the control groups

| SNP | Min/Maj | Chr. location | MAF (Control) | HWE (*P*) |
|---|---|---|---|---|
| **rs7754840** | CG | chr6:20661019 | 0.338 | 0.842 |
| **rs7756992** | GA | chr6:20679478 | 0.448 | 0.207 |

SNP = single nucleotide polymorphisms, Hardy–Weinberg equilibrium = HWE, minor allele = Min, major allele = Maj, MAF = frequency of minor allele

## Results

### General medical details of the study subjects

The current research examined a total of 1,002 participants, consisting of 502 non-GDM controls and 500 cases with gestational diabetes mellitus (GDM), to assess the CDKAL1 genotype. Table 1 shows the clinical data, including stratified characteristics. Interestingly, the GDM group had a significantly higher average mean age of 31.40 ± 40 years compared to the control group, which had a smaller average mean age of 29.00 ± 40 years ($P < 0.001$). Additionally, the GDM cases group exhibited a notable increase in pre-pregnancy BMI than the control group (20.53 ± 2.58 vs. 21.51 ± 3.10; $P < 0.001$). Furthermore, the GDM group had higher blood pressure, fasting plasma glucose (FPG), 1-hour postprandial glucose (1 h-PG), and 2-hour postprandial glucose (2 h-PG) than to the control group ($P < 0.05$). The study further stratified the participants by age and pre-BMI categories, revealing significant differences in glucose levels and blood pressure within these strata, indicating that age and BMI are significant factors in GDM risk. The distribution between primipara (first-time mothers) and multipara (mothers who have given birth more than once) showed significant differences between the healthy controls and GDM cases, with the GDM group having a greater proportion of women who have given birth multiple times (multipara), suggesting a potential correlation between parity and GDM.

### The association between genetic variations and the likelihood of developing gestational diabetes mellitus in all subjects

Table 2 provides information on the minor allele frequency, chromosomal location, and Hardy-Weinberg equilibrium status for two single nucleotide polymorphisms in the control group. The HWE analysis showed a significant conformity ($P > 0.05$).

### The association between genetic variations in the CDKAL1 gene and the risk of developing GDM in the general subjects

The results of Table 3 and 4 show the odds ratios, confidence intervals, and *p*-values for the relationship between CDKAL1 gene variants and GDM. These statistics were calculated using six different genetic models. In the case of CDKAL1 rs7756992, there was no significant association in any of the genetic models after adjustment for confounders, signifying that this SNP may have a minimal impact on GDM risk in the current study. However, analysis revealed significant associations under certain genetic models for SNP rs7754840. The CC genotype significantly increases the risk of GDM (Adjusted OR = 1.715, $P = 0.011$) compared to the GG genotype. The C allele is associated with a increased risk of GDM (Adjusted OR = 1.313, $P = 0.003$). The current study shows a significant association of SNP rs7754840 in the CDKAL1 gene with GDM risk.

### The SNPs in the CDKAL1 gene and their association to the risk of gestational diabetes mellitus in women who are 30 or older

Our stratified analysis by age and pre-pregnancy BMI revealed that the SNPs rs7754840 and rs7756992 were not associated with GDM in individuals aged 30 or older. Additionally, after accounting for relevant factors, rs7756992 was not consistently linked to an increased risk of GDM in any age group. Supplementary Table 1 (ST1) indicates that no notable associations were identified among individuals younger than 30. The results revealed that among individuals aged ≥ 30 years, the SNPs rs7754840 and rs7756992 in the CDKAL1 gene do not exhibit significant associations with the risk of developing GDM.

### The association between genetic variations (SNPs) and blood glucose levels

The current rsearch assessed the association between the CDKAL1 variations and glucose levels in pregnant women. They focused on two age groups: younger than 30 and 30 or older Table 5. The findings revealed that individuals aged below 30 years (< 30 years) with the rs7754840 CC genotype having a higher glucose level than those with GG genotype ($P < 0.05$). The CC genotype had significantly higher PG levels than the GC and GG genotypes, both for one hour and two hours after test. In individuals aged 30 years and older, no significant differences were observed among the genotypes for fasting plasma glucose (FPG), 1 h-PG, or 2 h-PG levels. The rs7756992 genetic variant did not appear to influence blood glucose levels (fasting, 1-hour, or 2-hour post-meal) in participants of any age Table 5.

### Linkage disequilibrium analyses and meta-analysis results

Additionally, an assessment was conducted to determine the linkage disequilibrium (LD) between the single nucleotide polymorphisms (SNPs). To obtain the LD coefficient D, the SHEsis program was employed. The current study's findings revealed a robust linkage disequilibrium ($D' > 0.82$) between two single nucleotide polymorphisms (SNPs), namely rs7754840 and rs7756992. This shows there is a difference in loci in the LD. This observation is depicted in Fig. 2, where the strong linkage between these SNPs is evident.

The final meta-analysis consisted of four studies examining the associations between rs7754840 and rs7756992 and diabetes mellitus (gestational diabetes mellitus (GDM) and type 2 diabetes mellitus (T2DM)). Detailed characteristics of the studies features can be found in Supplementary Table 2 (ST2). Overall, Fig. 3A demonstrated a modest association between the dominant model of CDKAL1 and GDM susceptibility (OR 1.16, 95% CI 1.104–1.29, $p = 0.0258$). While the statistical significance of the effect was established, its practical relevance was deemed limited due to its relatively small impact. Moreover, an analysis of other genetic models did not reveal any notable variations. The results from Eggers tests (all $P > 0.05$) consistently indicated the absence of publication bias. No significant association was observed in CDKAL1 rs7754840 after meta-analysis was done Fig. 3.

## Discussion

Gestational Diabetes Mellitus (GDM) is a significant public health concern, affecting a substantial proportion of pregnancies worldwide. GDM and Type 2 Diabetes Mellitus (T2DM) are complex disorders with multifactorial and polygenic origins, characterized by similar pathophysiological pathways [4–6]. Numerous studies have revealed a common genetic predisposition for both T2DM and GDM across diverse populations [20–23]. While its etiology is multifactorial, the present study aimed to compare clinical characteristics between GDM cases and healthy controls.

The current study assessed the relationship between the CDKAL1 gene and the risk of GDM. A total of 502 healthy pregnant women without a history of GDM in previous pregnancies or current signs of GDM were enrolled, along with 500 GDM cases. When comparing the healthy control group to the GDM cases, we found significant differences in average age, pre-pregnancy weight, fasting blood glucose, and diastolic blood pressure Table 1.

The presented data revealed statistically significant differences between GDM cases and healthy controls across multiple parameters. Notably, GDM cases exhibited higher mean age, pre-pregnancy BMI, fasting plasma

**Table 3** The association between genetic variations (SNPs) in the CDKAL1 gene and the likelihood of developing gestational diabetes mellitus in the general subjects

| Model | Control (Genotype Freq. &%) | GDM patients (Genotype Freq. &%) | Crude OR | Crude *P* | Adjusted OR | Adjusted *P* |
|---|---|---|---|---|---|---|
| | *N* = 502 | *N* = 500 | (95% CI)1 | | (95% CI)1 | |
| **rs7754840 G > C** | | | | | | |
| **Codominant Model** | | | | | | |
| **GG** | 219 (45.33) | 179(35.80) | 1(ref) | | 1(ref) | |
| **GC** | 228 (43.54) | 241(48.20) | 1.316 (1.095–1.581) | 0.0034 | 1.251 (0.943–1.660) | 0.121 |
| **CC** | 56 (11.13) | 80(16.00) | 1.748 (1.178–2.529) | 0.006 | 1.715 (1.133–2.595) | 0.011 |
| **Allele Model** | | | | | | |
| **G** | 665 (66.2) | 599 (59.9) | 1(ref) | | 1(ref) | |
| **C** | 339 (33.7) | 401 (40.1) | 1.313 (1.095–1.575) | 0.003 | 0.767 (0.633–0.928) | 0.006 |
| **Dominant Model** | | | | | | |
| **GG** | 219(45.33) | 179(35.80) | 1(ref) | | 1(ref) | |
| **CC + GC** | 283 (56.37) | 321 (64.2) | 1.388 (1.076–1.789) | 0.11 | 0.745 (0.570–0.975) | **0.**032 |
| **Recessive Model** | | | | | | |
| **GC + GG** | 446 (88.84) | 420 (84.00) | 1(ref) | | 1(ref) | |
| **CC** | 56 (11.13) | 80(16.00) | 1.517 (1.051–2.189) | 0.026 | 0.659 (0.449–0.968) | 0.034 |
| **Over dominant Model** | | | | | | |
| **CC + GG** | 275 (54.78) | 259 (51.8) | 1(ref) | | 1(ref) | |
| **GC** | 228(43.54) | 241(48.20) | 0.887 (0.692–1.137) | 0.344 | 0.920 (0.708–1.194) | 0.529 |
| **rs7756992 A > G** | | | | | | |
| **Codominant Model** | | | | | | |
| **AA** | 160 (31.87) | 141 (28.20) | 1(ref) | | 1(ref) | |
| **AG** | 234 (46.61) | 244 (48.80) | 1.105 (0.93–1.313) | 0.256 | 0.973 (0.696–1.360) | 0.871 |
| **GG** | 108 (21.51) | 115 (23.00) | 0.828 (0.585–1.171) | 0.285 | 0.833 (0.578-1.200) | 0.325 |
| **Allele Model** | | | | | | |
| **A** | 554 (55.10) | 526 (52.60) | 1(ref) | | 1(ref) | |
| **G** | 450 (44.80) | 474 (47.70) | 1.109 (0.9306–1.468) | 0.247 | 0.889 (0.739–1.070) | 0.212 |
| **Dominant Model** | | | | | | |
| **AA** | 160 (31.87) | 141 (28.20) | 1(ref) | | 1(ref) | |
| **GG + AG** | 342 (68.13) | 359 (71.80) | 1.91 (0.9088–1.561) | 0.205 | 0.848 (0.638–1.128) | 0.258 |
| **Recessive Model** | | | | | | |
| **AG + AA** | 394 (78.49) | 385 (77.00) | 1(ref) | | 1(ref) | |
| **GG** | 108 (21.51) | 115 (23.00) | 1.09 (0.809–1.468) | 0.5718 | 0.916 (0.669–1.254) | 0.583 |
| **Overdominant Model** | | | | | | |
| **GG + AA** | 268 (53.39) | 256 (51.20) | 1(ref) | | 1(ref) | |
| **AG** | 234 (46.61) | 244 (48.80) | 0.916 (0.715–1.174) | 0.488 | 0.925 (0.713–1.202) | 0.560 |

To identify factors associated to the outcome, we used multiple logistic regression analyses. The models included adjustments for age, pre-pregnancy body mass index, systolic and diastolic blood pressure, and parity. Variables with *p* values of 0.05 or lower were considered statistically significant

glucose (FPG), and one-hour and two-hour post-glucose plasma glucose levels (1 h-PG, 2 h-PG). These findings align with the research conducted by [22, 24], which identified pre-BMI, maternal age, BMI, and obesity as major risk factors for GDM. Interestingly, a study by [25] suggested that pre-pregnancy BMI is a risk factor for GDM in early pregnancy. Furthermore, systolic and diastolic blood pressure (SBP, DBP) were elevated in the GDM group. These findings align with the established literature on GDM, which consistently reports associations between these factors and the development of the condition [26].

The stratification of data by age category provided additional insights. While both younger and older GDM cases displayed elevated glucose levels compared to their age-matched controls, the magnitude of these differences was more pronounced in the younger group. This observation suggests that younger women may be particularly susceptible to the development of GDM, a finding that warrants further investigation.

The underlying mechanisms linking the observed variables to GDM are complex and multifaceted. Insulin resistance, a hallmark of GDM, is influenced by various factors, including genetic predisposition, obesity, and inflammation [2]. The increased BMI in GDM cases likely contributes to insulin resistance through adipose tissue-derived adipokines and chronic low-grade inflammation [27, 28]. used Homeostasis of Model Assessment -Insulin Resistance (HOMA-IR) to observe the importance of taking into account age risk groups and BMI when predicting GDM. The authors revealed that women with a normal BMI tend to have better outcomes with lower cut-offs. However, in cases of advanced maternal age, the use of HOMA-IR does not yield accurate predictions for GDM, as evidenced in our current study. Additionally, the higher FPG and post-load glucose levels indicate impaired glucose tolerance and beta-cell dysfunction, which are core features of GDM [29]. The role of hypertension in GDM pathogenesis is less clear, but it may contribute to endothelial dysfunction and oxidative stress, exacerbating insulin resistance [30].

The findings of this study highlight the need of early identifying and addressing risk factors associated with GDM. Pregnant women should routinely be screened for GDM, paying special attention to those who have a history of obesity, impaired glucose tolerance, or diabetes in their family. The prevention or delay of GDM and its accompanying consequences is mostly dependent on lifestyle treatments, such as physical exercise and weight management [2]. Furthermore, the statistics imply that more stringent screening and preventive actions might be necessary for younger women.

It is recommended that future research focus on identifying early biomarkers of GDM using proteomics and metabolomics to enhance our understanding of the disorder's pathophysiology. Additionally, further investigation is required to ascertain the long-term metabolic impacts of GDM on both the mother and her offspring.

The results of the current case-control study indicate that there is an association between CDKAL1 rs7754840 and the risk of GDM in the overall subject Table 3. The CC genotype significantly increases the risk of GDM (Adjusted OR = 1.715, $P = 0.011$) compared to the GG genotype. This current finding was consistent with a study conducted by [31, 32], in which the authors found a correlation between CDKAL1 rs7754840 and type 2 diabetes in the Chinese population. Insulin resistance and decreased insulin secretion are key characteristics of GDM [33]. Variants in the CDKAL1 gene have the potential to impact the expression of CDKAL1, leading to compromised $\beta$-cell activity and insulin production. Research conducted by [34] found that the CDKAL1 variant rs7754840 is linked to reduced fasting insulin levels and alterations in the homeostasis model for β-cell function (HOMA-β). Mutations in the intron region of genes, as highlighted in a study by [35], can disrupt the splicing pattern of pre-mRNAs, potentially leading to splicing errors and incorrect transcript products that impact gene function.

Besides, our study observed significant differences in allele frequencies and genotype frequencies between the GDM and non-GDM groups in Chinese pregnant women. However, these differences were not statistically significant ($P > 0.05$). These findings align with the research conducted by [36], further supporting the notion that the common susceptibility rs7754840 in CDKAL1 is indeed associated with GDM. Current findings suggest that CDKAL1 rs7756992 found no association in the dominant model against GDM. In a study conducted by [37], no significant correlation was found between CDKAL1 and T2DM. However, their researchers did observe that pregnant women in the study carried the risk alleles for T2D, specifically rs7754840 (C) and rs10811661 (T). While previous research has identified certain loci associated with GDM susceptibility, it's still unclear how these specific genetic markers influence the CDKAL1 gene's function and contribute to the development of the condition. Additional studies are needed to fully elucidate the biological mechanisms involved.

According to [14], the diagnosis of optimal glucose tolerance is achieved when plasma glucose values are below the threshold values, and vice versa. The findings of Wang et al. [38] revealed a link between the rs7754840 and elevated fasting glucose levels in overweight pregnant women. Our current research further supports these findings, that this genetic variant is linked to a higher fasting glucose and glucose levels measured one and two hours after eating. These findings align with the

**Table 4** The association between genetic variations (SNPs) in the CDKAL1 gene and the risk of developing GDM in the age 30 or older

| Model | Control (Genotype Freq. & %) | GDM patients (Genotype Freq. & %) | Crude OR | Crude *P* | Adjusted OR | Adjusted *P* |
|---|---|---|---|---|---|---|
| | *N* = 198 | *N* = 308 | (95% CI)1 | | (95% CI)1 | |
| **rs7754840 G > C** | | | | | | |
| **Codominant Model** | | | | | | |
| **GG** **85 (42.93)** | | 111(36.04) | 1(ref) | | 1(ref) | |
| **CG** **88 (44.44)** | | 148(48.05) | 1.288 (0.875–1.896) | 0.200 | 1.282 (0.862–1.907) | 0.220 |
| **CC** **25(12.63)** | | 49(15.91) | 1.501 (0.859–2.623) | 0.154 | 1.538 (0.868–2.727) | 0.140 |
| **Allele Model** | | | | | | |
| **G** | 258(65.1) | 370(60) | 1(ref) | | 1(ref) | |
| **C** | 138(34.8) | 246(39.9) | 1.243 (0.956–1.616) | 0.104 | 0.795 (0.608–1.039) | 0.093 |
| **Dominant Model** | | | | | | |
| **GG** | 85 (42.93) | 111(36.04) | 1(ref) | | 1(ref) | |
| **CC + GC** | 113 (57.07) | 197 (63.96) | 1.335 (0.927–1.923) | 0.121 | 1.342 (0.922–1.952) | 0.125 |
| **Recessive Model** | | | | | | |
| **GC + GG** | 173 (87.37) | 259 (84.09) | 1(ref) | | 1(ref) | |
| **CC** | 25(12.63) | 49(15.91) | 1.309 (0.779–2.199) | 0.309 | 1.360 (0.801–2.309) | 0.254 |
| **Over dominant Model** | | | | | | |
| **CC + GG** | 110 (55.56) | 160 (51.95) | 1(ref) | | 1(ref) | |
| **GC** | 88(44.44) | 148(48.05) | 0.865 (0.604–1.238) | 0.427 | 1.38 (0.787–1.643) | 0.493 |
| **rs7756992 A > G** | | | | | | |
| **Codominant Model** | | | | | | |
| **AA** | 65(32.83) | 90(29.22) | 1(ref) | | 1(ref) | |
| **AG** | 88(44.44) | 148(48.05) | 1.215 (0.803–1.838) | 0.357 | 1.179 (0.773–1.799) | 0.445 |
| **GG** | 45(22.73) | 70(22.73) | 1.123 (0.687–1.837) | 0.643 | 1.165 (0.698–1.943) | 0.559 |
| **Allele Model** | | | | | | |
| **A** | 218(0.55) | 328(0.532) | 1(ref) | | 1(ref) | |
| **G** | 178(0.449) | 288(0.467) | 1.075 (0.835–1.386) | 0.574 | 1.076 (0.830–1.394) | 0.580 |
| **Dominant Model** | | | | | | |
| **AA** | 65(32.83) | 90(29.22) | 1(ref) | | 1(ref) | |
| **GG + AG** | 133 (67.17) | 218 (70.78) | 1.184 (0.805–1.740) | 0.390 | 1.161 (0.783–1.721) | 0.457 |
| **Recessive Model** | | | | | | |
| **AG + AA** | 153 (77.27) | 238 (77.27) | ref | | Ref | |
| **GG** | 45(22.73) | 70(22.73) | 1.000 (0.653–1.531) | 1.000 | 1.025 (0.663–1.585) | 0.912 |
| **Overdominant Model** | | | | | | |
| **GG + AA** | 110 (55.56) | 160 (51.95) | 1(ref) | | 1(ref) | |
| **AG** | 88(44.44) | 148(48.05) | 1.156 (0.808–1.655) | 0.427 | 1.118 (0.775–1.614) | 0.551 |

To identify factors associated to the outcome, we used multiple logistic regression analyses. The models included adjustments for age, pre-pregnancy body mass index, systolic and diastolic blood pressure, and parity. Variables with *p* values of 0.05 or lower were considered statistically significant

**Table 5** The association between genetic variations (SNPs) and blood glucose levels

| Genotype | FPG (mmol/L) | 1 h-PG (mmol/L) | 2 h-PG (mmol/L) |
|---|---|---|---|
| **rs7754840 G > C** | | | |
| **Years (Age < 30)** | | | |
| **GG** | 4.65 ± 0.06 | 8.36 ± 0.16 | 7.24 ± 0.13[a] |
| **GC** | 4.58 ± 0.03 | 8.50 ± 0.11 | 7.39 ± 0.09[ab] |
| **CC** | 4.71 ± 0.08 | 8.66 ± 0.26 | 7.85 ± 0.24[b] |
| **F** | 1.10 | 0.64 | 3.25 |
| ***P*** | < 0.05 | < 0.05 | < 0.05 |
| **Age (years) ≥ 30** | | | |
| **GG** | 4.72 ± 0.03 | 9.46 ± 0.14 | 8.16 ± 0.14 |
| **GC** | 4.70 ± 0.03 | 9.52 ± 0.11 | 8.40 ± 0.11 |
| **CC** | 4.69 ± 0.05 | 9.62 ± 0.22 | 8.64 ± 0.18 |
| **F** | 0.23 | 0.19 | 2.23 |
| ***P*** | > 0.05 | > 0.05 | > 0.05 |
| **rs7756992 A > G** | | | |
| **Age (years) < 30** | | | |
| **AA** | 4.63 ± 0.08 | 8.37 ± 0.19 | 7.39 ± 0.16 |
| **AG** | 4.63 ± 0.03 | 8.54 ± 0.12 | 7.37 ± 0.10 |
| **GG** | 4.62 ± 0.04 | 8.44 ± 0.18 | 7.44 ± 0.15 |
| **F** | 0.01 | 0.37 | 0.07 |
| ***P*** | > 0.05 | > 0.05 | > 0.05 |
| **Age (years) ≥ 30** | | | |
| **AA** | 4.72 ± 0.03 | 9.40 ± 0.16 | 8.09 ± 0.15 |
| **AG** | 4.71 ± 0.03 | 9.63 ± 0.12 | 8.48 ± 0.12 |
| **GG** | 4.70 ± 0.04 | 9.44 ± 0.16 | 8.41 ± 0.16 |
| **F** | 0.04 | 0.86 | 2.35 |
| ***P*** | > 0.05 | > 0.05 | > 0.05 |

[a] the impact of rs7754840 genotypes on blood glucose levels was investigated using LSD. Statistically significant differences in blood glucose were observed between individuals with GG and CC genotypes ($P < 0.05$)

results of previous studies conducted by [39]. Our results also indicate that high glucose levels are associated with the C allele of the rs7754840 locus, which is consistent with the findings of [14, 39, 40]. It is possible that the CDKAL1 rs7754840 G allele disrupts the normal secretion of insulin. The role of CDKAL1 in the association and pathogenesis of GDM may stem from its ability to regulate insulin secretion even in glucotoxic conditions [41, 42]. This regulation of insulin secretion by CDKAL1 is believed to play a significant role in the development of GDM. We propose conducting further studies in this area in the future to enhance our understanding of the mechanism by which CDKAL1 plays a role in the development of GDM.

The current meta-analysis focuses on the CDKAL1 rs7754840 variation, contributing to the expanding research on the genetic factors associated with GDM. Figure 3A indicates a modest association and increase in GDM risk, with an overall effect size (OR) of 1.16 (95% CI: 1.04–1.29, $P = 0.0258$). Although statistically significant, the effect is modest, indicating a minimal clinical impact. Similar patterns have been observed in studies by [36, 43], although the magnitude of the effects varied, suggesting a potential role of CDKAL1 gene in glucose metabolism. This variation may be attributed to genetic factors specific to certain populations or differences in study methodologies. Studies by [14] and [40] have also reported odds ratios close to unity, suggesting that CDKAL1 may play a role in GDM. However, the specific role of CDKAL1 in GDM has been less extensively studied. While the observed association between CDKAL1 rs7754840 and GDM is statistically significant, its clinical utility is limited due to the small effect size. Currently, genetic testing for CDKAL1 is not recommended for GDM risk prediction in routine clinical practice. However, larger-scale studies are required to confirm these findings and to assess the potential interaction of CDKAL1 with other genetic and environmental risk factors for GDM.

The CDKAL1 gene is widely recognized for its importance in the biosynthesis of insulin within pancreatic beta cells. As noted by [44] CDKAL1 is involved in the modification of tRNA, which is crucial for the accurate translation and processing of proinsulin into insulin. Disruption caused by specific variants, such as rs7754840, may impair insulin secretion and potentially play a role in the pathophysiology of GDM during the insulin-resistant stages of pregnancy. While this mechanism has been established in the context of type 2 diabetes, further research on GDM is needed to confirm its relevance. It is recommended that additional studies be conducted to investigate the potential interactions between CDKAL1 variants and lifestyle factors, such as diet and exercise, in influencing the risk of GDM. Furthermore, tracking postpartum women from conception to delivery can assist in detecting alterations in the timing of genetic impacts on glucose metabolism. Lastly, conduct comprehensive functional analyses to delineate the biological pathways affected by the variant, potentially utilizing beta-cell models and CRISPR-Cas9 gene editing techniques. While the CDKAL1 rs7754840 variant may have a genetic predisposition to GDM susceptibility, our study's limited correlations indicate that interpretation should be approached with caution.

Despite these findings, the study has some limitations. A larger group of participants should be examined to verify our results which is one of the limitations of our current study. Additionally, the lack of fasting insulin data prevented us from accurately measuring pancreatic islet beta-cell function. We also acknowledge that our findings may not be fully representative of the entire GDM population, particularly those requiring insulin therapy. Therefore, we propose future study to encompass GDM patients requiring insulin therapy in order to compare and contrast the findings. Lastly, because the study's participants were restricted to Chinese people, more


**Fig. 2** Illustrates the association between genetic variations (rs7754840 G/C and rs7756992 A/G) within the CDKAL1 gene, as measured by linkage disequilibrium (LD) using the D'and R2 tests

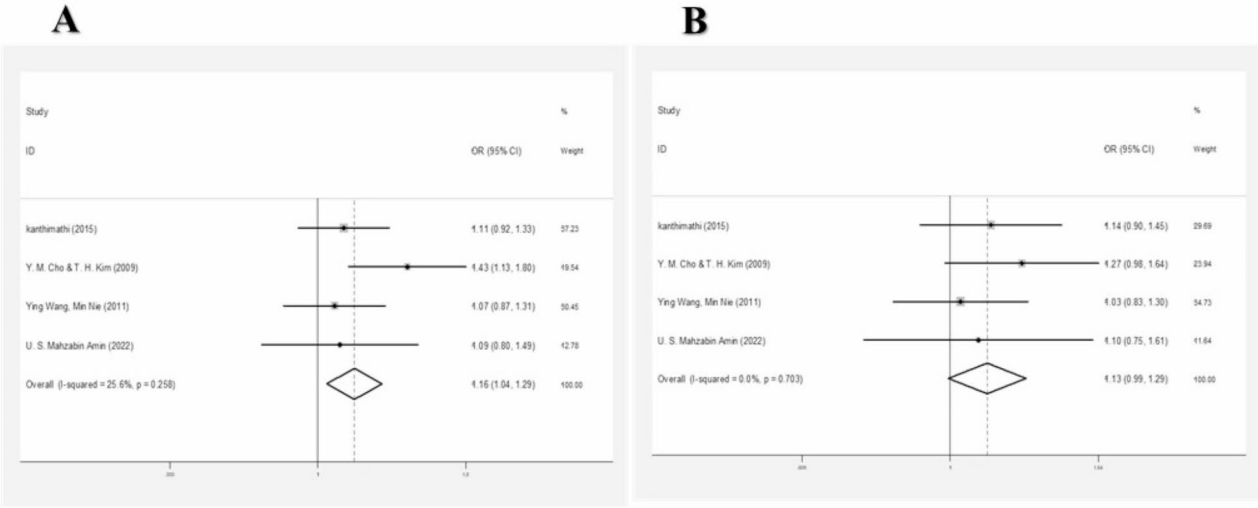


**Fig. 3** A meta-analysis examined the relationship between the CDKAL1 rs7754840 genetic variant and the risk of gestational diabetes mellitus. Using a fixed-effects model, the analysis focused on two genetic models: (**A**) a dominant model comparing individuals with at least one copy of the GC or CC to those with two copies of the GG, and (**B**) a codominant model comparing individuals with one copy of the GC to those with two copies of the GG. The results, presented in Fig. 3, show the odds ratios (ORs) and corresponding confidence intervals (CIs) for each genetic model. Additionally, the I-squared statistic was calculated to assess the level of heterogeneity among the included studies

investigation is required to validate our findings in other demographics such as Latin America, Africa, America, and Europe. Consequently, our study was limited by the absence of such information.

## Conclusion

In summary, we found associations between CDKAL1 rs7754840 and an increased risk of gestational diabetes mellitus (GDM). Yet, our findings observed that CDKAL1 rs7756992 may not be associated with GDM in

individuals. The meta-analysis about rs7754840 corroborates these findings, indicating a consistent association across different studies. These findings underscore the importance of further investigating the potential functional variant CDKAL1 rs7754840 in the development of GDM. Overall, our study provided the understanding of the role of CDKAL1 gene variations in GDM development in pregnant women, enhancing personalized diagnosis, management, prevention, and treatment. Future research should focus on CDKAL1 variants' functional characteristics and environmental factors.

**Abbreviations**

| | |
|---|---|
| GDM | Gestational diabetes mellitus |
| SNPs | Single Nucleotide Polymorphisms |
| CDKAL | Cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like1 |
| GWAS | Genome-wide association studies |
| LD | Linkage disequilibrium |
| HWE | Hardy-Weinberg equilibrium |
| 1h-PG | 1-hour postprandial glucose |
| 2h-PG | 2-hour postprandial glucose |
| DBP | Diastolic blood pressure |
| SBP | Systolic blood pressure |
| FPG | Fasting plasma glucose |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01874-8.

Supplementary Material 1

Supplementary Material 2

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**Author contributions**
This research was a collaborative effort with equal contributions from all authors. GWR, QZ, and HZ were co-first authors and played a leading role in the study design and execution. QZ, FH, and BT collected the clinical data and samples. GWR, QZ, and RG performed the data analysis and wrote the manuscript. All authors, including TS, TY, YW.ML, XC, and YW, provided significant guidance and supervision throughout the research process. Finally, all authors approved the final version of the manuscript.

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**Data availability**
The data that support the findings of this study are openly available in EVA at https://www.ebi.ac.uk/eva/?eva-study=PRJEB71647, accession number PRJEB71647.

## Declarations

**Ethics approval and consent to participate**
The current study involving human subjects were approved by the Shunde Women and Children's Hospital of Guangdong Medical University (Maternity and Child Healthcare Hospital of Shunde Foshan) ethics review committee (approval ID: 2020072). These studies were carried out in compliance with all relevant local legal frameworks and institutional standards. Prior to their participation, all participants provided informed consent, demonstrating their voluntary participation and understanding of the study's objectives and potential implications.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Department of Internal Medicine, Shunde Women and Children's Hospital, Maternity and Child Healthcare Hospital of Shunde Foshan, Guangdong Medical University, Foshan, Guangdong, China
[2]Key Laboratory of Research in Maternal and Child Medicine and Birth Defects, Guangdong Medical University, Foshan, Guangdong, China
[3]Maternal and Child Research Institute, Shunde Women and Children's Hospital, Maternity and Child Healthcare Hospital of Shunde Foshan, Guangdong Medical University, Foshan, Guangdong, China
[4]Department of Ultrasound, Shunde Women and Children's Hospital, Maternity and Child Healthcare Hospital of Shunde Foshan, Guangdong Medical University, Foshan, Guangdong, China
[5]Department of Obstetric, Shunde Women and Children's Hospital, Maternity and Child Healthcare Hospital of Shunde Foshan, Guangdong Medical University, Foshan, Guangdong, China
[6]Reproductive Medicine Center, Shunde Women and Children's Hospital, Maternity and Child Healthcare Hospital of Shunde Foshan, Guangdong Medical University, Foshan, Guangdong, China

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## Publisher's note