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Original article

Association of glucose kinase and glucokinase regulatory protein gene polymorphisms with type 2 diabetes mellitus susceptibility in the Asian population: A meta-analysis

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a condition in which the body struggles to regulate blood sugar levels. The glucose kinase (GCK) and glucokinase regulatory protein (GCKR) genes play a crucial role in glucose metabolism. GCK produces an enzyme essential for glucose sensing and insulin production, whereas GCKR regulates this enzyme's activity.
Objective: This meta-analysis aimed to investigate the GCK rs1799884 and GCKR rs780094 gene polymorphisms and their association with T2DM in an Asian population.
Methods: This study identified articles for two genetic variations (GCK rs1799884 and GCKR rs780094) and assessed their link with type 2 diabetes. We searched online databases, such as Scopus and PubMed, for studies comparing individuals with and without T2DM. Metagenyo was employed as a tool to analyze the data and determine whether these genetic variations increased the risk of developing T2DM.
Results: This study suggests that genetic variations in GCK are associated with a higher risk of developing T2DM, regardless of the gene polymorphism in the allelic, recessive, and dominant models. However, analysis of the GCKR rs780094 gene polymorphism and T2DM revealed that these were only associated in the recessive model.
Conclusion: This study reveals that the GCK rs1799884 and GCKR rs780094 polymorphisms are associated with a higher chance of developing T2DM in the Asian population.

Keywords: GCK, GCKR, gene polymorphism, glucose kinase, meta-analysis, type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a condition in which the body struggles to metabolize glucose for energy. This occurs when the cells become resistant to insulin, a hormone that helps transport glucose into cells, and the pancreas does not generate sufficient insulin or is not functioning properly. [1, 2] The number of people with diabetes has nearly doubled since 1980, and the prevalence of this severe form of high blood sugar levels is increasing worldwide. [3] Diabetes is becoming more prevalent, especially among adults aged 20 to 79 years. [4] T2DM is caused by difficulties with how the body uses or creates insulin and can result in metabolic syndrome, which may increase the risk of developing heart disease or a stroke. Insulin resistance, a major contributor to T2DM, is influenced by multiple genes and other factors. It is also a key risk factor that influences metabolic syndrome, along with high blood pressure and obesity, including abnormal cholesterol levels. [5, 6] The International Diabetes Federation (IDF) reported that 450 million individuals developed diabetes mellitus in 2019, and the majority of them (90 – 95%) had T2DM. Furthermore, they predict that this number could dramatically increase to 700 million by 2045. [7]

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While large-scale studies have investigated genes that potentially cause T2DM in various populations, the findings have been inconsistent. [8] Identifying single -nucleotide polymorphisms (SNPs), making and improving low-cost high-throughput genotyping technology, and conducting multi-center group large-scale genome-wide association studies (GWAS) are valuable methods to investigate the genetic risk factors for T2DM. [9] Genetic conditions substantially influence an individual's vulnerability to diabetes, particularly when there is a family history of the condition. In addition, obesity, and excess body fat, particularly around the abdomen, are key risk factors. [10] Beta cells in the pancreas and liver contain glucose kinase (GCK), which is the primary enzyme responsible for encoding the rate-limiting stage of glycolysis, stimulating insulin secretion in response to glucose, and controlling the glucose balance. [11] While GCK mutations that are inactivated, such as maturity onset diabetes of the young (MODY), induce neonatal diabetes mellitus, activated GCK mutations produce chronic hyperinsulinemic hypoglycemia. [12-14] Human glucose metabolism is tightly regulated by the activity of GCK located on chromosome number 7p15.3 – p15.1, consisting of 12 exons. [15] The glucokinase regulatory protein (GCKR), which functions as a negative regulator by confining GCK within the nucleus when blood glucose levels are low, regulates GCK activity. [16, 17]

T2DM is a widespread health concern, particularly in Asian populations. Genetic factors are known to contribute to T2DM susceptibility, and the GCK and GCKR genes play a crucial role in blood sugar regulation. Polymorphisms in these genes have been linked to the risk of developing T2DM in some studies; however, the findings remain inconclusive. This study investigated the combined evidence from multiple studies to determine whether the GCK rs1799884 and GCKR rs780094 polymorphisms are linked with a higher chance of developing T2DM among the Asian population.

Materials and methods

To ensure a comprehensive and reliable search process for this meta-analysis, we strictly adhered to the established PRISMA guidelines, as shown in **Figure 1**. Prospero verified that the study's prospective review method remained authorized (ID no.547159), which indicates this research's reliability.

Literature search

Relevant articles were obtained through comprehensive electronic searches conducted using Web of Science, Scopus, PubMed, and Embase from the year 2019 till May 2024 by utilizing the following keywords : "Type 2 diabetes mellitus," "T2DM," "gene

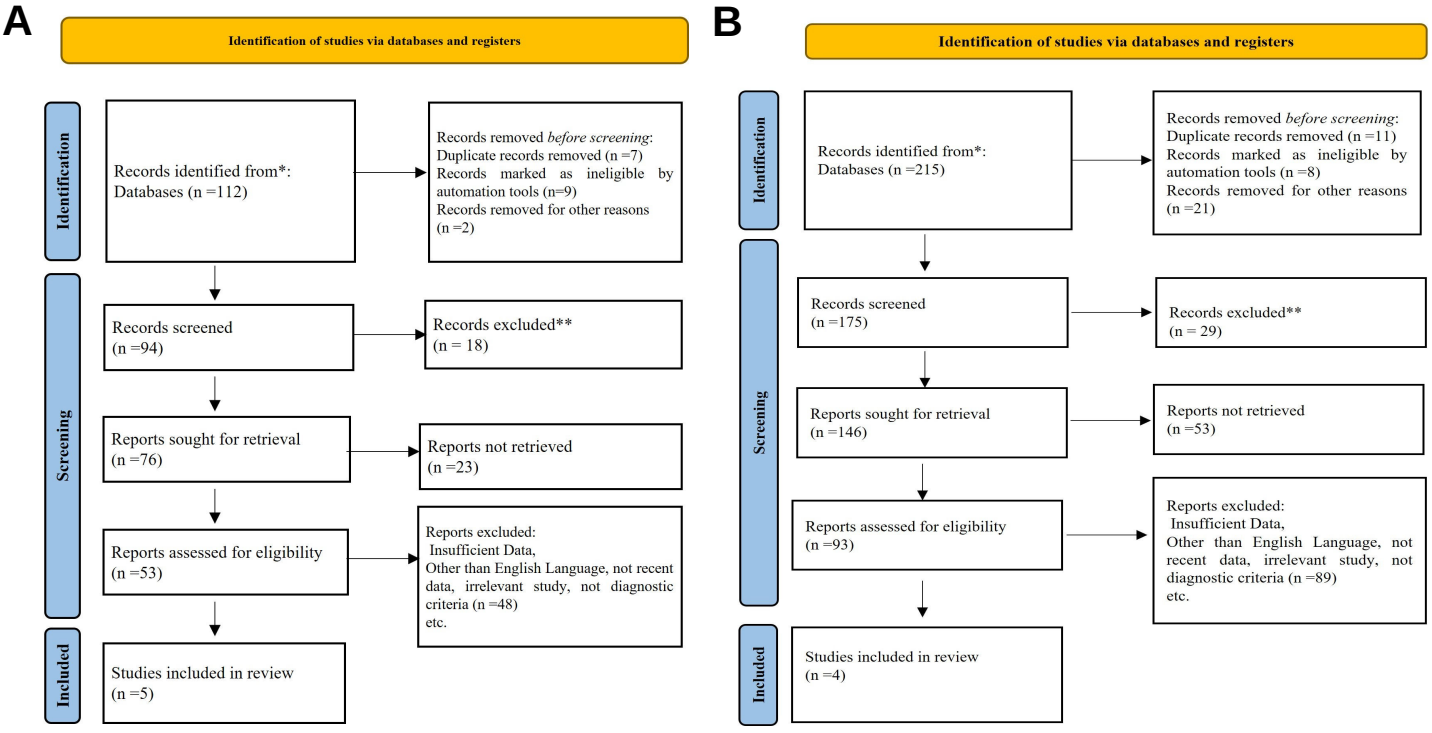

Figure 1. (A) Flowchart of literature screening of GCK rs1799884 and **(B)** GCKR rs780094 gene polymorphism.

polymorphism," "GCK," "GCKR,", "Glucokinase," "Glucokinase regulatory protein," "case *vs*. control," and "mutation." The examination strategy involved the Boolean operators "AND" and "OR" for precise results. In addition, we ensured data integrity by removing duplicates within the database, which encompassed reviews, original research, and existing meta-analyses.

Selection criteria

Inclusion criteria

The articles were carefully chosen for the meta-analysis based on particular selection norms. To meet the inclusion criteria, the study needed to examine GCK and GCKR gene polymorphisms in relation to T2DM. In particular, the study had to 1) have the full text be available in the English language; 2) be case-controlled using genetic association research on T2DM and variations in the GCK and GCKR gene; and 3) examine how the allele and genotype data are distributed among cases and controls.

Exclusion criteria

Studies that did not meet the following criteria were excluded: 1) Studies or prior meta-analyses pertaining to GCK and GCKR polymorphism associations with T2DM; 2) Investigations not linking the GCK and GCKR genes to T2DM risk; 3) Articles with duplicated data; and 4) Case studies and research on animals that overlapped with different areas of study.

Data extraction and quality assessment

Extracting key data from each study was crucial, including author, year, ethnicity, genotype, and allele frequencies for GCK and GCKR, as well as individual characteristics, such as age, gender, and sample size. The Hardy-Weinberg equilibrium (HWE) *P*-value must have been determined, and studies that satisfied the eligibility requirements were evaluated for possible methodological quality bias using the Newcastle–Ottawa scale (NOS). Evaluating the specific methods and possible errors of the research included in this meta-analysis was crucial, with a particular focus on assessing the risk of bias. To assess the reliability of the included studies, we used the Cochrane risk of bias 2 (ROB2) tool. This tool categorizes each study as having "high," "some concerns," or "low" risk of bias based on its design and reporting quality.

Protein-protein interactions

To understand the gene variations linked to T2DM and the protein function, we used the STRING database (version 11.0) to predict the functional changes and protein-protein interactions with a confidence score ≥ 0.4.

Statistical analysis

Statistical analysis was employed in analyzing the importance of the GCK and GCKR gene polymorphisms in relation to T2DM susceptibility. The association between the GCK and GCKR polymorphism and T2DM susceptibility was estimated, with the 95% confidence interval (CI) range of values lying within the degree of confidence. $P < 0.05$ was considered statistically significant. To assess the consistency of findings across all analyzed research, an Index of Inconsistency (I^2) was utilized. The I^2 score, which ranges from 0.0% to 100.0%, indicates the variance or diversity of the studies. A large I^2 number indicates inconsistency, while a low number indicates consistency in the findings across the studies. As the heterogeneity value was $< 50.0\%$, a fixed-effect model was employed. To determine the heterogeneity, a Chi-square test was conducted using Q statistics. The results of this test reveal whether there was a statistically significant difference between two studies. Furthermore, the Z test was used to compute the odds ratio (OR) for multiple comparisons. To assess the overall impact of the genetic factors, a combined OR across all studies was calculated. The study's significance was determined using Egger's test and I^2 statistics. The collective influence was considered statistically significant when the Z test achieved $P < 0.05$. Statistical analyses were performed using Metagenyo, a robust program for the meta-analysis of genetic association studies.

Results

Search results

The present research search criteria identified 243 studies, of which seven studies that included the GCK (rs1799884) and GCKR (rs780094) genes, with a total of 3517 T2DM cases and 8411 normal controls, were selected for this meta-analysis. **Figure 1A and 1B** illustrate the extraction method for the chosen case *vs.* control studies.

Figure 2. Risk of bias summary and graph for GCK rs1799884 and GCKR rs780094 gene polymorphism.

Risk bias

To evaluate the bias risk of the studies, we assessed their methodology quality using the Cochrane ROB2 tool . The details of this evaluation are presented in **Figure 2**, where each study is shown per row and each bias category is provided per column. The color assigned to each study represents the risk of bias, and each study included in the meta-analysis was deemed to have a low bias risk. The rigorous design, implementation, and reporting of these studies minimized the potential influence of bias or errors, thus strengthening the reliability of the results. The color green signifies a low risk of bias, red signifies a high risk, and yellow signifies an unclear risk of bias. This research demonstrates a notably lower level of risk bias among the Asian population.

Quantitative data analysis of the GCK and GCKR genes and T2DM

Based on the genotypes analyzed in this meta-analysis, two specific genes, GCK rs1799884 and GCKR rs780094, were selected for investigation for their association with T2DM. Multiple comparison models were employed, which were based on the HWE principle. Exposure to T2DM was significantly correlated with the GCK rs1799884 genetic variation in the allelic, recessive, and dominant models [allelic model (G *vs*. T; OR 0.4; 95% CI: 0.2 – 0.8; *P* = 0.007); recessive model (GG *vs*. GA + AA; OR 0.4; 95% CI: 0.2 – 0.8; *P* = 0.01); and dominant model (GG + GA *vs*. AA; OR 0.3; 95% CI: 1.7 – 0.7; *P* = 0.003)]. However, the overdominant model (G *vs*. GG+AA; OR 1.1; 95% CI: 0.8 – 1.6; *P* = 0.3) showed no statistically significant association **(Figure 3)**.

The results for the recessive model of the GCKR rs780094 genetic variation showed a strong link with T2DM [recessive model (TT *vs*. TC + CC; OR 3.2; 95% CI: 0.9 – 10.5; *P* = 0.05)]. For the allelic dominant and overdominant models, there was no significant link with T2DM [allelic model (T *vs*. C; OR 2.3; 95% CI: 0.9– 5.6; *P* = 0.06); dominant model (TT + TC *vs*. CC; OR 2.9; 95% CI: 0.9 – 9.3; *P* = 0.06); and overdominant model (TC *vs.* TT + TC; OR 1.5; 95% CI: 0.9 – 2.4; *P* = 0.1)] **(Figure 4)**. The findings suggest potential associations between the genetic polymorphisms of GCK rs1799884 and GCKR rs780094 and the susceptibility to T2DM. Because the study data only included Asian individuals, no subgroup analysis was performed. **Tables 1 and 2** report the HWE *P*-values for both the fixed- and random-effects models.

Publication bias and sensitivity analysis

This study examined the distribution of GCK and GCKR gene polymorphisms among individuals with T2DM compared with controls. To assess publication bias, we employed the Egger's test and a funnel plot. However, **Figure 5** did not reveal any prominent bias. A sensitivity analysis was conducted for both gene variants GCK rs1799884 and GCKR rs780094. The results remained the same , and our results were statistically consistent, as demonstrated in **Figure 6**.

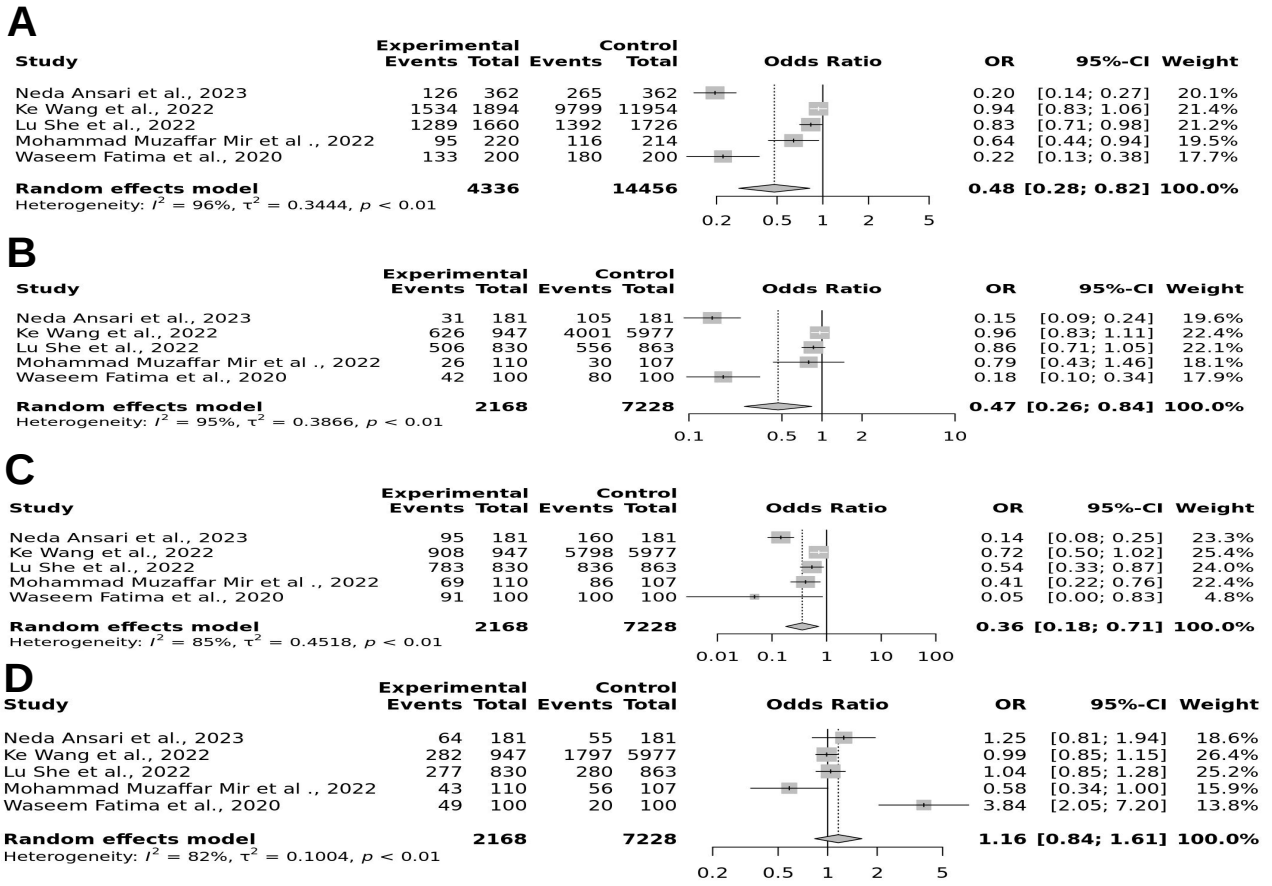

Figure 3. Forest plot for the association of GCK rs1799884 gene polymorphism with T2DM risk **(A)** allelic; **(B)** recessive; **(C)** dominant; and **(D)** over-dominant model.

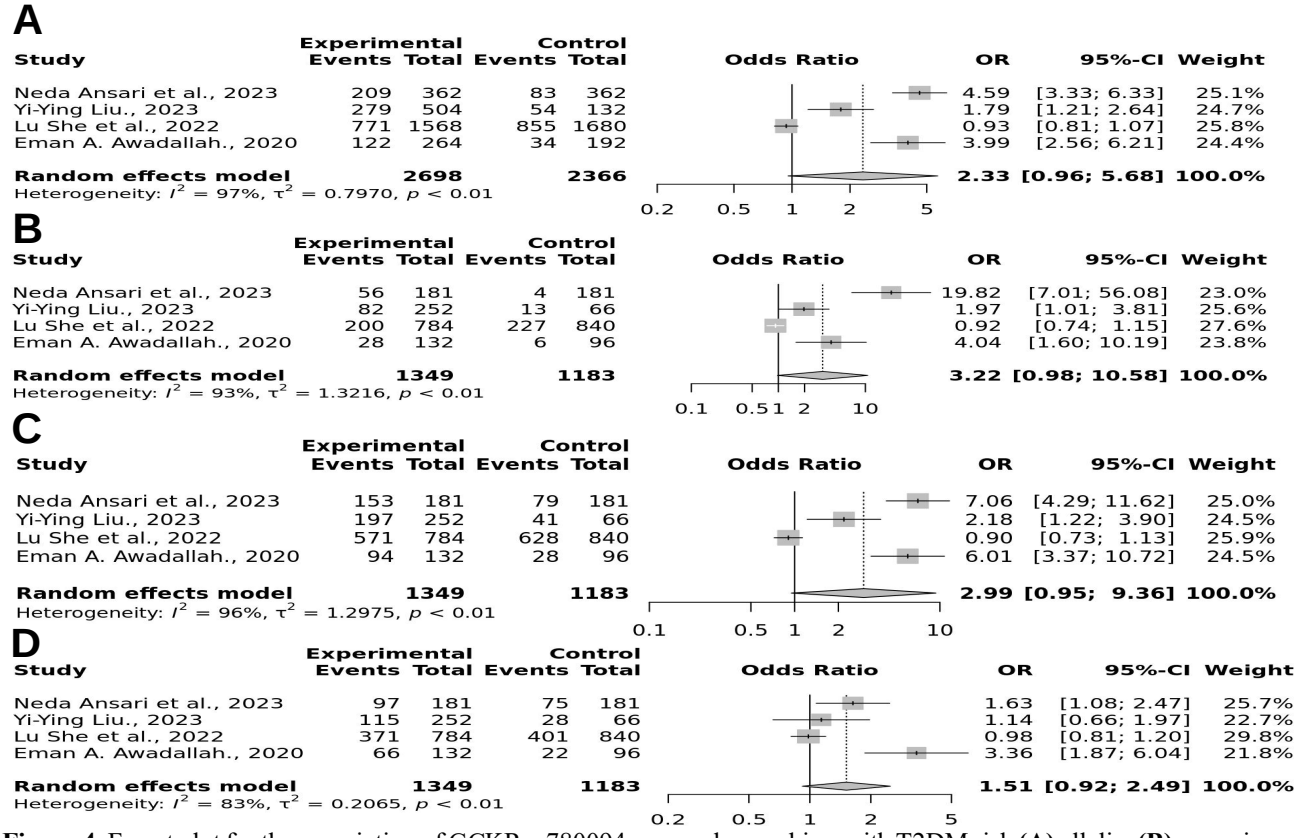

Figure 4. Forest plot for the association of GCKR rs780094 gene polymorphism with T2DM risk **(A)** allelic; **(B)** recessive; **(C)** dominant; and **(D)** over-dominant model.

Table 1. Characteristics of the studies for association of gene GCK rs1799884 polymorphism with T2DM.

Study	Ethnicity	Country	GG_ cases	GA_ cases	AA_ cases	GG_ controls	GA_ controls	AA_ controls	HW- *P*-value	HW- adjusted *P*-value
Ansari N, *et al*. [23]	Asian	Malay	31	64	86	105	55	21	0.0024	0.012
Wang K, *et al.* [17]	Asian	China	626	282	39	4001	1797	179	0.1821	0.3331
She L, *et al*. [24]	Asian	China	506	277	47	556	280	27	0.2462	0.3331
Mir M, *et al*. [25]	Asian	Saudi	26	43	41	30	56	21	0.5751	0.5751
Fatima W, *et al*. [26]	Asian	Saudi	42	49	9	80	20	0	0.2665	0.3331

*HWE-Hardy-Weinberg equilibrium

Table 2. Characteristics of the studies for association of GCKR rs780094 gene polymorphism with T2DM

Study	Ethnicity	Country	TT_ cases	TC_ cases	CC_ cases	TT_ controls	TC_ controls	CC_ controls	HW- *P*-value	HW- adjusted *P*-value
Ansari N, *et al*. [23]	Asian	Malay	56	97	28	4	75	102	0.0204	0.0726
Liu YY. [27]	Asian	China	82	115	55	13	28	25	0.3196	0.3196
She L, *et al*. [24]	Asian	China	200	371	213	227	401	212	0.1928	0.2571
Awadallah EA.[16]	Asian	Egypt	28	66	38	6	22	68	0.0363	0.0726

*HWE-Hardy-Weinberg equilibrium

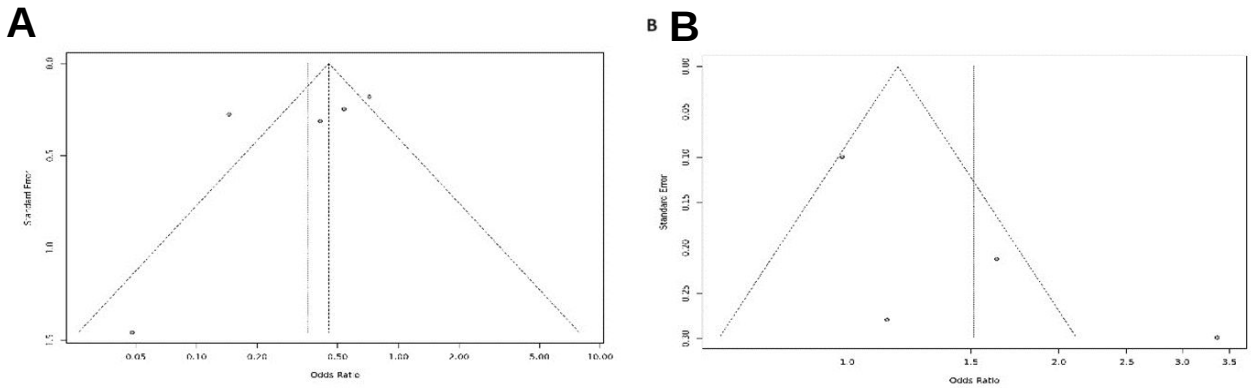

Figure 5. The distribution of the **(A)** GCK rs1799884 and **(B)** GCKR rs780094 plots among T2DM cases and controls.

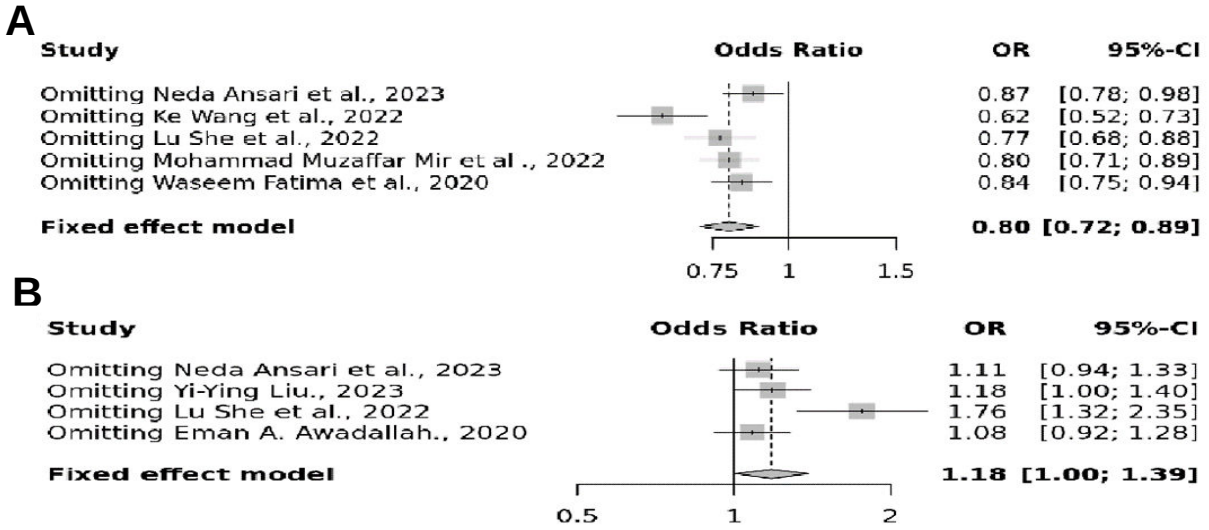

Figure 6. Sensitive analysis was performed for **(A)** GCK rs1799884 and **(B)** GCKR rs780094 gene polymorphism among T2DM cases and controls.

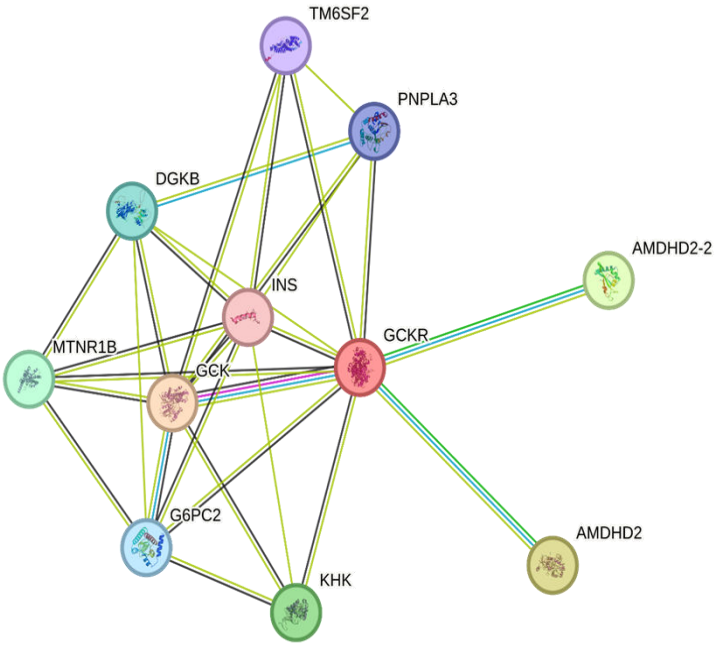

Figure 7. The protein-protein interaction (PPI) network of differentially expressed genes (DEGs) among the selected genes associated with T2DM. We present the total clusters of the PPI network, featuring 11 nodes and 29 edges.

Construction of the protein-protein interaction network

Construction and analysis of a protein-protein interaction network for the polymorphic proteins were performed using the STRING database for the GCK and GCKR genes. In the network, comprising 11 nodes and 29 edges, the GCK and GCKR genes have direct interaction with each other. The GCKR protein functions like a switch for GCK, an enzyme crucial for sugar processing. GCKR binds to GCK, forming an inactive complex that is transported to the cell's nucleus. This may serve as a storage pool for GCK. After a meal, when fructose levels increase, a specific type of fructose molecule (fructose 6-phosphate) binds to GCKR, increasing its binding to GCK. However, another form of fructose (fructose 1-phosphate) weakens this binding, which releases GCK back into the cytoplasm where it can become active and process incoming sugar. Mutational changes in GCK and GCKR revealed a significant association with T2DM **(Figure 7).**

Discussion

T2DM and the genes associated with it are recognized as major public health challenges in the 21st century. [18] T2DM affects approximately 77 million individuals of Indian descent aged 18 and older. An additional 25 million people are pre-diabetic, which puts them at a higher risk of developing diabetes in the near future. [19, 20] GCK regulates glucose metabolism by promoting the phosphorylation of glucose in pancreatic islet beta cells and hepatocytes in humans. It acts as a glucose sensor, controlling the function of pancreatic islet cells for the release of insulin and production of glycogen. During normal glucose metabolism, the GCK enzyme interacts with its inhibiting protein, GCKR, within the nucleus of the liver cells. This interaction leads to an increase in glucose concentration, which subsequently results in the separation of the GCK-GCKR complex. Consequently, GCK is transported to the cytoplasm, where it enhances the phosphorylation of glucose in hepatocyte cells, thereby promoting insulin release, and improves glycogen synthesis in pancreatic islet beta cells. [21] Subsequently, GCK is transformed into its dormant

state as GCKR. This study focused on the associations between the GCK rs1799884 and GCKR rs780094 polymorphisms and T2DM susceptibility until May 2024 as shown in **Figure 8**. Shen M, *et al.* found significant correlation interactions between the GCKR rs1260326 variant with T2DM. [22] The results from this meta-analysis reveal an intriguing link between the GCK rs1799884 and GCKR rs780094 gene polymorphisms and the risk of developing T2DM. The meta-analysis used a random-effects model to analyze heterogeneity-related studies. The allele, recessive and dominant models exhibited a strong correlation between GCK rs1799884 gene polymorphism and the risk of developing T2DM. The articles included in this study revealed a strong association between T2DM and the GCK rs1799884 and GCKR rs780094 gene polymorphisms. [16, 17, 23-27] Stephen SB *et al*. stated that T2DM has been linked to the TCF7 L2 rs12255372 gene polymorphism for all four models, whereas the rs7903146 polymorphism for these models has not been linked to the disease. [28] Aravindhan S, *et al*. reported the relationship between T2DM susceptibility and the VDR gene *Fok*I and *Bsm*I polymorphisms in both worldwide and racial-specific investigations. [29] Ikhanjal MA *et al*. revealed that polymorphisms in the FTO genes rs8050136 and rs9939609 were substantially associated with T2DM, but rs17817449 does not exhibit an association. [30] The sensitivity analysis revealed that no single study exerted a substantial influence on the overall pooled estimate. The study findings indicate that the GCK and GCKR gene variation conforms to the HWE principle. Publication bias was evaluated, and no bias was detected when analyzing the data using a funnel plot and the Egger's test.

A limitation of this study is that it only includes seven articles. Therefore, the generalizability of the findings is limited. In addition, by only focusing on Asian populations as a whole may miss genetic variations within this broad category. Furthermore, the analysis relies on observational studies; therefore, causation cannot be determined. Finally, the exploration of just four genetic models and the exclusion of potential gene-environment interactions may not capture the full extent of how these genes influence T2DM risk.

Conclusion

Based on the meta-analysis of this study, the GCK rs1799884 and GCKR rs780094 gene polymorphisms are associated with T2DM susceptibility in the Asian population.

Acknowledgements

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Conflict of interest

None of the authors disclose any potential conflict of interest.

Data sharing statement

All data generated or analyzed during the present study are included in this published article. Further details are available for non-commercial purposes from the corresponding author on reasonable request.

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