Meta-analysis of genetic association studies on gestational diabetes mellitus

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Abstract

Background

Several molecular epidemiological studies have analyzed the associations between genetic variants and the risk of gestational diabetes mellitus (GDM). However, all these studies suffer from inconsistent and conflicting results owing to relatively smaller sample sizes, fewer genetic variants included in the research, and limited statistical power. Hence, a coherent review and meta-analysis were carried out to provide a quantitative summary related to the associations of commonly studied SNPs with GDM risk.

Methods

Eligible studies were retrieved from PubMed, updated on Dec. 2019. Based on several inclusion and exclusion criteria, 71 articles with 42928 GDM patients and 77793 controls were finally considered for meta-analysis. The genotype data from 23 variants of sixteen genes were statistically analyzed using RevMan v 5.2 software. Newcastle-Ottawa Scale (NOS) was used to assess the quality of the research article. Heterogeneity among studies was tested by $I^2$ and odds ratio with 95% confidence interval (CI) was carried out for all five genetic models.

Results

The overall combined odds ratio reveals that variants like MTNR1B (rs1083963, rs1387153), GCK (rs1799884), CANP10 (rs3792267), and GCKR (rs780094) are significantly associated with GDM in all genetic models while CANP10 (rs5030952), ADRB (rs4994) and FTO (rs8050136) are not significantly associated with GDM in any genetic models. Variants MTNR1B (rs1083963, rs1387153) and GCK (rs1799884) are associated with increased risk (OR>1, p<0.05) of GDM, and all these are related to insulin secretion. Other variants related to insulin secretion like TCF7L2 (rs7903146) and SLC30A8 (rs1326634) are also associated with increased risk (OR>1, p<0.05) of GDM. On the contrary, CANP10 (rs3792267) and GCKR (rs780094) are found associated with decreased risk (OR<1, p<0.05) of GDM. Other variants are significantly associated with the GDM in at least one or more genetic models.

Conclusion

Our study identified that most of the variants related to insulin secretions like MTNR1B (rs1083963), GCK (rs1799884), TCF7L2 (rs7903146), GCKR (rs780094), and SLC30A8 (rs1326634) are more strongly associated (p<0.005) with GDM as compared to the variants related to the insulin resistance like PPARG (rs1801282), IRS1 (rs1801278) and ADIPOQ (rs266729).

Introduction

Gestational diabetes mellitus (GDM), a complex metabolic disorder, is defined as any degree of carbohydrate intolerance with onset or first recognition during pregnancy (American Diabetes Association, 2010). Risk factors include maternal age, pre-pregnancy obesity, and previous delivery of a newborn with congenital malformations such as macrosomia, previous/prior history of GDM, cesarean section, and a family history of diabetes in first degree relatives (Reece et al., 2009). However, intrinsic factors like environmental interaction and genetic predisposition can’t remain unaddressed (Shaat and Groop, 2007). Women with GDM had an increased risk of developing diabetes type 2 which accounts for 90% of cases of diabetes. GDM can progress when a genetic susceptibility to pancreatic islets cells are exposed to incremental insulin resistance during pregnancy. GDM is often associated with adverse pregnancy outcomes, including fetal macrosomia, stillbirth, neonatal metabolic disturbances, and related problems, and causes short- and long-term complications in women and their offspring (Bellamy et al., 2009; "Gestational Diabetes Mellitus," 2004; Reece et al., 2009). GDM women are at over seven-fold higher risk of developing type 2 diabetes mellitus (T2DM) later in life (Bellamy et al., 2009).

The Burden of GDM is growing at a much higher rate in developing and low-to-middle income countries than in developed countries. The prevalence of GDM varies widely from 1.8–25.1% of all pregnancies. It is higher among the Middle East and North Africa, South Asia, and Western Pacific regions while lowest in Europe (Zhu and Zhang, 2016). In the western world, the incidence of GDM is about 1–3% of all pregnancies while 5–10% in Asian pregnancies (Shaat and Groop, 2007). In India, the incidence of GDM is estimated to be 10-14.3% which is much higher than in developed countries (Lowe et al., 2016). This significant variation in its prevalence is attributed to racial and ethnic differences a social-economic variations (Zhu and Zhang, 2016). The Asian/Pacific Islander women have a higher incidence of GDM than non-Hispanic white, Black, or Hispanic women (Chu et al., 2009; Kim et al., 2012). Due to racial and regional differences in GDM prevalence, exploring the relationship of susceptible gene polymorphism in GDM women of different racial backgrounds will be quite informative.

In this study, we systematically analyzed all the current evidence regarding the genetic associations of GDM to quantitatively summarize the effect size of replicated single nucleotide polymorphisms (SNPs) on GDM risk and identify the possible sources of heterogeneity among the eligible researchers. A total of 23 different SNPs related to 16 genes were included for meta-analysis. These sixteen genes are namely TCF7L2 (Transcription factor 7-like 2), MTNR1B (Melatonin receptor 1B), FTO (Alpha-ketoglutarate-dependent dioxygenase), PPARG (Peroxisome proliferator-activated receptor-gamma), GCK (Glucokinase), GCKR (Glucokinase Regulator), ADIPOQ (Adiponectin), TNF (Tumor necrosis factor), IRS1 (Insulin receptor substrate 1), KNCN11 (Potassium inwardly-rectifying channel, subfamily J, member 1), IGFBP2 (Insulin-like growth factor 2 mRNA-binding protein 2), ADRB3 (Adrenoceptor beta 3), CDKAL1 (CDK5 regulatory subunit associated protein 1-like 1), HNF1A (Hepatocyte nuclear factor 1-alpha), CANP10 (Calpain-10), and SLC30A8 (Solute carrier family 30 member 8). These genes and their respective SNPs were involved in pathways like type 1 diabetes mellitus, type1 diabetes mellitus, insulin signalling pathway, Maturity onset diabetes of the young, PPAR signalling pathway, Adipocytokine signalling pathway, glycolysis, and amino sugar metabolism. To the best of our
knowledge, several studies reporting the association of different SNPs to GDM are present. However, a single study including all polymorphisms is lacking. Herein, we present a meta-analysis including all polymorphisms associated with GDM studied so far.

Materials And Methods

Search strategy

A systematic literature search in the PubMed, Scopus and Google Scholar databases (Canese et al., n.d.) was carried out for each Single Nucleotide Polymorphism (SNPs) studied so far from 1994 to 2019 for their association with GDM. The keywords used for article search were “SNPs” OR “Polymorphism” OR “Variant” OR “Genotype” OR “SNPs” AND Diabetes, Gestational [MESH] OR “Diabetes, Pregnancy-Induced” OR “Pregnancy-Induced Diabetes” OR “Gestational Diabetes” OR “Diabetes Mellitus, Gestational” OR “Gestational Diabetes Mellitus.” Cross-references were also screened for the literature retrieved.

Study selection

The inclusion criteria considered for selection of eligible studies were as follows: (1) English publication (2) Studies with case-control design (3) proper diagnostic criteria for Gestational Diabetes Mellitus (GDM) (4) studies with adequate data for genotyping in case and control (5) literature with sufficient data to estimate the odds ratio (ORs) with 95% confidence interval (CI). The Criteria included for exclusion were as follows: (1) Abstract, reviews, and meta-analysis (2) studies with duplicate data (3) studies without control design (4) Irrelevant studies with insufficient data. All identified studies were critically reviewed by two investigators independently to determine their eligibility for inclusion or exclusion in meta-analysis. Screening based on inclusion and exclusion criteria led to the identification of a total of 71 potential studies containing 42928 GDM patients and 77793 controls to be included in the meta-analysis.

Methodological quality appraisal

The modified Newcastle-Ottawa Scale (NOS) (Cook and Reed, 2015) was employed to identify high-quality research. The methodological quality of each study was assessed for three parameters: selection (0-4 points), comparability (0-2 points), and exposure (0-3 points). Each meeting point was given a score, and thus each study was scored from 0 to 9. According to the modified NOS, articles with no less than five scores were defined as high quality.

Data extraction

All 71 eligible studies were independently reviewed by two reviewers, and the following information was extracted from each study: first author, publication year, ethnicity, country, mean age, genotyping method, gene, genetic variants, size of the sample, number of cases and controls, study design, genotype distribution in case and control groups, allele frequency and NOS quality score. Disagreements were resolved through discussion with all authors.

Statistical analysis

All statistical analysis was performed using REVMAN software version 5.2 (Schmidt et al., 2019). The P-values <0.05 were considered statistically significant unless otherwise emphasized. To explore the significant deviation from HWE among controls in each study, the Chi-square test was calculated (Wigginton et al., 2005). OR and 95% CI were used to calculate the strength of associations between different polymorphisms and GDM susceptibility. I² tests were utilized to assess the heterogeneity of ORs (Higgins, 2003). If I² < 50%, the heterogeneity was regarded as not significant. The associations between genetic polymorphisms and GDM were examined under the allele model (A vs B, where A is the risk allele), the recessive model (AA vs AB + BB), the dominant model (AB + AA vs. BB), the homozygous contrast model (AA vs. BB), and the heterozygote contrast model (AA vs. AB).

Networking and KEGG pathway enrichment

All sixteen genes were uploaded in STRING v 11.0 (Mering, 2003), and a PPI network was constructed. All these genes were also enriched for their biological process, molecular function, and KEGG pathways using DAVID v 6.7 (Huang et al., 2009).

Results

Literature search and Characteristics of eligible Studies

According to the search strategy, a total of 243 articles were initially retrieved from PubMed, Scopus and Google Scholar (Fig. 1). After excluding 15 duplicate articles, a total of 228 articles were considered for full-text review. Among these, meta-analysis (n=13), review (n=4), and articles related to other disease and non-clinical data (n=97) were excluded, leaving 114 articles for eligibility check. Further, thirty-seven articles were excluded due to insufficient data, and four abstracts were also excluded. Finally, 75 articles with a total of 42928 GDM cases and 77793 controls were included in the meta-analysis study. The characteristics of the studies included in the meta-analysis are summarized in Table 1. All included studies were published from 1994 to 2019 and were of moderate to high quality, with NOS scores of more than five stars. The studies had a heterogeneous population with all three races. These 71 studies include a total of 23 polymorphisms related to 16 genes. The genotype and allele distribution for each of these polymorphisms is listed in Table 2. The genotype distribution of the control group was in accordance with HWE in all studies (P > 0.05).

Overall meta-analysis
In the present study, a total of 23 SNPs related to 16 different genes were analyzed. Characteristic features of genes and their related alleles are provided in Table 3. Of these, CANP10 and TCF7L2 have three polymorphisms; MTNR1B, FTO, and GCKR have two polymorphisms, while the rest genes have only one SNP included in the study (Fig. 2A). Association between all twenty-three polymorphism and GDM risk were assessed in five genetic models, and detailed results have been shown in Table 4. Out of 23 SNPs analyzed, the results showed that only 17 SNPs were significantly associated with GDM risk in at least one genetic model (Fig. 2B and D, Table 4). A total of 13 polymorphisms regarding genotypes in the dominant model, 11 polymorphisms regarding genotypes in the recessive model, 14 polymorphisms regarding genotypes in the homozygous model, ten polymorphisms regarding genotypes in the heterozygote model and ten polymorphisms regarding genotypes in the allele model were found to be significantly (p<0.05) associated with GDM risk (Fig. 2D). The four polymorphisms, namely rs780094 (GCKR), rs1387153 (MTNR1B), rs1799884 (GCK), rs1083963 (MTNR1B) were showing significant association (p<0.05) with GDM risk in all five genetic models (Fig. 2C). On the other hand, two polymorphisms (rs3792267, rs9939609) exclusively present the dominant, recessive, homozygote, and heterozygote model each while another two polymorphisms (rs2975760, rs12255572) exclusively present in the dominant, recessive, homozygote, and allele models were found to be significantly (p<0.05) associated with GDM risk (Fig. 2C).

Association between polymorphisms and GDM

In all five genetic models analyzed, the number of polymorphisms associated with increased risk (OR>1) of GDM is larger than those polymorphisms which have protective effects (OR<1) (Fig 3A). Analysis of all 23 SNPs in the dominant genetic model revealed significant heterogeneity (p<0.05) in only seven polymorphisms. Thus, a random-effect model was conducted to pool results for total OR estimation. Genotype analysis indicates that all these seven polymorphisms are significantly associated with increased risk (OR>1, p<0.05) of GDM (Supplementary file 1). In recessive models (Fig. 3B), significant heterogeneity (p<0.05) was found in 10 polymorphisms out of 23 analyzed. Random effect model showed significant protective association (OR=1) of eight polymorphisms while two polymorphisms GCK rs1799884 (OR = 1.77(1.56-2.00); I² = 86%, p=0.00001) and TCF7L2 rs12255572 (OR = 2.24(1.81-2.77); I² = 87%, p<0.00001) are significantly associated with increased risk (OR=1) of GDM. In the homozygote model (Fig. 3B), significant heterogeneity was observed in total eleven polymorphisms, of which ten were strongly associated with increased risk (OR>1) of GDM while only one, i.e., GCKR rs780094 was showing protective association (OR = 0.52(0.38-0.70); I² = 83%, p=0.00001). A significant heterogeneity (p<0.05) was observed in six polymorphisms out of 23 in the analysis of the heterozygote model (Fig. 3B). Genetic analysis through the random effect model revealed that five polymorphisms are significantly associated with increased risk (OR>1) of GDM while GCKR rs780094 showed protective association (OR = 0.72(0.53-0.97); p = 0.03). Genotypes in the allele model (Fig. 3B) revealed a total of nine significant (p<0.05) heterogeneity, of which six were significantly associated with increased risk (OR>1) while three were showing protective association (OR<1) for GDM. The overall results revealed the significant heterogeneity (p<0.05) of five polymorphisms, namely rs1326634 (SLC30A8), rs780094 (GCKR) rs1083963 (MTNR1B), rs7903146 (TCF7L2), rs9939609 (FTO) in all five genetic models analyzed. Among these five, rs780094 (GCKR) rs1083963 (MTNR1B) were significant for overall effect in all five genetic models analyzed. Polymorphisms rs1799884 (GCK) and rs1387153 (MTNR1B) were also significantly associated with the disease. However, they are not significant at the heterogeneity level in all five genetic models analyzed.

Association of GDM with genetic variants related to insulin secretion

Transcription factor 7-like 2 (TCF7L2)

This meta-analysis studied three variants of TCF7L2, namely rs7903146, rs12255372, and rs7901695, which were studied in this meta-analysis rs7903146 was the most widely studied variant in the association with GDM. A meta-analysis of twenty-five studies (Cho et al., 2009; de Melo et al., 2015; Ekelund et al., 2012; Franzago et al., 2018; Freathy et al., 2010; Huerta-Chagoya et al., 2015; Khan et al., 2019; Lauenborg et al., 2009; Pagán et al., 2014; Papadopoulou et al., 2011; Papadopoulou et al., 2011; Pappa et al., 2011; Reyes-López et al., 2014; Rizk et al., et al., 2012) involving a total of 16672 controls and 6692 GDM cases, showed the significantly (p<0.0001 except Recessive Model) increased susceptibility for the rs7903146 allele or genetic models (Fig. 4) associated with an increased risk of GDM (Dominant Model: OR=1.59; Recessive model: OR=1.03; Homozygote Model: OR=2.03; Heterozygote Model: OR=1.46; Allelic model: OR=1.60). Overall heterogeneity was substantial under all comparisons (I²: 43%-92%).

For rs12255372, a total of eleven studies (Cho et al., 2009; de Melo et al., 2015; Pagán et al., 2014; Papadopoulou et al., 2011; Popova et al., 2017; Reyes-López et al., 2019, 2014; Rizk et al., et al., 2012) involving 2923 controls and 2842 GDM cases, while only five studies involving 1233 controls and 2093 GDM cases for rs7901695 (Gorczyca-Siudak et al., 2016; Pagán et al., 2014; Papadopoulou et al., 2011; Stuebe et al., 2013) were included for the data synthesis. Overall-effect analysis showed significantly increased susceptibility for the rs12255372 allele or genetic models (Supplementary fig. 1A) with increased GDM risk (Dominant Model: OR=1.37; Recessive model: OR=2.24; Homozygote Model: OR=1.69; Heterozygote Model: OR=1.10; Allelic model: OR=1.80). In the case of rs7901695, significantly increased susceptibility with increased GDM risk was found only in the dominant (OR=1.41; p=0.01) and homozygote model (OR=1.69; p=0.0005) (Supplementary fig. 2A). Overall heterogeneity for rs12255372 ranged from moderate to considerable (20%-87%), while for rs7901695, it was substantial (41%-95%).

Glucokinase (GCK)

The rs1799884 variant in the GCK gene has been widely investigated in GDM risk (Chiu et al., 2000; Freathy et al., 2010; Popova et al., 2017; Shaat et al., 2006; Tarnowski et al., 2017; Zaidi et al., 1997). In the present meta-analysis, for rs1799884, a total of eight studies involving 7923 controls and 2416 GDM cases were analyzed for five genetic models. There was significantly (p<0.00001) increased susceptibility for the rs1799884 allele or genetic models (Fig. 5) with increased GDM risk (Dominant Model: OR=1.88; Recessive model: OR=1.77; Homozygote Model: OR=1.98; Heterozygote Model: OR=1.62; Allelic model: OR=1.52). Overall heterogeneity for rs1799884 was very less (0-40%) except recessive models (86%).

Glucokinase Receptor (GCKR)
Two variants of GCKR, namely rs780094 and rs1260326, have been investigated in the present study. A total of seven studies involving 2317 controls and 667 GDM cases for the rs780094 variant (Angeheb-Oliveira et al., 2017; Jamalpour et al., 2018; Stuebe et al., 2013; Tamowski et al., 2017) (Fig. 6A) while four studies involving 1230 controls and 462 GDM cases for the rs1260326 variant (de Melo et al., 2015; Franzago et al., 2018; Stuebe et al., 2013) (Fig. 6B) were assessed and analyzed in the present study. Overall-effect analysis indicated the significantly (p<0.05, except recessive model in both variant) decreased susceptibility for both variants in homozygote (rs780094: rs1260326, OR=0.52:0.51), heterozygote (rs780094: rs1260326, OR=0.72:0.66) and allelic model (rs780094: rs1260326, OR=0.51:0.54).

Melatonin receptor 1B (MTNR1B)

Kim et al. (2011) first studied the two variants of MTNR1B, namely rs10830963 and rs1387153. For rs10830963, a total of fourteen studies (Alharbi et al., 2019; Ao et al., 2015; Grotenfelt et al., 2016; Junior et al., 2015; Kim et al., 2011; Liu et al., 2010; Popova et al., 2017; Tamowski et al., 2017; Vejrazkova et al., 2014; Vlassi et al., 2012; Wang et al., 2011) involving 5121 controls and 4564 GDM cases were analyzed, while for rs1387153, a total of five studies (Alharbi et al., 2019; Kim et al., 2011; Liu et al., 2010; Popova et al., 2017; Vlassi et al., 2012) involving 2139 controls and 2138 GDM cases were included in the present study. In the case of rs10830963, the overall-effect analysis revealed the significantly(p<0.0001) increased susceptibility with increased GDM risk in all genetic models except recessive model (Dominant Model: OR-1.81; Homozygote Model: OR-2.82; Heterozygote Model: OR-1.82; Allelic model: OR-1.85) (Fig. 7A). Similarly, for the rs1387153, the significantly increased susceptibility with increased GDM risk was found in all genetic models except the recessive model (Dominant Model: OR-1.68; Homozygote Model: OR-3.42; Heterozygote Model: OR-1.73; Allelic model: OR-2.0) (Fig. 7B). Overall heterogeneity for rs10830963 was considerable (64%-88%) while for rs1387153 it was highly variable (0%-90%).

Zinc transporter 8 (SLC30A8)

The rs1326634 variant in SLC30A8 has recently gained much interest in GDM risk. In the present meta-analysis, a total of six studies (Cho et al., 2009; Dereke et al., 2012; Khan et al., 2019; Lauenborg et al., 2009; Teleginski et al., 2017) involving 3861 controls and 1946 GDM cases were analyzed. Overall-effect analysis showed the significantly (p<0.0001) increased susceptibility with increased GDM risk only in the dominant (OR-1.91) and heterozygote model (OR-2.90), while in the allelic models, there was significantly (p<0.05) decreased susceptibility (OR-0.76) associated with GDM risk (Fig. 8).

Gene-interaction, functional and pathway enrichment

The protein-protein interaction network reveals a high degree of interaction among these sixteen genes (Fig. 9A). Gene ontology enrichment analysis highlights the role of these sixteen genes in significant biological processes like regulation of glucose metabolism and insulin secretion, cellular response to insulin stimulus, and fatty acid oxidation (Fig. 9B). Significant pathways being regulated by these genes are the PPAR signalling pathway, mTOR signalling pathway, Maturity onset of diabetes in young (MODI), and type II diabetes mellitus pathway (Fig. 9C).

Heterogeneity

Heterogeneity was measured in all comparisons. Both Cochrane’s Q test and I-square statistic suggest different levels of heterogeneity (from less/no to very severe) across all studies or for each subgroup. Hence, both the fixed effect model and random effect model were employed to pool all studies. Moderate (I^2=50%) or no heterogeneity (I^2=0%) was found in seven SNPs namely rs3792267 (CANP10), rs5030952 (CANP10), rs4994 (ADRB3), rs1801278 (RS1), rs1800629 (TFN), rs1260326 (GCKR), and rs8050136 (FTO), out of 23 SNPs analyzed. The remaining sixteen SNPs show considerable (I^2, 50% - 90%) and substantial (I^2, 75% - 100%) heterogeneity.

Sensitivity analysis

For maternal genotype sensitivity analysis, the overall OR after exclusion of any individual study showed no change, ranging from 0.71 to 0.81, including the robust at-risk effect of the rs1326634, rs7754840 rs1083963, rs9939609 genotype against gestational diabetes.

Publication bias analysis

Egger’s test was performed to assess the publication bias. No statistically significant evidence of publication bias was observed for studies included in the analyses.

Discussion

In the present meta-analysis, all studied genetic variants related to type1 and type2 diabetes was investigated for their association with the GDM risk. Several previous studies have included only a few variants or have missed some variants (Ref.). Moreover, the pathophysiology of GDM shares similarities with type1 (insufficient insulin secretion) and type2 diabetes (insulin resistance). Both insulin insufficiency and insulin resistance play a significant role in the development and progression of GDM. Besides, these two pathways, glucose and lipid metabolism pathway, also play an essential role in the pathophysiology of GDM. Hence in this meta-analysis, we have used rigorous statistical analysis to rule out the most significantly associated variants with increased GDM risk and related pathways. Further, we also tried to identify those pathways whose genetic variants are strongly associated with the increased GDM risk. Thus, our replication study provides a more comprehensive and concise summary of the currently available evidence regarding GDM genetic variants.

Pregnancy is accompanied by a number of changes in metabolic activity, which helps in dwelling the interaction between mothers and growing fetuses to meet their energy needs. There is a slight enhancement of insulin sensitivity seen during early gestation; however, this insulin sensitivity declines during 12-14 weeks. Moreover, in the third trimester, this insulin sensitivity increases, and these values, as reported in some cases, approach the values of T2DM. This
condition is termed GDM; evidence has reported that GDM develops when a genetic predisposition of pancreatic islet B-cells impairment is unmasked by the increased insulin resistance during pregnancy. A GWAS study confirmed the association of various SNPs with impaired b-cell function (MTNR1), insulin resistance, and abnormal utilization of glucose (GCK, CANP10). We came across many studies with heterogeneous results, and this variation is liable to ethnicity, study design, and tissue is taken. Overall, we observed that variants related to insulin secretions pathways like MTNR1B (rs1083963), GCK (rs1799884), TCF7L2 (rs7903146), GCKR (rs780094), and SLC30A8 (rs1326634) are more strongly associated (p<0.005) with increased GDM compared to the variants related to the insulin resistance like PPAR (rs1801282), IRS1 (rs1801278) and ADIPOQ (rs266729).

The MTNR1B polymorphisms

The MTNR is reported to modulate pancreatic islet B-cells function. Our study coincides with the result of Kim et al., who first reported a significant association of GDM with MTNR1B rs1387153. A study conducted by Zheng et al. in 2013 observed the T allele of rs1387153 associated with increased risk of GDM, Vlassi et al. (2012) studies supported. However, the study on Chinese women conducted by Wang et al. disregarded the findings.

The GCK polymorphisms

The Glucokinase (GCK) with the rs1799884 has been widely studied in different ethnic populations with conflicting results. Chiu et al. and Zaidi et al. reported no association between GDM and rs1799884. However, Shaat et al., Freathy et al., Santas et al. found significant association when they conducted research on a relatively larger population. Our replication study also aligned with their findings and the meta-analysis also presented the significant association with no significant heterogeneity.

The CANP10 polymorphism

The CAPN10 gene belongs to the calpain family and is a Ca2+ dependent intracellular cysteine protease. CAPN10 is found to be involved in glucose homeostasis as it regulates the activity of pancreatic B islet-cells, liver, skeletal muscle, and adipocytes. However, the direct association between GDM and rs3792267 remains elusive due to reported contradictory results (Heinz et al., Luo et al., N Shaat et al., Thomas et al.)

Conclusion

The superiority of this study was that multiple databases were included to search the literature as thoroughly as possible. The subgroup and random effect analysis were utilized to decline heterogeneity, and the comprehensive assessment of publication bias was done, which identified the results of our study effectively and reliably. These findings suggest insulin resistance or defects in insulin secretion have major implications in aetiology in GDM however ethnicity plays a crucial role in it.

Declarations

Conflict of Interest

Authors declare no any conflict of interest.

References

Alharbi, K.K., Al-Sulaiman, A.M., Bin Shedaid, M.K., Al-Shangiti, A.M., Marie, M., Al-Sheikh, Y.A., Ali Khan, I., 2019. MTNR1B genetic polymorphisms as risk factors for gestational diabetes mellitus: a case-control study in a single tertiary care center. Ann Saudi Med 39, 309–318. https://doi.org/10.5144/0256-4947.2019.309
American Diabetes Association, 2010. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 33, S62–S69. https://doi.org/10.2337/dc10-S062
Anghebem-Oliveira, M.I., Webber, S., Alberton, D., de Souza, E.M., Klassen, G., Picheth, G., Rego, F.G. de M., 2017. The GCKR Gene Polymorphism rs780094 is a Risk Factor for Gestational Diabetes in a Brazilian Population. J. Clin. Lab. Anal. 31, e22035. https://doi.org/10.1002/jcla.22035
Ao, D., Wang, H., Wang, L., Song, J., Yang, H., Wang, Y., 2015. The rs2237892 Polymorphism in KCNQ1 Influences Gestational Diabetes Mellitus and Glucose Levels: A Case-Control Study and Meta-Analysis. PLoS ONE 10, e0128901. https://doi.org/10.1371/journal.pone.0128901
Bellamy, L., Casas, J.-P., Hingorani, A.D., Williams, D., 2009. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet 373, 1773–1779. https://doi.org/10.1016/S0140-6736(09)60731-5
Canese, K., Jentsch, J., Myers, C., n.d. 2. PubMed: The Bibliographic Database 12.
Chiu, K.C., Chuang, L.-M., Yoon, C., Saad, M.F., 2000. [No title found]. BMC Genet 1, 2. https://doi.org/10.1186/1471-2156-1-2
Cho, Y.M., Kim, T.H., Lim, S., Choi, S.H., Shin, H.D., Lee, H.K., Park, K.S., Jang, H.C., 2009. Type 2 diabetes-associated genetic variants discovered in the recent genome-wide association studies are related to gestational diabetes mellitus in the Korean population. Diabetologia 52, 253–261.
https://doi.org/10.1007/s00125-008-1196-4
Chu, S.Y., Abe, K., Hall, L.R., Kim, S.Y., Njoroge, T., Qin, C., 2009. Gestational diabetes mellitus: All Asians are not alike. Preventive Medicine 49, 265–268.
https://doi.org/10.1016/j.ypmed.2009.07.001
Lowe, W.L., Scholtens, D.M., Sandler, V., Hayes, M.G., 2016. Genetics of Gestational Diabetes Mellitus and Maternal Metabolism. Curr Diab Rep 16, 15.

Dereke, J., Nilsson, C., Landin-Olsson, M., Hillman, M., 2012. Prevalence of transportor 8 antibodies in gestational diabetes mellitus. Diabetic Medicine 29, e436–e439. https://doi.org/10.1111/j.1464-5491.2012.03766.x

Ekelund, M., Shaat, N., Almgren, P., Anderberg, E., Landin-Olsson, M., Lyssenko, V., Groop, L., Bemtorp, K., 2012. Genetic prediction of postpartum diabetes in women with gestational diabetes mellitus. Diabetes Research and Clinical Practice 97, 394–398. https://doi.org/10.1016/j.diabres.2012.04.020

Franzoni, M., Fraticelli, F., Marchetti, D., Celentano, C., Liberati, M., Stuppia, L., Vitacolonna, E., 2018. Nutrigenetic variants and cardio-metabolic risk in women with or without gestational diabetes. Diabetes Research and Clinical Practice 137, 64–71. https://doi.org/10.1016/j.diabres.2018.01.001

Freathy, R.M., Hayes, M.G., Urbanek, M., Lowe, L.P., Lee, H., Ackerman, C., Frayling, T.M., Cox, N.J., Dunger, D.B., Dyer, A.R., Hattersley, A.T., Metzger, B.E., Lowe, W.L., for the HAO Study Cooperative Research Group, 2010. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Common Genetic Variants in GCK and TCF7L2 Are Associated With Fasting and Postchallenge Glucose Levels in Pregnancy and With the New Consensus Definition of Gestational Diabetes Mellitus From the International Association of Diabetes and Pregnancy Study Groups. Diabetes 59, 2682–2689. https://doi.org/10.2337/db10-0177

Gestational Diabetes Mellitus, 2004. . Diabetes Care 27, S88–S90. https://doi.org/10.2337/diacare.27.2007.S88

Huang, D.W., Sherman, B.T., Lempicki, R.A., 2009. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 4, 44–57. https://doi.org/10.1038/nprot.2008.211

Huerta-Chagoya, A., Vázquez-Cárdenas, P., Moreno-Macías, H., Tapia-Maruri, L., Rodríguez-Guillén, R., López-Vite, E., García-Escalante, G., Escobedo-Aguirre, F., Parra-Covarrubias, A., Cordero-Briefo, R., Manzo-Carrillo, L., Zacarías-Castillo, R., Vargas-García, C., Aguilar-Salinas, C., Tusie-Luna, T., 2015. Genetic Determinants for Gestational Diabetes Mellitus and Related Metabolic Traits in Mexican Women. PLoS ONE 10, e0126408. https://doi.org/10.1371/journal.pone.0126408

Jamalpour, S., Zain, S.M., Mosavat, M., Mohamed, Z., Omar, S.Z., 2018. A case-control study and meta-analysis confirm glucokinase regulatory gene rs780094 is a risk factor for gestational diabetes mellitus. Gene 650, 34–40. https://doi.org/10.1016/j.gene.2018.01.091

Junior, J.P.L., Freiger, H.R., dos Santos-Weiss, I.C.R., de Souza, E.M., Rego, F.G.M., Picheth, G., Alberton, D., 2015. The MTNR1B gene polymorphism rs10830963 is associated with gestational diabetes in a Brazilian population. Gene 568, 114–115. https://doi.org/10.1016/j.gene.2018.01.091

Kim, J.Y., Cheong, H.S., Park, B.-L., Baik, S.H., Park, S., Lee, S.W., Kim, M.-H., Chung, J.H., Choi, J.S., Kim, M.-Y., Yang, J.-H., Shin, H.D., Kim, S.-H., 2015. Melatonin receptor 1 B polymorphisms associated with the risk of gestational diabetes mellitus. BMC Med Genet 12, 82. https://doi.org/10.1186/1471-2350-12-82

Kim, S., England, L., Sappenfield, W., Wilson, H., Bish, C., Salihu, H., Sharma, A., 2012. Racial/Ethnic Differences in the Percentage of Gestational Diabetes Mellitus Cases Attributable to Overweight and Obesity, Florida, 2004-2007. Prev. Chronic. Dis. https://doi.org/10.5888/pcd9.110249

Lauenborg, J., Grarup, N., Damm, P., Borch-Johnsen, K., Jørgensen, T., Pedersen, O., Hansen, T., 2009. Common Type 2 Diabetes Risk Gene Variants Associate with Gestational Diabetes. The Journal of Clinical Endocrinology & Metabolism 94, 145–150. https://doi.org/10.1210/jc.2008-1336

Liu, C., Wu, Y., Li, H., Qi, Q., Langenberg, C., Loos, R.J., Lin, X., 2010. MTNR1B Research article rs10830963 is associated with fasting plasma glucose, HbA1C and impaired beta-cell function in Chinese Hans from Shanghai 7.

Lowe, W.L., Scholtens, D.M., Sandler, V., Hayes, M.G., 2016. Genetics of Gestational Diabetes Mellitus and Maternal Metabolism. Curr Diab Rep 16, 15. https://doi.org/10.1007/s11892-015-0709-z

Mering, C. v. 2003. STRING: a database of predicted functional associations between proteins. Nucleic Acids Research 31, 258–261. https://doi.org/10.1093/nar/gkg034
Gestational diabetes mellitus is associated with TCF7L2 gene polymorphisms independent of HLA-DQB1*0602 genotypes and islet cell autoantibodies: TCF7L2 and HLA-DQB1 in gestational diabetes mellitus. Diabetic Medicine 28, 1018–1027. https://doi.org/10.1111/j.1464-5491.2011.03359.x

Pappa, K.I., Gazouli, M., Economou, K., Daskalakis, G., Anastasiou, E., Anagnost, N.P., Amtaaklis, A., 2011. Gestational diabetes mellitus shares polymorphisms of genes associated with insulin resistance and type 2 diabetes in the Greek population. Gynecological Endocrinology 27, 267–272. https://doi.org/10.3109/09513590.2010.496069

Popova, P.V., Klyushina, A.A., Vasilyeva, L.B., Tkachuk, A.S., Bolotko, Y.A., Gerasimov, A.S., Pustozero, E.A., Kravchuk, E.N., Predeus, A., Kostareva, A.A., Grineva, E.N., 2017. Effect of gene-lifestyle interaction on gestational diabetes risk. Oncotarget 8, 112024–112035. https://doi.org/10.18632/oncotarget.22999

Reece, E.A., Leguizamón, G., Wiznitzer, A., 2009. Gestational diabetes: the need for a common ground. The Lancet 373, 1789–1797. https://doi.org/10.1016/S0140-6736(09)60515-8

Reyes-López, R., Pérez-Luque, E., Malacara, J.M., 2019. Relationship of lactation, BMI, and rs12255372 TCF7L2 polymorphism on the conversion to type 2 diabetes mellitus in women with previous gestational diabetes. Gynecological Endocrinology 35, 412–416. https://doi.org/10.1080/09513590.2018.1531984

Reyes-López, R., Pérez-Luque, E., Malacara, J.M., 2014. Metabolic, hormonal characteristics and genetic variants of TCF7L2 associated with development of gestational diabetes mellitus in Mexican women: TCF7L2 Gene in GDM Mexican Women. Diabetes Metab Res Rev 30, 701–706. https://doi.org/10.1002/dmrr.2538

Rizk, N., Al-Al, K.A., Jose, E., Al-Katheri, A., Sumbul, B., Shaltout, H., Shaltout, T., n.d. Qatar University, Doha, Qatar Hamad Medical Corporation, Doha, Qatar nassrizk@qu.edu.qa 1.

Schmidt, L., Shokraneh, F., Steinhausen, K., Adams, C.E., 2019. Introducing RAPTOR: RevMan Parsing Tool for Reviewers. Syst Rev 8, 151. https://doi.org/10.1186/s13643-019-1070-0

Shaht, N., Groop, L., 2007. Genetics of Gestational Diabetes Mellitus. CMC 14, 569–583. https://doi.org/10.2174/0929867077880059643

Shaht, N., Karlsson, E., Lemmark, Å., Ivarsson, S., Lynch, K., Parikh, H., Almgren, P., Berntorp, K., Groop, L., 2006. Common variants in MODY genes increase the risk of gestational diabetes mellitus. Diabetologia 49, 1545–1551. https://doi.org/10.1007/s00125-006-0258-8

Shaht, N., Lemmark, Å., Karlsson, E., Ivarsson, S., Parikh, H., Berntorp, K., Groop, L., 2007. A variant in the transcription factor 7-like 2 (TCF7L2) gene is associated with an increased risk of gestational diabetes mellitus. Diabetologia 50, 972–979. https://doi.org/10.1007/s00125-007-0623-2

Stuebe, A., Wise, A., Nguyen, T., Herring, A., North, K., Siega-Riz, A., 2013. Maternal Genotype and Gestational Diabetes. Amer J Perinatol 31, 069–076. https://doi.org/10.1055/s-0033-1334451

Tarnowski, M., Malinowski, D., Safranow, K., Dziedziejko, V., Czerewaty, M., Pawlik, A., 2017. Hematopoietically expressed homeobox (HHEX) gene polymorphism (rs5015480) is associated with increased risk of gestational diabetes: Genetic polymorphisms and gestational diabetes. Clin Genet 91, 843–848. https://doi.org/10.1111/cge.12875

Teleginski, A., Welter, M., Frigeri, H.R., Réa, R.R., Souza, E.M., Alberton, D., Rego, F.G.M., Picheth, G., 2017. Leptin (rs7799039) and solute carrier family 30 zinc transporter (rs13266634) polymorphisms in Euro-Brazilian pregnant women with gestational diabetes. Genet. Mol. Res. 16.

Thomas, N., Mahesh, D.M., Chapla, A., Paul, J., Shwetha, N., Christina, F., Asha, H.S., 2014. Does TCF7L2 polymorphisms increase the risk of gestational diabetes mellitus in South Indian population? EJEA. https://doi.org/10.1530/endoabs.34.P270

Včelák, J., Vejražková, D., Vaňková, M., Lukášová, P., Bradnová, O., Hálková, T., Bešťák, J., Andělová, K., Kvasničková, H., Hoskocová, P., Vondra, K., Vrbiková, J., Bendlová, B., 2012. T2D Risk Haplotypes of the TCF7L2 Gene in the Czech Population Sample: the Association With Free Fatty Acids Composition. Physiol Res 229–240. https://doi.org/10.33549/physiolres.932272

Vejražková, D., Lukasova, P., Vankova, M., Vcelak, J., Bradnova, O., Cirmanova, V., Andelova, K., Krejci, H., Bendlova, B., 2014. MTNR1B Genetic Variability Is Associated with Gestational Diabetes in Czech Women. International Journal of Endocrinology 2014, 1–7. https://doi.org/10.1155/2014/508923

Vlassi, M., Gazouli, M., Paltoglou, G., Christopoulos, P., Florentin, L., Kassi, G., Mastorakos, G., 2012. The rs10830963 variant of melatonin receptor MTNR1B is associated with increased risk for gestational diabetes mellitus in a Greek population. Hormones 11, 70–76. https://doi.org/10.1007/BF03401539

Wang, Y., Nie, M., Li, W., Ping, F., Hu, Y., Ma, L., Gao, J., Liu, J., 2011. Association of Six Single Nucleotide Polymorphisms with Gestational Diabetes Mellitus in a Chinese Population. PLoS ONE 6, e26953. https://doi.org/10.1371/journal.pone.0026953
Wigginton, J.E., Cutler, D.J., Abecasis, G.R., 2005. A Note on Exact Tests of Hardy-Weinberg Equilibrium. The American Journal of Human Genetics 76, 887–893. https://doi.org/10.1086/429864

Zaidi, F.K., Wareham, N.J., McCarthy, M.I., Holdstock, J., Kalloo-Hosein, H., Krook, A., Swinn, R.A., O’Rahilly, S., 1997. Homozygosity for a Common Polymorphism in the Islet-specific Promoter of the Glucokinase Gene is Associated with a Reduced Early Insulin Response to Oral Glucose in Pregnant Women. Diabet. Med. 14, 228–234. https://doi.org/10.1002/(SICI)1096-9136(199703)14:3<228::AID-DIA330>3.0.CO;2-N

Zhu, Y., Zhang, C., 2016. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. Curr Diab Rep 16, 7. https://doi.org/10.1007/s11892-015-0699-x

Tables

Table 1: Characteristics of the studies included in the meta-analysis
| Sl. No. | Author (Year)         | Study Design | Ethnicity  | Country | No. of Controls | No. of Cases | Mean Age cases/controls | GDM Criteria          | Genotyping Method | NOS Score |
|--------|-----------------------|--------------|------------|---------|----------------|--------------|-------------------------|----------------------|-------------------|-----------|
| 1      | N. Shaat et al. (2004)| Case–control | Arabian     | Sweden  | 122            | 100          | 31.9/NA                 | OGTT-2 hour          | RFLP–PCR          | 6         |
| 2      | N. Shaat et al. (2005)| Case–control | Caucasian   | Sweden  | 1189           | 587          | 32.2/30.5               | EASD-DPSG criteria   | TaqMan allelic discrimination assay | 6         |
| 3      | N. Shaat et al. (2006)| Case–control | Caucasian   | Sweden  | 1229           | 642          | 32.3/30.5               | EASD-DPSG criteria   | RFLP–PCR          | 6         |
| 4      | N. Shaat et al. (2007)| Case–control | Caucasian   | Sweden  | 1111           | 585          | 32.3/30.5               | EASD-DPSG criteria   | TaqMan allelic discrimination assay | 6         |
| 5      | Popova et al. (2017)  | Case–control | Caucasian   | Russia  | 179            | 278          | 31.8/29.4               |                     | IADPSG            | NA        |
| 6      | Cho et al. (2009)     | Case–control | Asian       | Korea   | 627            | 868          | 32/64.7                 |                     | TaqMan allelic discrimination assay | 6         |
| 7      | Lauenborg et al. (2009)| Case–control | Caucasian   | Denmark | 2353           | 276          | 43.1/45.2               | WHO criteria 1999    | TaqMan allelic discrimination assay | 7         |
| 8      | Freathy et al. (2010) | Case–control | Caucasian   | Australia and UK | 3811 | 614 | NA | IADPSG 2010 criteria | TaqMan allelic discrimination assay | 5         |
| 9      | SF de Melo et al. (2015)| Case–control | Caucasian   | Brazil  | 200            | 200          | 33.0 ± 6.4              | ADA                  | Taq-Man assay     | 7         |
| 10     | M Franzago et al. (2018)| Case–control | Caucasian   | Italy   | 124            | 104          | 26.0 ± 8.4              | IADPSG               | HRM               | 5         |
| 11     | RR Lopez et al. (2014)| Case–control | Hispanic/Latino | Mexico | 108           | 90           | 29/31                   | ADA                  | PCR               | 6         |
| 12     | Thomas et al. (2014)  | Case–control | Asian       | India   | 49             | 117          | NA                      | NA                  | PCR               | 5         |
| 13     | Thomas et al. (2013)  | Case–control | Caucasian   | Germany | 297            | 204          | NA                      | NA                  | PCR               | 6         |
| 14     | Beysel et al. (2019)  | Case–control | Caucasian   | Turkey  | 145            | 160          | 29.16/28.01             | OGTT-2 hour          | RT-PCR            | 5         |
| 15     | Pappa et al. (2011)   | Case–control | Caucasian   | Greece  | 107            | 148          | 32.5/26.67              | Fourth IWCADM criteria | RFLP–PCR          | 6         |
| 16     | S. Jamalpour et al. (2017)| Case–control | Asian       | Malaysia | 582           | 182          | 31.31/29.89             | 75-g mOGTT           | Sequenom MassARRAY | 6         |
| 17     | A Pagan et al. (2014) | Case–control | Caucasian   | Spain   | 24             | 45           | 31.2/34.31              | OM/NDDG              | Sequencing        | 6         |
| 18     | A Papadpoupolou et al. (2011)| Case–control | White       | Sweden  | 1110           | 803          | NA                      | IADPSG               | Taq-Man assay     | 6         |
| 19     | Wang et al. (2011)    | Case–control | Asian       | China   | 1029           | 700          | 32.0/30.0               | ADA criteria         | TaqMan allelic discrimination assay | 6         |
| 20     | Stuebe et al. (2014)  | Case–control | Caucasian   | US, African | 792  | 52   | NA                      | Other criteria       | Sequenom iPLEX platform | 6         |
| 21     | Chao Li et al. (2013) | Case–control | Asia        | China   | 480            | 350          | NA                      | NA                  | Sequencing        | 6         |
| 22     | Chao Li et al. (2018) | Case–control | Asia        | China   | 243            | 215          | NA                      | NA                  | RFLP–PCR          | 4         |
| 23     | Rizk et al. (2011)    | Case–control | Caucasian   | Qatar    | 74             | 40           | NA                      | TaqMan allelic discrimination assay | 5         |
| No. | Authors               | Case–control | Ethnicity | Country  | Number | Mean | Standard Deviation | Methodology                  | Allele Specific Assay | Genotyping Assay |
|-----|-----------------------|--------------|-----------|----------|--------|------|---------------------|------------------------------|----------------------|------------------|
| 24  | Shi et al. (2014)     | Case–control | Asian     | China    | 100    | 100  | 27.4/24.2           | IADPSG                      | NA                   | TaqMan SNP Genotyping Assay |
| 25  | DG Siudak et al. (2016)| Case–control | Caucasian | Poland   | 26     | 50   | 30.36/30.88         | NA                          | TAqMan SNP Genotyping Assay |
| 26  | IA Khan et al. (2018) | Case–control | Asian     | India    | 150    | 137  | 26.7/27.6           | OGTT-2 hour                 | RFLP–PCR             |
| 27  | Vlassi et al. (2012)  | Case–control | Caucasian | Greece   | 91     | 77   | 35.45/31.39         | ADA criteria               | RFLP–PCR             |
| 28  | Vcelak et al. (2012)  | Case–control | Caucasian | Greece   | 376    | 261  | 35.45/31.39         | ADA criteria               | RFLP–PCR             |
| 29  | Aris et al. (2012)    | Case–control | Asian     | Malay    | 114    | 173  | NA                  | ADA criteria               | Illumina             |
| 30  | M. Ekelund et al. (2012)| Case–control | Caucasian | Sweeden  | 41     | 125  | 32.2/32.8           | NA                          | TaqMan SNP Genotyping Assay |
| 31  | KK Alharbi et al. (2019)| Case–control | Asian     | Korea    | 966    | 908  | 33.17/32.24         | Carpenter and Coustan criteria | TaqMan allelic discrimination assay | 3 |
| 32  | Liu et al. (2015)     | Case–control | Asian     | China    | 674    | 674  | 31.8/28.78          | OGTT                        | Mass spectrometry     |
| 33  | JY Kim et al. (2011)  | Case–control | African   | Korea    | 966    | 908  | 33.17/32.24         | Carpenter and Coustan criteria | TaqMan allelic discrimination assay | 3 |
| 34  | Saucedo et al. (2017) | Case–control | Caucasian | Mexico   | 81     | 80   | 30 (26.7–32.8)      | ADA criteria               | TaqMan assay         |
| 35  | Tok et al. (2006)     | Case–control | Caucasian | Turkey   | 100    | 62   | NA                  | NDDG criteria              | RFLP–PCR             |
| 36  | S Chon et al. (2013)  | Case–control | East Asian| Korea    | 41     | 94   | 29.2/26.7           | NA                          | TaqMan SNP Genotyping Assay |
| 37  | M. Tarnowski et al. (2017)| Case–control | Caucasian | Poland   | 207    | 204  | 29.3 ± 5.9          | IADPSG                      | TaqMan SNP Genotyping Assay |
| 38  | Z. Liang et al. (2010)| Case–control | Asian     | China    | 79     | 50   | NA                  | PCR                         | TaqMan SNP Genotyping Assay |
| 39  | G Silva et al. (2011) | Case–control | Caucasian | Brazil   | 168    | 79   | NA                  | RFLP–PCR                    |
| 40  | Fallucca et al. (2006)| Case–control | Caucasian | Italy    | 277    | 309  | 34.1/32.7           | Carpenter and Coustan criteria | TaqMan SNP Genotyping Assay |
| 41  | Zhang X. et al. (2019)| Case–control | Asian     | China    | 152    | 138  | 28.2/27.5           | NA                          | TaqMan SNP Genotyping Assay |
| 42  | Heinz et al. (2014)   | Case–control | Caucasian | Austria  | 40     | 43   | 31.0/33.6           | NA                          | TaqMan SNP Genotyping Assay |
| 43  | Luo et al. (2009)     | Case–control | Asian     | China    | 120    | 42   | 28.5/29.1           | NA                          | TaqMan SNP Genotyping Assay |
| 44  | Deng et al. (2011)    | Case–control | Asian     | China    | 91     | 87   | 29.7/31.8           | OGTT                        | Sequencing           |
| 45  | Tarnowski et al. (2017)| Case–control | European  | Poland   | 207    | 99   | NA                  | RT-PCR                      |
| 46  | Vejrazkova et al. (2014)| Case–control | European  | Czech    | 422    | 458  | NA                  | TaqMan SNP Genotyping Assay |
| 47  | Junior et al. (2017)  | Case–control | NA        | NA       | 183    | 183  | NA                  | PCR                         |
| 48  | NE. Grotenfelt et al. (2016)| Case–control | Caucasian | Finland  | 106    | 120  | NA                  | Sequenom iPLEX              |
| 49  | Cheng et al. (2010)   | Case–control | Asian     | China    | 173    | 55   | 27/29.6             | PCR–denaturing HPLC        |
| 50  | Yan et al. (2014)     | Case–control | East Asian| China    | 180    | 156  | NA                  | RFLP                        |
| 51  | Du et al. (2012)      | Case–control | East Asian| China    | 69     | 66   | NA                  | RFLP                        |
| 52  | Papa et al. (2011)    | Case–control | Caucasian | Greece   | 107    | 148  | 32.5/26.67          | Fourth IWCGDM               | RFLP–PCR             |
| Study                        | Type             | Ethnicity | Country | Cases | Controls | Sex | Criteria                              | Methodology               | Reference |
|------------------------------|------------------|-----------|---------|-------|----------|-----|----------------------------------------|---------------------------|-----------|
| Heude et al. (2011)          | Case-control     | Caucasian | France  | 1587  | 109      | NA  | 50-g glucose load                     | RFLP–PCR or TaqMan allelic | 5         |
| Chiu et al. (1994)           | Case-control     | Caucasian | USA     | 99    | 97       | NA  | OGTT 2 h glucose                      | PCR-SSCP                  | 6         |
| Zaidi et al. (1997)          | Case-control     | Caucasian | UK      | 92    | 47       | NA  | OGTT 2 h glucose                      | RFLP–PCR                  | 5         |
| Santos et al. (2010)         | Case-control     | Caucasian | Brazil  | 600   | 150      | NA  | ADA 2009 criteria                     | RFLP–PCR                  | 6         |
| Kan et al. (2014)            | Case-control     | Asian     | China   | 100   | 100      | 30.7/30.9 | OGTT | TaqMan Allelic discrimination assay   |                           | 5         |
| Huerta-Chagoya et al. (2015) | Case-control     | Latino    | Mexico/Hispanic/ | 342 | 408      | NA  | Carpenter and Coustan                 |                           | 5         |
| Klein et al. (2012)          | Case-control     | Caucasian | Australia | 125 | 125      | NA  | IADPSG                                |                           | 6         |
| J. Dereke et al. (2016)      | Case-control     | Arabian   | Sweden  | 536   | 511      | NA  | EASD                                  | PCR-RFLP                  | 7         |
| A. Teleginski et al. (2017)  | Case-control     | Caucasian | Brazil  | 180   | 134      | NA  | SBD                                   | TaqMan                    | 5         |
| Festa et al. (1997)          | Case-control     | Caucasian | Austria | 109   | 70       | NA  | OGTT 1 h                              | RFLP–PCR                  | 6         |
| Alevizavaki et al. (2000)    | Case-control     | Caucasian | Greek   | 130   | 176      | NA  | ADA criteria                          | RFLP–PCR                  | 5         |
| Tsai et al. (2004)           | Case-control     | Asian     | China   | 258   | 41       | NA  | OGTT (not specified)                  | RFLP–PCR                  | 6         |
| Noury et al. (2018)          | Case-control     | Caucasian | Egypt   | 51    | 47       | NA  | ADA criteria                          | TaqMan Allelic discrimination assay | 5         |
| Wu et al. (2015)             | Case-control     | Asian     | China   | 180   | 153      | 23.3 ± 2.1 | IADPSG | PCR-RFLP                          |                           | 5         |
| Kanthimathi et al. (2015)    | Case-control     | Asian     | India   | 910   | 495      | 27.5 ± 2.4 | IADPSG system | MassARRAY  |                           | 7         |
| Beltcheva et al. (2014)      | Case-control     | Caucasian | America | 259   | 130      | NA  | NA                                    | TaqMan                    | 6         |
| Pavlik et al. (2017)         | Case-control     | Europe    | Poland  | 207   | 204      | NA  | NA                                    | TaqMan                    | 7         |
| Chang et al. (2005)          | Case-control     | Asian     | China   | 35    | 35       | 30/28 | OGTT (not specified)                  | RFLP–PCR                  | 6         |
| Montazeri et al. (2010)      | Case-control     | Asian     | Malaysia | 102  | 110      | NA  | WHO criteria 1999                     | RFLP–PCR                  | 5         |
| Flores et al. (2013)         | Case-control     | NA        | NA      | 44    | 51       | NA  | NA                                    | NA                        | NA        |
| A Oliveira et al. (2016)     | Case-control     | Caucasian | Brazil  | 125   | 127      | 32.7 ± 6.3 | ADA criteria | Taq-Man assay            |                           | 5         |
| A. Pagan et al. (2014)       | Case-control     | Caucasian | Spain   | 25    | 45       | 30.95 ± 0.86 | NDDG | Direct sequencing                   |                           | 6         |
| Imran et al. (2014)          | Case-control     | Asian     | India   | 150   | 137      | 24/26.7 | NA                      | RFLP–PCR                  | 6         |

**Table 2: Genotype and allele distribution among cases and controls in included studies**
| Sl. No. | Author (Year) | Gene [Variants] | Number of Participants | Genotypes in Control | Genotypes in GDM | M | Minor Allele | Ct |
|--------|---------------|----------------|------------------------|----------------------|------------------|---|-------------|----|
| 1      | N. Shaat et al. (2004) | PPARG [rs1801282]Arabian | 122 100 | 106 15 1 91 9 0 | G 6.1 |
|        |                | PPARG [rs1801282]Scandinavian | 428 400 | 317 105 6 286 111 3 | G 1.2 |
|        |                | PPARG [rs1801282] | 550 500 | 423 120 7 377 120 3 | G 1.2 |
| 2      | N. Shaat et al. (2005) | IRS1 [rs1801278] | 1189 587 | 1078 111 0 534 49 4 | A 4. |
|        |                | KCNJ11 [rs5219] | 1180 588 | 440 576 164 185 310 93 | T 3.6 |
|        |                | CANP10 [rs2975760] | 1181 226 | 787 351 43 32 177 17 | C 1.6 |
|        |                | CANP10 [rs3792267] | 1181 577 | 620 476 85 305 220 52 | A 27 |
| 3      | N. Shaat et al. (2006) | GCK [rs1799884] | 1229 642 | 889 316 24 435 181 26 | A 14 |
|        |                | HNF1A [rs1169288] | 1214 614 | 559 508 147 242 298 74 | T 3.2 |
| 4      | N. Shaat et al. (2007) | TCF7L2 [rs7903146] | 1111 585 | 650 392 69 271 255 59 | T 2.3 |
|        |                | PPARG [rs1801282] | 1232 637 | 918 298 16 468 158 11 | G 1.5 |
|        |                | ADRB3 [rs4994] | 1227 639 | 1060 158 9 534 100 5 | G 7.3 |
| 5      | Popova et al. (2017) | TCF7L2 [rs7903146] | 179 278 | 104 63 12 161 104 13 | T 2.4 |
|        |                | TCF7L2 [rs12255372] | 176 276 | 110 56 10 168 93 14 | T 2.1 |
|        |                | MTNR1B [rs10830963] | 243 215 | 87 121 35 54 102 59 | G 3.5 |
|        |                | MTNR1B [rs10830963] | 179 278 | 93 69 17 96 133 49 | G 2.5 |
|        |                | MTNR1B [rs1387153] | 179 278 | 93 75 11 104 131 43 | T 2.7 |
|        |                | FTO [rs9939609] | 275 176 | 79 136 60 61 87 28 | A 4.2 |
|        |                | GCK [rs1799884] | 179 278 | 142 37 0 185 81 12 | A 1.6 |
|        |                | IRS1 [rs1801278] | 179 278 | 160 19 0 257 21 0 | A 5.3 |
|        |                | KCNJ11 [rs5219] | 179 278 | 56 92 31 102 122 54 | T 4.3 |
|        |                | IGFBP2 [rs4402960] | 179 278 | 77 76 26 120 134 24 | T 3.6 |
|        |                | CDKAL1 [rs7754840] | 179 278 | 81 85 13 116 128 34 | C 3.1 |
| 6      | Cho et al. (2009) | TCF7L2 [rs7903146] | 627 868 | 596 31 0 803 63 2 | T 2.3 |
|        |                | TCF7L2 [rs12255372] | 630 867 | 628 2 0 860 7 0 | T 0.3 |
|        |                | FTO [rs8050136] | 629 864 | 486 132 11 643 208 13 | A 1.2 |
|        |                | PPARG [rs1801282] | 632 865 | 567 63 2 793 71 1 | G 5.3 |
|        |                | KCNJ11 [rs5219] | 629 846 | 254 273 102 298 407 141 | T 3.7 |
|        |                | IGFBP2 [rs4402960] | 627 857 | 313 257 57 389 365 103 | T 2.5 |
|        |                | CDKAL1 [rs7754840] | 630 863 | 178 319 133 171 389 303 | C 4.6 |
|        |                | SLC30A8 [rs13266634] | 627 861 | 107 306 214 126 372 363 | C 5.6 |
| 7      | Lauenborg et al. (2009) | TCF7L2 [rs7903146] | 2353 276 | 1292 863 198 118 125 33 | T 2.6 |
|        |                | FTO [rs9939609] | 2329 276 | 833 1101 395 82 133 61 | A 4.6 |
|        |                | PPARG [rs1801282] | 2383 265 | 1790 542 51 201 60 4 | G 1.5 |
|        |                | KCNJ11 [rs5219] | 2411 255 | 985 1101 325 91 124 40 | T 3.6 |
|        |                | IGFBP2 [rs4402960] | 2334 274 | 1138 972 224 115 132 27 | T 3.6 |
|        |                | SLC30A8 [rs13266634] | 2344 279 | 266 998 1080 22 119 138 | C 6.7 |
|   | Study                          | Gene      | SNP        | Minor allele | Total Cases | Total Controls | OR  | 95% CI      | p-value |
|---|-------------------------------|-----------|------------|--------------|-------------|---------------|-----|-------------|---------|
| 8 | Freathy et al. (2010)         | TCF7L2    | rs7903146  | T            | 381 11      | 614 1884 1557 | 370 | 293 246    | 75 2.1 |
|   |                               | TCF7L2    | rs7903146  | T            | 3197        | 614 1591 1311 | 295 | 293 246    | 75 2.1 |
|   |                               | TCF7L2    | rs7903146  | T            | 1706        | 384 1549 157  | 0   | 338 46     | 0 4.   |
|   |                               | GCK       | rs1799884  | T            | 3811        | 614 2575 1114 | 122 | 388 194    | 32 17.  |
|   |                               | GCK       | rs1799884  | T            | 1706        | 384 1375 311  | 20  | 288 91     | 5 1.   |
| 9 | SF de Melo et al. (2015)      | TCF7L2    | rs7903146  | T            | 200 200     | 98 86       | 16  | 76 104     | 20 2.1 |
|   |                               | TCF7L2    | rs12255372 | T            | 200 200     | 102 75      | 23  | 92 88      | 20 3.   |
|   |                               | FTO       | rs9939609  | A            | 200 200     | 71 97       | 32  | 68 100     | 32 4.   |
|   |                               | FTO       | rs8050136  | A            | 200 200     | 74 96       | 30  | 73 102     | 25 3.   |
|   |                               | GCKR      | rs1260326  | A            | 200 200     | 74 96       | 30  | 73 102     | 25 3.   |
| 10| M Franzago et al. (2018)      | TCF7L2    | rs7903146  | T            | 124 104     | 59 48       | 17  | 38 38      | 28 3.   |
|   |                               | FTO       | rs9939609  | A            | 124 104     | 38 60       | 26  | 33 42      | 29 4.   |
|   |                               | PPARG     | rs1801282  | T            | 124 104     | 101 23      | 0   | 79 25      | 0 9.   |
|   |                               | GCKR      | rs1260326  | T            | 124 104     | 26 68       | 30  | 25 58      | 21 5.   |
| 11| RR López et al. (2014)        | TCF7L2    | rs7903146  | T            | 108 90      | 81 23       | 4   | 55 29      | 6 14.  |
|   |                               | TCF7L2    | rs12255372 | T            | 108 90      | 101 5       | 2   | 60 23      | 7 4.   |
|   |                               | TCF7L2    | rs12255372 | T            | 83 47       | 62 18       | 3   | 29 11      | 7 14.  |
| 12| Thomas et al. (2014)          | TCF7L2    | rs7903146  | T            | 49 117      | 27 18       | 4   | 55 46      | 16 2.1 |
|   |                               | TCF7L2    | rs12255372 | T            | 49 116      | 33 14       | 2   | 70 38      | 8 1.   |
| 13| Thomas et al. (2013)          | CANP10    | rs5030952  | T            | 297 204     | 253 42      | 2   | 180 23     | 1 7.   |
|   |                               | CANP10    | rs3792267  | A            | 297 204     | 152 122     | 23  | 103 78     | 23 2.   |
| 14| Beysel et al. (2019)          | FTO       | rs9939609  | A            | 145 160     | 73 54       | 18  | 59 62      | 39 31.  |
|   |                               | FTO       | rs9939609  | A            | 101 90      | 40 52       | 9   | 31 45      | 14 3.   |
|   |                               | HNF1A     | rs1169288  | T            | 101 90      | 57 37       | 7   | 36 46      | 8 2.1  |
|   |                               | HNF1A     | rs1169288  | T            | 145 160     | 50 78       | 17  | 33 94      | 33 3.   |
| 15| Pappa et al. (2011)           | TCF7L2    | rs7903146  | T            | 107 148     | 62 38       | 7   | 49 81      | 18 2.4 |
|   |                               | IRS1      | rs1801278  | A            | 107 148     | 60 40       | 7   | 58 73      | 17 2.   |
|   |                               | KCNJ11    | rs52219    | T            | 107 148     | 70 33       | 4   | 96 42      | 10 1.5 |
| 16| Jamalpour et al. (2017)       | GCKR      | rs780094   | A            | 582 182     | 84 284      | 214 | 18 69      | 95 61.  |
|   |                               | GCKR      | rs780094   | A            | 163 48      | 23 76       | 64  | 5 30       | 13 6.   |
|   |                               | GCKR      | rs780094   | A            | 102 32      | 16 47       | 39  | 3 13       | 16 6.1 |
| 17| A Pagán et al. (2014)         | TCF7L2    | rs7903146  | T            | 24 45       | 10 12       | 2   | 19 18      | 8 3.   |
|   |                               | TCF7L2    | rs12255372 | T            | 25 45       | 9 14        | 2   | 19 20      | 6 3.   |
|   |                               | TCF7L2    | rs7901695  | T            | 25 45       | 10 13       | 2   | 17 20      | 8 3.4  |
| 18| A Papadppoulo et al. (2011)   | TCF7L2    | rs7903146  | T            | 1110 803    | 644 384     | 82  | 363 352    | 88 2.4 |
|   |                               | TCF7L2    | rs12255372 | T            | 1102 801    | 633 385     | 84  | 387 333    | 81 2.   |
|   |                               | TCF7L2    | rs7901695  | C            | 1102 794    | 607 405     | 90  | 343 356    | 95 2.   |
| 19| Wang et al. (2011)            | MTNR1B    | rs10830963 | G            | 1029 700    | 329 509     | 191 | 199 364    | 137 4.2|
| Study/Genotype   | rsID     | Gene/SNP   | Minor Allele | Major Allele | Minor Allele Frequency | Major Allele Frequency | Alpha Appliance Tag | p-Value |
|-----------------|----------|------------|--------------|--------------|------------------------|------------------------|---------------------|---------|
| Steube et al. (2014) | IGFBP2 [rs4402960] | 1025 | 705 | 605 | 361 | 1 | T | 23 |
| CDKAL1 [rs7754840] | 1020 | 697 | 197 | 512 | 311 | 159 | 339 | 199 | C | 55 |
| GCKR [rs780094] | 792 | 52 | 266 | 376 | 24 | 23 | 5 | A | 42 |
| Vlassi et al. (2017) | GCKR [rs1260326] | 840 | 56 | 291 | 395 | 25 | 26 | 5 | T | 41 |
| Chao Li et al. (2013) | MTNR1B [rs10830963] | 480 | 350 | 172 | 233 | 75 | 113 | 158 | 79 | G | 35 |
| Chao Li et al. (2018) | MTNR1B [rs10830963] | 243 | 215 | 87 | 121 | 35 | 54 | 102 | 59 | G | 35 |
| Chao Li et al. (2014) | PPARG [rs1801282] | 78 | 72 | 67 | 11 | 0 | 65 | 7 | 0 | G | 71 |
| Rizk et al. (2011) | TCF7L2 [rs7903146] | 74 | 40 | 29 | 37 | 8 | 16 | 18 | 6 | T | 35 |
| TCF7L2 [rs12255372] | 74 | 40 | 25 | 38 | 11 | 6 | 28 | 6 | T | 40 |
| Shi et al. (2014) | TCF7L2 [rs7903146] | 100 | 100 | 55 | 38 | 7 | 40 | 36 | 24 | T | 26 |
| DG Siudak et al. (2016) | TCF7L2 [rs7903146] | 26 | 50 | 10 | 15 | 1 | 19 | 29 | 2 | T | 32 |
| IA Khan et al. (2018) | TCF7L2 [rs7903146] | 150 | 137 | 76 | 63 | 11 | 53 | 60 | 24 | T | 25 |
| Vlassi et al. (2012) | MTNR1B [rs10830963] | 98 | 77 | 56 | 30 | 12 | 30 | 31 | 16 | G | 27 |
| MTNR1B [rs1387153] | 98 | 77 | 52 | 35 | 11 | 39 | 26 | 12 | T | 25 |
| Vcelak et al. (2012) | TCF7L2 [rs7903146] | 376 | 261 | 156 | 185 | 35 | 142 | 102 | 17 | T | 32 |
| TCF7L2 [rs12255372] | 376 | 260 | 206 | 147 | 23 | 123 | 115 | 22 | T | 25 |
| Aris et al. (2012) | TCF7L2 [rs7903146] | 114 | 173 | 0 | 15 | 99 | 1 | 43 | 129 | T | 9 |
| CDKAL1 [rs7754840] | MTNR1B [rs1387153] | 113 | 169 | 64 | 37 | 12 | 64 | 81 | 24 | C | 26 |
| M. Ekelund et al. (2012) | TCF7L2 [rs7903146] | 476 | 125 | 239 | 195 | 42 | 49 | 56 | 20 | T | 25 |
| FTQ [rs8050136] | 480 | 126 | 180 | 223 | 77 | 39 | 62 | 25 | A | 35 |
| KK Alharbi et al. (2019) | MTNR1B [rs10830963] | 200 | 200 | 96 | 65 | 39 | 64 | 87 | 49 | G | 36 |
| MTNR1B [rs1387153] | 200 | 200 | 91 | 81 | 28 | 64 | 92 | 44 | T | 34 |
| Liu et al. (2015) | MTNR1B [rs10830963] | 674 | 674 | 195 | 362 | 117 | 162 | 334 | 178 | G | 44 |
| MTNR1B [rs1387153] | 690 | 674 | 367 | 246 | 77 | 341 | 228 | 105 | T | 26 |
| JY Kim et al. (2011) | MTNR1B [rs10830963] | 966 | 908 | 294 | 469 | 203 | 217 | 435 | 256 | G | 45 |
| MTNR1B [rs1387153] | 972 | 909 | 313 | 455 | 204 | 235 | 433 | 241 | T | 44 |
| Saucedo et al. (2017) | FTQ [rs9939609] | 80 | 80 | 59 | 20 | 1 | 61 | 18 | 1 | A | 13 |
| FTQ [rs8050136] | 80 | 80 | 59 | 20 | 1 | 61 | 18 | 1 | A | 13 |
| Tok et al. (2006) | PPARG [rs1801282] | 100 | 62 | 84 | 16 | 0 | 50 | 12 | 0 | G | 8 |
| IRS1 [rs1801278] | 100 | 62 | 89 | 11 | 0 | 53 | 9 | 0 | A | 5 |
| S Chon et al. (2013) | PPARG [rs1801282] | 41 | 94 | 34 | 7 | 0 | 89 | 5 | 0 | G | 8 |
| IGFBP2 [rs4402960] | 41 | 94 | 15 | 24 | 2 | 57 | 30 | 7 | T | 34 |
| M. Tarnowski et al (2017) | GCK [rs1799884] | 207 | 204 | 163 | 42 | 2 | 147 | 52 | 5 | A | 11 |
| GCKR [rs780094] | 207 | 204 | 73 | 101 | 33 | 77 | 99 | 28 | C | 40 |
| No. | Reference | Gene | SNP ID | Meta | NA1 | NA2 | NA3 | NA4 | NA5 | NA6 | NA7 | NA8 | NA9 | NA10 | NA11 | NA12 | NA13 | NA14 | NA15 | NA16 | NA17 | NA18 | NA19 | NA20 | NA21 | NA22 | NA23 | NA24 | NA25 | NA26 | NA27 | NA28 | NA29 | NA30 | NA31 | NA32 | NA33 | NA34 | NA35 | NA36 | NA37 | NA38 | NA39 | NA40 | NA41 | NA42 | NA43 | NA44 | NA45 | NA46 | NA47 | NA48 | NA49 | NA50 | NA51 | NA52 | NA53 | NA54 | NA55 | NA56 | NA57 | NA58 | NA59 | NA60 | NA61 | NA62 | NA63 |
|   | Study                        | Gene           | rs   | C1  | C2  | C3  | C4  | C5  | C6  | C7  | C8  | C9  | C10 | C11 | C12 | C13 | C14 |
|---|------------------------------|----------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|64 | Noury et al. (2018)          | CDKAL1 [rs7754840] | 51   | 47  | 8   | 23  | 20  | 3   | 26  | 18  | C   | 61  |
|65 | Wu et al (2015)              | CDKAL1 [rs7754840] | 180  | 153 | 52  | 95  | 33  | 45  | 79  | 29  | C   | 44  |
|66 | Kanthimathi et al. (2015)    | CDKAL1 [rs7754840] | 910  | 495 | 46  | 306 | 558 | 49  | 172 | 274 | C   | 76  |
|67 | Beltcheva et al. (2014)      | ADIPOQ [rs266729] | 259  | 130 | 126 | 103 | 30  | 80  | 44  | 6   | G   | 31  |
|68 | Pawlik et al. (2017)         | ADIPOQ [rs266729] | 207  | 204 | 115 | 75  | 17  | 92  | 91  | 21  | G   | 26  |
|69 | Chang et al. (2005)          | TNF [rs1800629]   | 35   | 35  | 22  | 5   | 8   | 10  | 7   | 18  | A   | 36  |
|70 | Montazeri et al. (2010)      | TNF [rs1800629]   | 102  | 110 | 94  | 6   | 2   | 103 | 4   | 3   | A   | 4.1 |
|71 | Flores et al. (2013)         | TNF [rs1800629]   | 44   | 51  | 39  | 5   | 0   | 43  | 7   | 1   | A   | 5   |
|72 | A Oliveira et al. (2016)     | GCKR [rs780094]   | 125  | 127 | 43  | 68  | 14  | 64  | 48  | 15  | C   | 36  |
|73 | A. Pagan et al. (2014)       | FTO [rs9939609]   | 25   | 45  | 5   | 15  | 5   | 23  | 15  | 7   | A   | 5   |
|74 | Imran et al. (2014)          | CANP10 [rs2975760] | 150  | 137 | 97  | 42  | 11  | 85  | 40  | 12  | C   | 21  |

Table 3: Features of genes and genetic variants included in the meta-analysis
| Sl. No. | Gene                  | Description                              | SNPs               | Alleles          | Variants          | Biological Process                                           |
|--------|-----------------------|------------------------------------------|--------------------|------------------|-------------------|-------------------------------------------------------------|
|        |                       |                                          |                    |                  |                   |                                                             |
| 1      | TCF7L2                | Transcription factor 7-like 2            | [rs7903146]        | C>G / C>T        | Intron Variant    | positive regulation of insulin secretion                   |
|        |                       |                                          | [rs12255372]       | G>A / G>T        | Intron Variant    |                                                             |
|        |                       |                                          | [rs7901695]        | T>C              | Intron Variant    |                                                             |
| 2      | MTNR1B                | Melatonin receptor 1B                    | [rs10830963]       | C>G              | Intron Variant    | negative regulation of insulin secretion                   |
|        |                       |                                          | [rs1387153]        | C>T              | None              |                                                             |
| 3      | FTO                   | Alpha-ketoglutarate-dependent dioxygenase| [rs9939609]        | T>A              | Intron Variant    | regulation of lipid storage                               |
|        |                       |                                          | [rs8050136]        | C>A              | Intron Variant    |                                                             |
| 4      | PPARG                 | Peroxisome proliferator-activated receptor| [rs1801282]       | C>G              | Missense Variant  | cellular response to insulin stimulus                      |
|        | gamma                 | gamma                                    |                    |                  |                   |                                                             |
| 5      | GCK                   | Glucokinase                              | [rs1799884]        | G>A              | 2KB Upstream Variant| positive regulation of insulin secretion                   |
| 6      | GCKR                  | Glucokinase Regulator                     | [rs780094]         | T>C              | Intron Variant    | negative regulation of glucokinase activity                |
|        |                       |                                          | [rs1260326]        | C>T              | Missense Variant  |                                                             |
| 7      | ADIPOQ                | Adiponectin                              | [rs266729]         | C>A / C>G / C>T  | 2KB Upstream Variant| cellular response to insulin stimulus                      |
|        |                       |                                          |                    |                  |                   |                                                             |
| 8      | TNF                   | Tumor necrosis factor                     | [rs1800629]        | G>A              | 2KB Upstream Variant| negative regulation of glucose import                     |
| 9      | IRS1                  | Insulin receptor substrate 1             | [rs1801278]        | C>G / C>T        | Missense Variant  | insulin receptor signaling pathway                          |
| 10     | KCNJ11                | Potassium inwardly rectifying channel,   | [rs5219]           | C>T              | Stop Gained      | negative regulation of insulin secretion                   |
|        | subfamily J, member 11|                                          |                    |                  |                   |                                                             |
| 11     | IGF2BP2               | Insulin-like growth factor 2 mRNA-binding| [rs4402960]        | G>T              | Intron Variant    | regulation of cytokine biosynthetic process                |
|        | protein 2             | protein 2                                |                    |                  |                   |                                                             |
| 12     | ADRB3                 | Adrenoceptor beta 3                      | [rs4994]           | T>C              | Missense Variant  | carbohydrate metabolic process                             |
| 13     | CDKL1                 | CDK5 regulatory subunit associated protein| [rs7754840]        | G>A / G>C / G>T  | Intron Variant    | maintenance of translational fidelity                      |
|        | 1-like 1              | protein 1-like 1                         |                    |                  |                   |                                                             |
| 14     | HNF1A                 | Hepatocyte nuclear factor 1-alpha         | [rs1169288]        | G>T              | Missense Variant  | insulin secretion                                           |
| 15     | CANP10                | Calpain-10                               | [rs2975760]        | T>C              | Intron Variant    | positive regulation of insulin secretion                   |
|        |                       |                                          | [rs5030952]        | C>G / C>T        | None              |                                                             |
|        |                       |                                          | [rs3792267]        | G>A              | Intron Variant    |                                                             |
| 16     | SLC30A8               | Solute carrier family 30 member 8         | [rs13266634]       | C>A / C>T        | Missense Variant  | positive regulation of insulin secretion                   |

Table 4: Association between GDM risk and genetic variants
| S.no. | Gene   | rs ID     | Genotype       | Model         | Heterogeneity | Overall effect | p-value | p-value |
|-------|--------|-----------|----------------|---------------|---------------|---------------|---------|---------|
|       |        |           |                |               | r² Value  | p-value     | OR (95% C.I.) |         |
| 1     | SLC30A8| rs1326634 | CC vs.TT+ CT   | Dominant      | 92%           | <0.00001     | 1.91(1.57-2.32) | <0.00001 |
|       |        |           | TT vs. CC+CT   | Recessive     | 77%           | 0.0006       | 0.99(0.81-1.19) | 0.88     |
|       |        |           | TT vs. CC      | Homozygote    | 86%           | <0.00001     | 0.88(0.71-1.08) | 0.22     |
|       |        |           | TT vs. CT      | Heterozygote  | 96%           | <0.00001     | 2.90(2.26-3.72) | <0.00001 |
|       |        |           | C vs. T allele | Allele        | 75%           | 0.001       | 0.76(0.58-1.00) | 0.05     |
| 2     | CANP10 | rs3792267 | GG vs. AA+ GA  | Dominant      | 13%           | 0.33        | 1.40(1.04-1.88) | 0.03     |
|       |        |           | AA vs. GG+GA   | Recessive     | 83%           | 0.001       | 0.64(0.47-0.86) | 0.003    |
|       |        |           | AA vs. GG      | Homozygote    | 21%           | 0.28        | 0.72(0.53-0.98) | 0.03     |
|       |        |           | AA vs. GA      | Heterozygote  | 10%           | 0.34        | 0.66(0.48-0.91) | 0.01     |
|       |        |           | G vs. A allele | Allele        | 6%            | 0.37        | 0.99(0.71-1.38) | 0.95     |
| 3     | CANP10 | rs5030952 | CC vs.TT+ CT   | Dominant      | 0%            | 0.44        | 2.24(1.96-5.20) | 0.06     |
|       |        |           | TT vs. CC+CT   | Recessive     | 82%           | 0.004       | 0.71(0.45-1.11) | 0.13     |
|       |        |           | TT vs. CC      | Homozygote    | 0%            | 0.66        | 1.88(0.77-4.6)  | 0.16     |
|       |        |           | TT vs. CT      | Heterozygote  | 0%            | 0.42        | 2.24(0.86-5.88) | 0.1      |
|       |        |           | C vs. T allele | Allele        | 0%            | 0.48        | 1.09(0.71-1.68) | 0.71     |
| 4     | CANP10 | rs2975760 | TT vs.CC+ TC   | Dominant      | 0%            | 0.39        | 0.49(0.32-0.75) | 0.01     |
|       |        |           | CC vs. TT+TC   | Recessive     | 93%           | <0.00001    | 0.31(0.28-0.49) | <0.00001 |
|       |        |           | CC vs. TT      | Homozygote    | 92%           | <0.00001    | 3.84(2.34-6.31) | <0.00001 |
|       |        |           | CC vs. TC      | Heterozygote  | 67%           | 0.05        | 1.16(0.76-1.77) | 0.5      |
|       |        |           | T vs. C allele | Allele        | 92%           | <0.00001    | 2.92(1.96-4.35) | <0.00001 |
| 5     | HNF1A  | rs1169288 | GG vs.TT+ GT   | Dominant      | 83%           | 0.07        | 1.17(0.90-1.52) | 0.23     |
|       |        |           | TT vs. GG+GT   | Recessive     | 0%            | 0.39        | 0.34(0.26-0.44) | 0.00001  |
|       |        |           | TT vs. GG      | Homozygote    | 84%           | 0.002       | 1.68(1.25-2.26) | 0.0005   |
|       |        |           | TT vs. GT      | Heterozygote  | 61%           | 0.08        | 0.95(0.72-1.26) | 0.74     |
|       |        |           | G vs. T allele | Allele        | 75%           | 0.02        | 2.42(1.55-3.77) | <0.00001 |
| 6     | CDKAL1 | rs7754840 | GG vs.CC+ GC   | Dominant      | 93%           | <0.00001    | 1.78(1.55-2.04) | <0.00001 |
|       |        |           | CC vs. GG+GC   | Recessive     | 89%           | <0.00001    | 0.90(0.78-1.04) | 0.14     |
|       |        |           | CC vs. GG      | Homozygote    | 97%           | <0.00001    | 2.70(2.26-3.21) | <0.00001 |
|       |        |           | CC vs. GC      | Heterozygote  | 93%           | <0.00001    | 1.86(1.59-2.71) | <0.00001 |
|       |        |           | G vs. C allele | Allele        | 73%           | 0.001       | 1.11(0.83-1.48) | 0.48     |
| 7     | ADRB3  | rs4994    | TT vs.CC+ TC   | Dominant      | 60%           | 0.08        | 0.68(0.30-1.56) | 0.31     |
|       |        |           | CC vs. TT+TC   | Recessive     | 48%           | 0.12        | 1.13(0.91-1.41) | 0.28     |
|       |        |           | CC vs. TT      | Homozygote    | 0%            | 0.7         | 0.79(0.32-1.94) | 0.61     |
|       |        |           | CC vs. TC      | Heterozygote  | 0%            | 0.56        | 0.83(0.33-2.09) | 0.69     |
|       |        |           | T vs. C allele | Allele        | 0%            | 0.55        | 0.74(0.43-1.28) | 0.28     |
| 8     | IGFBP2 | rs4402960 | GG vs.TT+ GT   | Dominant      | 0%            | 0.5         | 1.28(1.04-1.56) | 0.02     |
|       |        |           | TT vs. GG+GT   | Recessive     | 91%           | <0.00001    | 0.25(0.20-0.32) | <0.00001 |
|       |        |           | TT vs. GG      | Homozygote    | 65%           | 0.02        | 1.33(1.08-1.65) | 0.008    |
|       |        |           | TT vs. GT      | Heterozygote  | 70%           | 0.01        | 1.08(0.87-1.33) | 0.5      |
|       |        |           | G vs. T allele | Allele        | 59%           | 0.04        | 1.05(0.78-1.33) | 0.14     |
| 9     | KCNJ11 | rs5219    | CC vs.TT+ CT   | Dominant      | 31%           | 0.22        | 1.07(0.91-1.25) | 0.43     |
|       |        |           | TT vs. CC+CT   | Recessive     | 92%           | <0.00001    | 1.05(0.91-1.22) | 0.43     |
| Gene | rs Number | Term  | Effect | Minor Allele | Frequency | P Value | OR 95% CI | OR 95% CI |
|------|-----------|-------|--------|--------------|-----------|---------|-----------|-----------|
|      |           |       | Homozygote |               | 95%       | <0.0001 | 1.47(1.22-1.76) | <0.0001 |
|      |           |       | Heterozygote |               | 0%        | 0.5     | 1.19(0.96-1.47) | 0.12     |
|      |           |       | Allele |               | 0%        | 0.83    | 1.23(0.88-1.73) | 0.22     |
|     10 | IRS1      | rs1801278 | GG vs. AA+ GA | Dominant | 28%      | 0.25    | 3.10(1.38-6.94) | 0.006    |
|      |           |       | AA vs. GG+GA | Recessive | 56%      | 0.06    | 0.98(0.77-1.25) | 0.87     |
|      |           |       | AA vs. GG | Homozygote | 0%        | 0.45    | 4.50(1.92-10.56) | 0.0006   |
|      |           |       | AA vs. GA | Heterozygote | 47%      | 0.15    | 2.53(1.10-5.83) | 0.03     |
|      |           |       | G vs. A allele | Allele | 0%        | 0.42    | 1.66(1.05-2.62) | 0.03     |
|     11 | TNF       | rs1800629 | GG vs. AA+ GA | Dominant | 73%      | 0.01    | 2.49(1.19-5.22) | 0.02     |
|      |           |       | AA vs. GG+GA | Recessive | 13%      | 0.33    | 1.07(0.67-1.79) | 0.78     |
|      |           |       | AA vs. GG | Homozygote | 0%        | 0.92    | 1.71(0.73-4.00) | 0.21     |
|      |           |       | AA vs. GA | Heterozygote | 2%        | 0.38    | 0.96(0.35-2.63) | 0.94     |
|      |           |       | G vs. A allele | Allele | 0%        | 0.54    | 1.64(1.02-2.51) | 0.04     |
|     12 | ADIPOQ    | rs266729 | CC vs.GG+ CG | Dominant | 57%      | 0.07    | 0.85(0.56-1.29) | 0.45     |
|      |           |       | GG vs. CC+CG | Recessive | 89%      | <0.0001 | 0.58(0.41-0.83) | 0.003    |
|      |           |       | GG vs. CC | Homozygote | 77%      | <0.005  | 0.88(0.57-1.36) | 0.57     |
|      |           |       | GG vs. CG | Heterozygote | 0%        | 0.43    | 0.75(0.47-1.20) | 0.23     |
|      |           |       | C vs. G allele | Allele | 81%      | <0.001  | 1.06(0.76-1.48) | 0.73     |
|     13 | GCKR      | rs1260326 | CC vs.TT+ CT | Dominant | 0%       | 0.56    | 0.68(0.48-0.96) | 0.03     |
|      |           |       | TT vs. CC+CT | Recessive | 61%      | 0.05    | 1.25(0.91-1.72) | 0.17     |
|      |           |       | TT vs. CC | Homozygote | 34%      | 0.21    | 0.51(0.31-0.84) | 0.008    |
|      |           |       | TT vs. CT | Heterozygote | 0%        | 0.64    | 0.66(0.45-0.98) | 0.04     |
|      |           |       | C vs. T allele | Allele | 18%      | 0.3     | 0.54(0.33-0.87) | 0.01     |
|     14 | GCKR      | rs780094 | TT vs.CC+ TC | Dominant | 87%      | <0.0001 | 1.35(1.02-1.770) | 0.03     |
|      |           |       | CC vs. TT+TC | Recessive | 83%      | <0.0001 | 0.69(0.53-0.90) | 0.06     |
|      |           |       | CC vs. TT | Homozygote | 51%      | 0.06    | 0.52(0.38-0.70) | <0.00001 |
|      |           |       | CC vs. TC | Heterozygote | 65%      | <0.008  | 0.72(0.53-0.97) | 0.03     |
|      |           |       | T vs. C allele | Allele | 56%      | <0.04   | 0.51(0.39-0.67) | <0.00001 |
|     15 | GCK       | rs1799884 | GG vs. AA+ GA | Dominant | 22%      | 0.27    | 1.88(1.42-2.47) | <0.00001 |
|      |           |       | AA vs. GG+GA | Recessive | 86%      | <0.0001 | 1.77(1.56-2.00) | <0.00001 |
|      |           |       | AA vs. GG | Homozygote | 0%        | 0.41    | 1.98(1.50-2.62) | <0.00001 |
|      |           |       | AA vs. GA | Heterozygote | 13%      | 0.33    | 1.62(1.22-2.17) | 0.001    |
|      |           |       | G vs. A allele | Allele | 0%       | 0.9     | 1.52(1.11-2.09) | 0.001    |
|     16 | FTO       | rs8050136 | CC vs. AA+ CA | Dominant | 65%      | 0.04    | 1.30(0.92-1.83) | 0.14     |
|      |           |       | AA vs. CC+CA | Recessive | 69%      | 0.02    | 1.01(0.83-1.23) | 0.89     |
|      |           |       | AA vs. CC | Homozygote | 48%      | 0.12    | 1.18(0.78-1.77) | 0.43     |
|      |           |       | AA vs. CA | Heterozygote | 0%        | 0.53    | 0.92(0.64-1.35) | 0.68     |
|      |           |       | C vs. A allele | Allele | 81%      | 0.001   | 0.86(0.37-1.32) | 0.5      |
|     17 | MTNR1B    | rs1387153 | CC vs.TT+ CT | Dominant | 8%       | 0.36    | 1.68(1.43-1.98) | <0.00001 |
|      |           |       | TT vs. CC+CT | Recessive | 94%      | <0.0001 | 0.69(0.57-0.83) | <0.00001 |
|      |           |       | TT vs. CC | Homozygote | 90%      | <0.0001 | 3.42(2.69-4.36) | <0.00001 |
|      |           |       | TT vs. CT | Heterozygote | 0%        | 0.62    | 1.73(1.43-2.10) | <0.00001 |
|      |           |       | C vs. T allele | Allele | 66%      | <0.02   | 2.0(1.64-3.24) | <0.00001 |
|     18 | TCF7L2    | rs7901695 | TT vs.CC+ TC | Dominant | 66%      | 0.02    | 1.41(1.07-1.85) | 0.01     |
|     | Gene   | rs Number | Model | Frequency | Odds Ratio | 95% CI         | P-value |
|-----|--------|-----------|-------|-----------|------------|----------------|---------|
| 19  | TCF7L2 | rs7903146 | CC vs. TT+TC | Recessive | 95% | <0.00001 | 1.16(0.90-1.48) | 0.25 |
|     |        |           | CC vs. TT  | Homozygote | 84% | <0.0001 | 1.69(1.26-2.27) | 0.0005 |
|     |        |           | CC vs. TC  | Heterozygote | 41% | 0.14 | 1.25(0.94-1.57) | 0.13 |
|     |        |           | T vs. C allele | Allele | 82% | 0.0002 | 0.89(0.64-1.23) | 0.48 |
|     |        |           | CC vs. TT  | Homozygote | 84% | <0.0001 | 1.69(1.26-2.27) | 0.0005 |
|     |        |           | TT vs. CC  | Recessive | 63% | <0.00001 | 2.03(1.79-2.31) | <0.00001 |
|     |        |           | TT vs. CT  | Heterozygote | 45% | 0.01 | 1.46(1.29-1.66) | <0.00001 |
|     |        |           | T vs. C allele | Allele | 66% | <0.00001 | 1.60(1.38-1.86) | <0.00001 |
| 20  | TCF7L2 | rs12255572 | GG vs. TT+GT | Dominant | 43% | 0.02 | 1.59(1.42-1.78) | <0.00001 |
|     |        |           | TT vs. GG+GT | Recessive | 87% | <0.00001 | 2.24(1.81-2.77) | <0.00001 |
|     |        |           | TT vs. GG  | Homozygote | 38% | 0.11 | 1.69(1.33-2.15) | <0.00001 |
|     |        |           | TT vs. GT  | Heterozygote | 21% | 0.25 | 1.10(0.86-1.41) | 0.44 |
|     |        |           | G vs. T allele | Allele | 56% | 0.01 | 1.80(1.41-2.30) | <0.00001 |
| 21  | MTNR1B | rs1083963 | CC vs. GG+CG | Dominant | 64% | 0.006 | 1.81(1.63-2.02) | <0.00001 |
|     |        |           | GG vs. CC+CG | Recessive | 87% | <0.00001 | 0.55(0.49-0.61) | <0.00001 |
|     |        |           | GG vs. CC  | Homozygote | 88% | <0.00001 | 2.82(2.42-3.30) | <0.00001 |
|     |        |           | GG vs. CG  | Heterozygote | 72% | <0.00001 | 1.82(1.61-2.06) | <0.00001 |
|     |        |           | C vs. G allele | Allele | 79% | <0.00001 | 1.85(1.50-2.29) | <0.00001 |
| 22  | FTO    | rs9939609 | TT vs. AA+TA | Dominant | 66% | 0.004 | 1.32(1.08-1.62) | 0.007 |
|     |        |           | AA vs. TT+TA | Recessive | 82% | <0.00001 | 0.72(0.60-0.86) | 0.00004 |
|     |        |           | AA vs. TT  | Homozygote | 86% | <0.00001 | 1.86(1.42-2.43) | <0.00001 |
|     |        |           | AA vs. TA  | Heterozygote | 64% | 0.007 | 1.40(1.11-1.75) | 0.004 |
|     |        |           | T vs. A allele | Allele | 77% | <0.00001 | 1.16(0.87-1.55) | 0.3 |
| 23  | PPARG  | rs1801282 | CC vs. GG+CG | Dominant | 0% | 0.7 | 0.72(0.44-1.15) | 0.17 |
|     |        |           | GG vs. CC+CG | Recessive | 46% | 0.03 | 0.95(0.85-1.07) | 0.41 |
|     |        |           | GG vs. CC  | Homozygote | 13% | 0.32 | 0.69(0.57-1.38) | 0.59 |
|     |        |           | GG vs. CG  | Heterozygote | 0% | 0.5 | 0.62(0.38-1.00) | 0.05 |
|     |        |           | C vs. G allele | Allele | 77% | <0.00001 | 0.55(0.43-0.70) | <0.00001 |

Figures
Figure 1: Flow chart showing selection of studies for inclusion in meta-analysis.

Flow chart showing selection of studies for inclusion in meta-analysis
Figure 2

Venn diagram and Bar graph: Bar graph is showing the genes and their associated variants which have been included in the study. TCF7L2, MTNR1B, FTO, GCKR and CANP10 have more than one variant. Venn diagram shows the number of variants which have been found to be significantly associated with GDM risk in all five genetic models. Out of 23 variants analyzed, only four variants namely rs780094, rs1387153, rs1799884, and rs1083963 have been found to be significantly associated with increased risk of GDM.

Figure 3

Distribution of OR among SNPs in different model
Odds Ratio distribution: A. Most of the SNPs have odds ratio greater than one in all genetic models analyzed (except recessive; OR<1) and hence are associated with increased risk of GDM. B. Value of ORs significantly associated with GDM among different genetic models have been plotted.

Figure 4

Forest plot: of association between TCF7L2 rs7903146 polymorphism and risk of gestational diabetes (all genetic model). The shadowed squares and their lateral tips indicate the ORs and the corresponding 95% CIs in individual studies, with the sizes of squares proportional to weights used in the meta-analyses. The central lines and lateral tips of the diamonds indicate the pooled ORs and the corresponding 95% CIs. The solid vertical lines indicate no effect.
Figure 5

Forest plot: The risk of GDM in association of genetic variants GCK rs1799884. The shadowed squares and their lateral tips indicate the ORs and the corresponding 95% CIs in individual studies, with the sizes of squares proportional to weights used in the meta-analyses. The central lines and lateral tips of the diamonds indicate the pooled ORs and the corresponding 95% CIs. The solid vertical lines indicate no effect.
Figure 6

Forest plot: The risk of GDM in association of genetic variants GCKR rs780904. The shadowed squares and their lateral tips indicate the ORs and the corresponding 95% CIs in individual studies, with the sizes of squares proportional to weights used in the meta-analyses. The central lines and lateral tips of the diamonds indicate the pooled ORs and the corresponding 95% CIs. The solid vertical lines indicate no effect.
Figure 7

Forest plot: The risk of GDM in association of genetic variants of MTNR1B A. rs1083963 B. rs1387153. The shadowed squares and their lateral tips indicate the ORs and the corresponding 95% CIs in individual studies, with the sizes of squares proportional to weights used in the meta-analyses. The central lines and lateral tips of the diamonds indicate the pooled ORs and the corresponding 95% CIs. The solid vertical lines indicate no effect.
Figure 8

Forest plot: The risk of GDM in association of genetic variants SLC30A8 rs1326634. The shadowed squares and their lateral tips indicate the ORs and the corresponding 95% CIs in individual studies, with the sizes of squares proportional to weights used in the meta-analyses. The central lines and lateral tips of the diamonds indicate the pooled ORs and the corresponding 95% CIs. The solid vertical lines indicate no effect.
Figure 9

Networking, GO and KEGG pathway enrichment. A. String network of all 16 genes shows the high interconnection among these genes. B. Gene Ontology (GO) enrichment analysis revealed major function; processes and cellular components related to these genes and have been plotted against log of p-value. C. Significant pathways associated with these have been plotted against log of p-value.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplemteryfile1.xlsx
- SF1.tif
- SF2.tif