GWAS in Gestational Diabetes Mellitus: Research Advances

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Abstract: As a prevalent metabolic disorder arising in pregnancy, gestational diabetes mellitus (GDM) poses substantial risks to maternal and fetal well-being. The development of GDM is substantially influenced by hereditary components, with variations observed across different racial groups. Genome wide association studies (GWAS) are an effective tool that provides new insights into the genetic mechanism of GDM. This review details the current application of GWAS in GDM research. It sums up the identified susceptibility gene loci and their potential functions in the Chinese population with GDM. Moreover, it underscores the importance of independent research. By establishing a relatively comprehensive reference framework, this study intends to enhance the exploration of the genetic basis of GDM, improve the capacity of precise risk assessment, and develop customized treatment strategies in a clinical context.

1 Introduction

Genome wide association study (GWAS) is a population genetic method to study the genetic mechanism of complex biological traits based on linkage disequilibrium using high-density molecular markers in the whole genome. This association is formed by evolutionary factors such as mutation, gene drift and natural selection, and gradually disintegrates through gene recombination.[1] Single nucleotide polymorphisms (SNPs) represent a fundamental type of genetic variation characterized by the presence of alternative nucleotide bases (adenine, thymine, cytosine, or guanine) at particular genomic locations across distinct individuals.[2] SNPs frequently manifest in both coding sequences and non-coding regions of the genome, with each polymorphic site typically exhibiting two or more allelic variants that contribute to genetic diversity within populations. [3]

One of the most common metabolic diseases in pregnancy is gestational diabetes mellitus (GDM), which is mainly manifested as abnormal glucose metabolism first appeared or diagnosed during pregnancy. This disease belongs to a special metabolic disorder, which is characterized by impaired glucose tolerance during pregnancy. [4] Recent epidemiological studies have shown that the incidence of gestational diabetes mellitus worldwide has shown a significant growth trend. The number of patients with this metabolic disease continues to rise worldwide and has become a health problem that cannot be ignored. According to the latest International Diabetes Federation (IDF) diabetes Atlas (10th Edition), gestational diabetes mellitus (GDM) affects about one sixth of pregnant women worldwide, and there are huge geographical differences between different regions and populations, with an average prevalence of about 16.7%[5]. As a populous country, China faces a particularly prominent challenge with GDM, where the prevalence among pregnant women is 14.8%, with notable regional disparities (15.7% in the north and 20.3% in the south).[6] GDM not only threatens maternal health, increasing the likelihood of conditions such as gestational hypertension and cesarean delivery, but also leads to adverse outcomes for the fetus and newborn, including macrosomia (birth weight >4 kg), neonatal hypoglycemia, and respiratory distress syndrome. Compared with the healthy group without disease, women who experienced gestational diabetes mellitus has significantly possibility to develop type 2 diabetes after delivery. Specifically, the probability of T2D in this group of people is about 10 times higher than that of normal women. This metabolic abnormality makes patients with GDM become a high-risk group of diabetes, and special attention should be paid to their long-term health risks. Their offspring also face elevated risks of obesity during adolescence and cardiovascular diseases in adulthood. [4], [7] These long-term health implications highlight GDM as a significant challenge to global public health.

Genetic factors are pivotal in the pathogenesis of GDM and are influenced by ethnic differences. A growing number of studies have revealed the population heterogeneity of GDM, suggesting that the interplay between the genetic backgrounds of different races and environmental factors may form unique molecular pathological pathways. In the past decade, through large-scale genetic data analysis of individuals of European descent, researchers have successfully identified a series of core gene loci closely related to disease susceptibility. (e.g., MTNR1B). However, the genetic mechanism in East Asian populations, particularly the Chinese population, remains poorly understood. Notably, with the establishment of large - scale pregnancy cohorts in China, recent research has gradually uncovered GDM - specific risk loci in the Chinese population (e.g., ESR1 and

SLC30A8). These findings not only supplement crucial data to the genetic map of East Asian populations but also underscore the significance of ethnicity - specific molecular mechanisms in disease development.

2 Application status of GWAS in GDM

Conventional GWAS employs a case-control approach and depends on stringent statistical criteria ($p<5 \times 10^{-8}$) to minimize false positives. However, it encounters several obstacles in researching GDM: (1) limitations in sample size: the dynamic variations in phenotypes throughout pregnancy make it challenging to establish large sample cohorts, resulting in inadequate statistical power; (2) population diversity: the majority of current studies concentrate on populations of European or East Asian descent, with insufficient cross-ethnic validation, impacting the generalizability of discovered loci; (3) ambiguous functional mechanisms: many prominent SNPs are found in non-coding regions, requiring further study their biological relevance through functional experiments or cross-omics integration. Consequently, the methodologies used in GWAS have been progressively enhanced in recent years, yielding significant insights into the genetic mechanisms underlying GDM.

2.1 Sample collection and genotyping techniques

Over the past few years, high-throughput sequencing technology has undergone significant and rapid advancements and the utilization of copy number variation (CNV) analysis, powered by high-throughput sequencing, has steadily gained traction in the field of prenatal diagnosis, providing improved accuracy and depth in identifying genetic abnormalities.[8] Traditional GWAS rely on chip or high-depth sequencing to detect single nucleotide polymorphisms (SNPs) by high-throughput genotyping. CNV-seq technology effectively makes up for the defects of karyotyping and chip detection, as well as the specificity of GDM patients. Noninvasive prenatal testing (NIPT) obtains genetic information from maternal peripheral blood free DNA by low depth whole genome sequencing and combines it with clinical phenotype data (such as oral glucose tolerance test) for GWAS analysis. [8]NIPT data are cost-effective and convenient for sample collection, which is particularly suitable for large-scale pregnancy cohort studies. It also allows the simultaneous integration of fetal genetic information, such as fetal DNA ratios.

2.2 Statistical analysis method

2.2.1 multi-ancestry meta-analysis.

The cross-ethnic meta-analysis integrates genetic data from diverse populations (such as European, East Asian, African, etc.) and employs a random effect model for comprehensive analysis. This approach effectively mitigates population stratification bias and enhances the statistical power of genetic association studies, thereby enabling the more precise identification of genetic variants linked to complex diseases[9]. For instance, The 2013 cross-ethnic GWAS study[10] involving population samples from four distinct ancestries revealed that HKDC1 is the most strongly associated locus with GDM, and several gene variants within HKDC1 are linked to maternal glucose metabolism. Pervjakova et al. utilized MR-MEGA to simulate heterogeneity in GWAS by incorporating a genetic variation axis that reflects ancestry within the meta-regression framework. They also conducted a fixed effects meta-analysis that accounted for both multi-ancestry and ancestry-specific variations. Ultimately, their multi-ancestry meta-analysis highlighted five gene loci that were significantly associated with GDM on a genome-wide scale. This revealed some of the common genetic bases between GDM and T2D.[11]

Multi - lineage meta - analysis diversifies genetic backgrounds, enhancing the generalizability and reproducibility of studies. However, this approach presents certain limitations. Genetic heterogeneity among different populations complicates the interpretation of results, and it necessitates large sample sizes and high - quality data to support the analysis.

2.2.2 multi omics data integration.

With the continuous development of sequencing technology, transcriptomics (RNA SEQ), epigenomics and metabolomics have provided researchers with more insights. The integration of multi omics technology and GWAS can analyze the molecular mechanism of complex diseases from the gene, epigenetic, protein and other levels, and give priority to screening single nucleotide polymorphisms (SNPs) with high functional relevance. Transcriptome-wide association studies (TWAS) can identify reveal the key relationship between regulatory genes and target traits.[12] This method can effectively identify the important gene regulatory networks that affect specific traits and provide a new perspective for understanding the genetic basis of complex traits. Zhu et al revealed the potential mechanism of ESR1 affecting blood glucose by regulating arterial gene expression (such as tibial artery) through TWAS, promoting the transformation from genetic association to functional mechanism. However, there are also some limitations of multi omics integration, such as the high complexity of data integration, the need for strong computational resources and bioinformatics support, and the heterogeneity between different omics data leads to insufficient interpretation of the pathological mechanism and the genetic factors involved. [13]

3 GWAS findings in Chinese gestational diabetes mellitus population

With the continuous development of GWAS research, we increasingly find that there is population heterogeneity in GDM related gene loci among different ethnic groups. [10], [14]Recently, several large-scale GWAS results of Chinese

GDM population were published, confirming the necessity of independent research. We selected four representative genes for brief elaboration and the Table 4 presented other gene sites.

3.1 MTNR1B

The melatonin receptor 1B gene (MTNR1B) is responsible for encoding the MT2 melatonin receptor. This receptor plays a crucial role in maintaining glucose homeostasis and regulating insulin secretion. Variations in the MTNR1B gene have been associated with irregular glucose metabolism in pregnant individuals, affecting fasting blood glucose (FPG), 1-hour postprandial blood glucose (OGTT1h), and glycated hemoglobin (HbA1c) levels.[10] Moreover, the elevation of melatonin during pregnancy may influence placental function, [15]further highlighting the possible significance of MTNR1B in metabolic regulation throughout this period.

Initially, MTNR1B was considered a type 2 diabetes mellitus (T2D) susceptibility gene[16]. However, later research showed a stronger association with GDM. A 2012 GDM GWAS in South Korean found the rs10830962 locus in GDM women (OR = 1.47) had a much higher effect size than in East Asian T2D patients (OR = 1.04) [17]. A 2022 multi - ancestry study confirmed its cross - population GDM susceptibility[11]. A 2024 Finnish study[18] established MTNR1B (rs10830963) as a core GDM risk gene, showing its link to pregnancy metabolic indicators. These studies shifted MTNR1B's genetic role from T2D to GDM, likely due to the placental environment, melatonin fluctuation, and β - cell function demand.

In studies involving Chinese populations, the rs10830963 polymorphism has been linked to diminished β-cell function and elevated FPG, reinforcing its implications as a genetic locus for gestational diabetes mellitus (GDM) risk. Additionally, the T allele of rs7936247 has been found to heighten GDM risk in women lacking a family history of diabetes, potentially due to its relationship with SNORA8 regulation and histone modification[19]. A large - scale Chinese GWAS showed MTNR1B has a stronger role in GDM than CDKAL1, highlighting genetic differences between GDM and T2D. Despite its identification as a GDM susceptibility gene in both European and East Asian populations, the rs3781637 locus in the Chinese population has a different allele frequency, indicating the need for population - specific genetic research. For more information, see Table 1.

Table 1. The list of GWAS signal for MTNR1B.

Research	Ancestry	Sample size	SNP	OR value	P value
Zhu et al. (2024)[20]	East Asian	14,744	rs3781637	/	3.29×10^{-09}
Zhen et al. (2024) [21]	East Asian	30699	rs10830963	1.57	4.42×10^{-29}
Li et al. (2024) [22]	East Asian	8067	rs10830963	1.55	3.43×10^{-18}
Xie et al. (2019)[23]	East Asian	1985	rs10830963 rs7936247	1.20 1.20	0.007 0.014
Elliott et al. (2024) [18]	Europ	143441	rs10830963	/	8.65×10^{-175}
Kwak SH et al. (2012) [17]	East Asian	3424	rs10830962	1.454	2.49×10^{-13}
Pervjakova et al. (2022) [11]	multi-ancestry	353341	rs10830963	1.41	4.3×10^{-54}

3.2 ESR1

The gene ESR1 (estrogen receptor 1) encodes the estrogen receptor α (ERα), a member of the nuclear receptor superfamily. [24] ERα plays a central role in female reproductive development, bone metabolism, cardiovascular homeostasis, and glucose and lipid metabolism. It does so by binding to estrogen (such as estradiol) to form dimers and regulating the transcription of downstream target genes [25].

In a 2024 study conducted in Finland, which involved 12,332 cases of gestational diabetes mellitus (GDM) and 131,109 controls, ESR1 was identified for the first time as a novel susceptibility gene for GDM[18]. The study also revealed its strong association with fasting blood glucose (FPG) and insulin resistance during pregnancy. Subsequently, a large - scale GWAS study of 14,744 pregnant women by Chinese scholars found a significant correlation between the rs3020430 locus of ESR1 and the likelihood of developing GDM. Additional GWAS co-location analysis within an independent cohort further confirmed ESR1's role in regulating fasting blood glucose levels throughout pregnancy. Functional analysis showed that there were three clinically pathogenic variants (rs397509428, rs1131692059, rs1057519827) in exon 5 of the ESR1 correlation peak. All of these variants were related to estrogen resistance syndrome and breast neoplasia [26]. Among them, rs397509428 is located at a key site of LBD. It may lead to a compensatory imbalance of the insulin signaling pathway by destroying the estrogen - binding ability.[27], [28]

The identification of ESR1 (listed in Table 2) enhances the understanding of the genetic framework underlying blood glucose characteristics in pregnancy, particularly among East Asian populations. Future functional studies and clinical trials on ESR1 will further reveal its role in GDM.

Table 2. The list of GWAS signal for ESR1.

Research	Ancestry	Sample size	SNP	OR value	P value
Zhu et al. (2024) [20]	East Asian	14,744 30699 (GWAS-GWAS colocalization analysis)	rs3020430 rs9322351 (in LD with rs3020430)	/	1.36×10^{-8} 6.91×10^{-6}
Elliott et al. (2024) [18]	Europ	143441	rs10830963	/	3.82×10^{-8}

3.3 CDKAL1

CDKAL1 (Cyclin-dependent kinase-like 1) encodes a protein that regulates functions associated with cyclin-dependent kinase 5 (CDK5). Variations in this gene can diminish insulin sensitivity to glucose, which is associated with defects in proinsulin conversion. [25]Since 2007, when GWAS first reported its strong correlation with type 2 diabetes mellitus (T2D)[29], many cross - population studies have regarded CDKAL1 as the second - strongest genetic locus for T2D within the East Asian demographic (OR = 1.15 - 1.30)[30]. Although its genetic variation is involved in the common pathogenesis of T2D and gestational diabetes mellitus (GDM), the specific mechanism in GDM requires further analysis.

In recent years, large - scale GWAS on the Chinese population have shown CDKAL1's key role in GDM susceptibility (more details in Table 3). A study of 30,699 pregnant women found that the rs7766070 - A locus of CDKAL1 was correlated with OGTT1H and OGTT2H, but not FPG. [21] A study of 14,744 Chinese maternities showed that after excluding pre - pregnancy diabetes, the rs35261542 locus became the second GDM susceptibility site. [20]A meta - analysis based on a Chinese multi - center cohort[31] (n = 1,681 cases/1,789 controls) confirmed the connection between the rs7754840 locus and GDM risk and its interaction with choline metabolism, suggesting an impact on pregnancy glucose metabolism via mitochondrial dysfunction.

However, the genetic effect of CDKAL1 in the Chinese population shows significant heterogeneity. A study of 1,705 pregnant women[32]found loci like rs4712527 (OR = 0.87) and rs7748720 (OR = 0.89) had a reducing effect. Given the limitations of current research, which include a small sample size (n = 835 - 1,705) and a focus on geographical regions (eastern coastal areas), a cross - regional large - sample cohort (n > 10000) is needed to confirm its population universality.

Table 3. The list of GWAS signal for CDKAL1.

Research	Ancestry	Sample size	SNP	OR value	P value
Zhu et al. (2024)[20]	East Asian	14,744	rs35261542	/	3.88×10^{-12}
Zhen et al. (2024) [21]	East Asian	30699	rs7766070	1.27	8.07×10^{-12}
Elliott et al. (2024) [18]	Europ	143441	rs34499031	/	5.1×10^{-16}
Pervjakova et al. (2022) [11]	multi-ancestry	353341	rs10830963	1.13	1.6×10^{-14}

3.4 SLC30A8

The gene SLC30A8 is responsible for encoding the zinc transporter known as ZnT8. This transporter primarily facilitates the transport of zinc ions into pancreatic β cells, helping to maintain zinc homeostasis, which in turn influences the synthesis and secretion of insulin.[33] A loss - of - function mutation of SLC30A8 leads to impaired zinc - transport function, thus affecting glucose - stimulated insulin secretion, which may increase the susceptibility to diabetes. Currently, the genetic changes of SLC30A8 may increase the risk of GDM development by affecting placental function, zinc homeostasis, and insulin secretion.[34] Previous studies have found that the variation of the SLC30A8 gene, especially the polymorphism of rs13266634, is related to the susceptibility to gestational diabetes in the Asian population[35].

Genome - wide association studies of 30,699 pregnant women in China first confirmed that the mutation of the SLC30A8 (SNP rs13266634 - C) gene is closely related to GDM risk. This suggests that SLC30A8 is a susceptibility gene worthy of attention in the Chinese population. Although this is the largest GDM genetic research in Asia currently, its conclusions need to be repeatedly verified by cross - regional multicenter cohorts (including western and rural populations). Additionally, it is necessary to further combine single - cell sequencing and CRISPR editing technology to analyze the dynamic regulatory network of SLC30A8 in the adaptive remodeling of β cells during pregnancy. Based on the above evidence, the zinc - steady - state regulation strategy targeting SLC30A reveals a new direction of analyzing the genetic mechanism and treatment of GDM, but its safety and effectiveness need to be evaluated through strictly designed clinical trials.

Table 4. The risk-related genes of GDM population in China, except those described above.[20], [21], [36], [37], [38]

Gene	SNP	Protein function
TBR1-SLC4A10	rs117781972	TBR1, a transcription factor, plays a crucial role in brain development, while SLC4A10 functions in ion transport across the cell membrane.
TRPV3	rs62069863	TRPV3 is associated with the exacerbation of postpartum insulin resistance.
PRMT6	rs2232016	PRMT6 is involved in processes such as DNA repair, signal transduction, and cell - cycle regulation.
HHEX/EXOC6	rs1112718	HHEX is crucial for the development of the liver, gallbladder, and thyroid during the embryonic period. EXOC6 is involved in the process of intracellular substance transport. Both are representative genes associated with β - cell dysfunction.
GLIS3	rs927316	GLIS3 is a key transcription factor in pancreatic islet β - cell generation, and its mutations are associated with various diseases such as diabetes and neurodevelopmental disorders.
LPIN2	rs10460009	LPIN2 is a crucial molecule in lipid metabolism, related to adipogenesis and exerting functions in the inflammatory response.
FTO	rs1121980	The FTO gene is implicated in the modulation of lipid levels, the process of fat cell formation, and the regulation of body mass.
KCNQ1	rs163182	KCNQ1, is a voltage-sensitive potassium channel and important to the secretion of insulin.
MC4R	rs12970134	MC4R regulates appetite and energy balance, and is closely related to the development of obesity.
PROX1	rs340841	PROX1 plays important roles in aspects such as lymphatic vessel formation and retinal development.

4 Conclusion

With the continuous innovation of GWAS technology, an expanding array of research has shown that GDM possesses a distinct genetic foundation. Some gene loci associated with GDM exhibit characteristics of differential racial - specific correlations. Recent GWAS findings on the Chinese GDM population have firmly confirmed that the GDM population in China has a unique genetic basis, significantly expanding our understanding of the genetic architecture of GDM.[20], [21], [31]

With the identification of numerous novel gene loci, future research should focus on uncovering their specific functions in pregnancy - related metabolic regulation via multi - omics integration, such as single - cell transcriptomics and epigenomics. Additionally, establishing some cross - regional and multi - ethnic large - scale pregnancy cohort system can facilitate the analysis of the genetic heterogeneity of GDM in the Chinese population.

In summary, the swift advancement of genetic research on GDM within the Chinese population not only offers new targets for disease prevention and treatment but also contributes crucial data to the global precision medicine research on pregnancy - related metabolic disorders. Through the continuous deepening of interdisciplinary research, accurate prediction and individualized intervention of GDM are expected to be achieved in the future.

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