



Review

Mechanisms and Physiological Roles of Polymorphisms in Gestational Diabetes Mellitus

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Abstract: Gestational diabetes mellitus (GDM) is a significant pregnancy complication linked to perinatal complications and an elevated risk of future metabolic disorders for both mothers and their children. GDM is diagnosed when women without prior diabetes develop chronic hyperglycemia due to β -cell dysfunction during gestation. Global research focuses on the association between GDM and single nucleotide polymorphisms (SNPs) and aims to enhance our understanding of GDM's pathogenesis, predict its risk, and guide patient management. This review offers a summary of various SNPs linked to a heightened risk of GDM and explores their biological mechanisms within the tissues implicated in the development of the condition.

Keywords: SNPs; gestational diabetes mellitus; genetics; GWAS



Citation: Suthon, S.; Tangjittipokin, W. Mechanisms and Physiological Roles of Polymorphisms in Gestational Diabetes Mellitus. *Int. J. Mol. Sci.* **2024**, *25*, 2039. <https://doi.org/10.3390/ijms25042039>

Academic Editors: Alessandra Puddu and Davide Maggi

Received: 5 January 2024

Revised: 3 February 2024

Accepted: 5 February 2024

Published: 7 February 2024



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1. Introduction

Gestational diabetes mellitus (GDM) refers to diabetes diagnosed in the second or third trimester of pregnancy that was not present before gestation and carries risks for the mother, fetus, and newborn. GDM is often indicative of underlying β -cell dysfunction and increases the risk for later development of diabetes, which is often type 2 diabetes (T2D), in the mother after delivery [1].

The maternal body undergoes a sequence of physiological changes to accommodate the needs of the developing fetus, with insulin sensitivity representing a vital metabolic adaptation during this process. An upsurge in local and placental hormones during mid- to late gestation induces insulin resistance. GDM occurs when pancreatic β -cells cannot adequately respond to the heightened requirement for insulin secretion, leading to the onset of spontaneous hyperglycemia during pregnancy. Both the malfunction of β -cells and the resistance of body tissues to insulin are integral aspects of the pathophysiology of GDM [2].

GDM is a multifactorial disorder that is influenced by interactions between genetic and environmental factors. The interplay between these factors suggests the complexity of the mechanistic pathways underlying GDM. Genome-wide association studies (GWAS) have identified specific genetic variations called single nucleotide polymorphisms (SNPs) associated with the risk of developing GDM. These SNPs not only help researchers understand the causes of GDM for potential drug development, but also have practical applications in clinical settings, which can be used to predict the risk of GDM, guide treatment choices, and manage GDM patients during pregnancy and postpartum, enhancing our understanding and approach to this condition [3].

Several genes, such as the transcription factor 7-like 2 (*TCF7L2*) gene, the haematopoietically expressed homeobox gene (*HHEX*), the adiponectin, C1Q, and collagen domain

containing (*ADIPOQ*) gene, and the vascular endothelial growth factor A (*VEGFA*) gene, are expressed in major tissues contributing to GDM, including the placenta. Their SNPs have been reported to be associated with GDM. This review will explore the biological and physiological effects of these SNPs on the development of GDM. We retrieved the prediction of transcription factors on each SNP by JASPAR CORE 2022 [4] from the UCSC Genome Browser [5]. We also discuss how each tissue contributes to the pathogenesis of GDM, as shown in Figure 1.

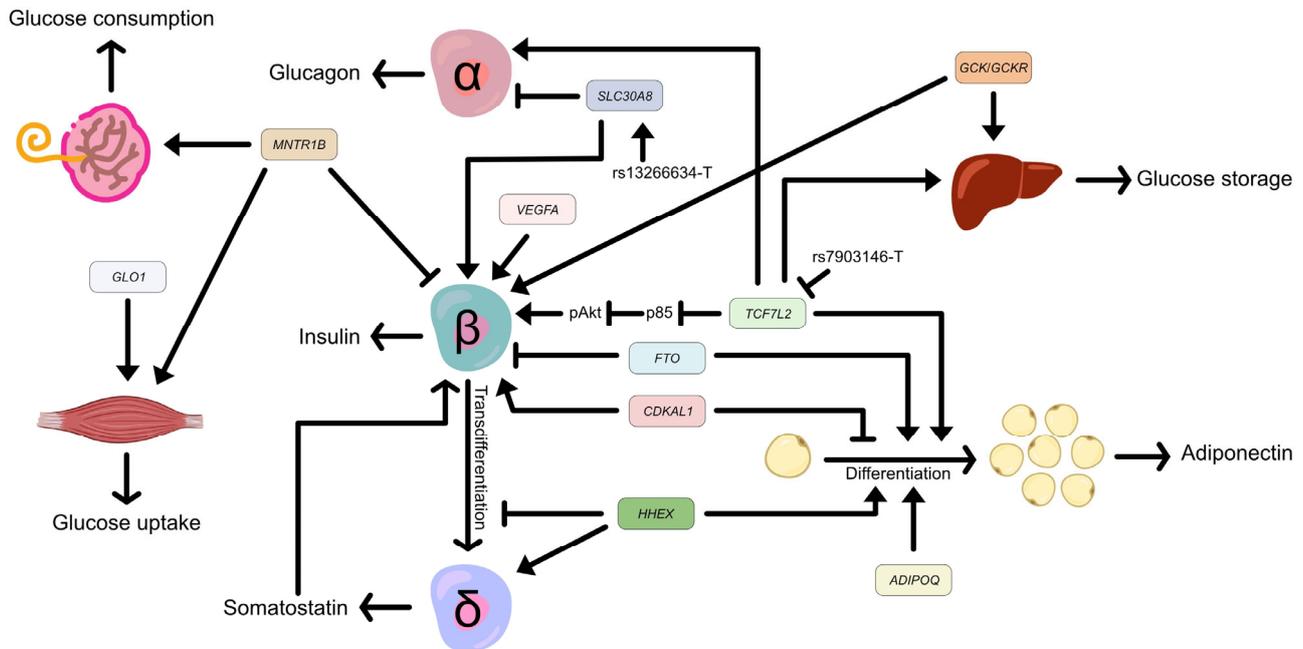


Figure 1. Effects of associated genes and SNPs in major tissues contribute to gestational diabetes mellitus. *TCF7L2* promotes glucose storage in the liver, activates insulin secretion in β -cells by suppressing the expression of p85, and inhibits adipogenesis. The *TCFL2* rs7903146 minor allele, T, downregulates the expression of *TCF7L2*. *HHEX* increases somatostatin secretion and adipocyte differentiation but inhibits the transdifferentiation of β -cells to δ -cells. *SLC30A8* activates insulin secretion and reduces glucagon secretion. The *SLC30A8* missense variant rs13266634 allele T improves glucose responsiveness and enhances proinsulin conversion. *ADIPOQ* activates adipogenesis. *FTO* inhibits insulin secretion and promotes adipocyte differentiation, and vice versa by *CDKAL1*. *VEGFA* maintains β -cell function. *MTNR1B* increases glucose consumption in the placenta and skeletal muscle, but decreases insulin secretion in pancreatic β -cells. *GLO1* activates glucose uptake in skeletal muscle and *GSK/GSKR* promotes glucose storage in the liver. The transcription factor 7-like 2 (*TCF7L2*) gene, the haematopoietically expressed homeobox (*HHEX*) gene, the solute carrier family 30 member 8 gene (*SLC30A8*), the adiponectin, C1Q, and collagen domain containing (*ADIPOQ*) gene, the human fat mass and obesity-related (*FTO*) gene, the CDK5 regulatory subunit associated protein 1 like 1 (*CDKAL1*) gene, the vascular endothelial growth factor A (*VEGFA*) gene, the melatonin receptor 1B (*MTNR1B*) gene, the glyoxalase I (*GLO1*) gene, the glucokinase (*GSK*) gene, and the glucokinase regulator (*GSKR*) gene.

2. *TCF7L2*

The transcription factor 7-like 2 gene (*TCF7L2*) is located on chromosome 10q25.3 and contains 18 exons, presenting complex splicing in different tissues. *TCF7L2* is a member of the T-cell factor/lymphoid enhancer binding factor family (TCF/LEF), the transcription factor of the Wnt/ β -catenin signaling pathway. Mechanistically, *TCF7L2* heterodimerizes with β -catenin, then binds to DNA through a high-mobility group (HMG)-box domain to act as either a stimulator or repressor of target gene expression [6].

Several *TCF7L2* SNPs have been reported to be associated with a high risk of developing GDM in various populations [7–10]. Notably, all SNPs are in intronic regions, as shown in Table 1, suggesting the regulatory function of the SNPs in cell-context specificity. Among *TCF7L2* variants, rs7903146 (C > T) presented a strong association with GDM risk and increased more than fivefold in the TT genotype in Caucasian women [11]. In contrast, there were no significant differences in the frequencies of the *TCF7L2* rs7903146 genotypes between GDM and normal healthy women in the Chinese population; however, this SNP affected glycolipid metabolism in GDM women [9]. The risk allele at SNP rs7903146, identified through fine mapping, coincided with enhanced histone marks in both islets and adipose tissue [12]. This SNP was associated with the offspring's birth weight [13]. Notably, *TCF7L2* SNPs rs7895340 and rs11196205 demonstrated a significant association with T2D in Thai patients similar to the association observed with SNP rs7903146 in Europeans, suggesting the effect of SNPs on the association in different ethnicities [14]. *TCF7L2* is expressed in many tissues involved in glucose and lipid metabolism, such as adipose tissue, liver, pancreas, and placenta.

Table 1. Gestational diabetes mellitus-associated SNPs.

Genes	SNPs	Location	Risk Allele	Predicted TF (JASPAR)	Expression in Placenta
<i>TCF7L2</i>	rs34872471	Intron 4	C	ZNF354A, Six3, JUND	Y
	rs7901695	Intron 4	C	n/a	
	rs4506565	Intron 4	T	PLAGL2	
	rs7903146	Intron 4	T	ZNF211	
	rs12243326	Intron 4	C	ZNF211	
	rs12255372	Intron 5	T	n/a	
	rs290487	Intron 8	T	NFIC::TLX1	
<i>HHEX</i>	rs1111875	Intergenic	C	ETV2::FOXI1, ERF::FOXI1, FOXO1::FLI1, SPIB, GABPA, Erg	
	rs5015480	Intergenic	C	n/a	Y
	rs7923837	Intergenic	G	FOXO, FOXA, FOXP	
<i>SLC30A8</i>	rs13266634	Missense	C	PAX1, PAX2, PAX9	N
	rs3802177	3' UTR	G	PAX1, PAX9	
	rs2466293	3' UTR	G	NR1D2, RXRA::VDR	
<i>ADIPOQ</i>	rs17300539	Promoter	A	n/a	
	rs266729	Promoter	G	THAP1	
	rs2241766	Exon 2	G	Tfcp2l1, RARB, RARG	
	rs1501299	Intron 2	T	ZNF354A, POU4F3	
<i>FTO</i>	rs1421085	Intron 2	No association	ONECUT1, ONECUT3, CUX1, CUX2	Y
	rs1121980	Intron 2	G	SIX2	
	rs8050136	Intron 2	No association	ONECUT1, ONECUT2, CUX1	
	rs9939609	Intron 2	A	POU2F1::SOX2	
<i>VEGFA</i>	rs2010963	Exon 1	No association	ZNF701, IRF2	Y
	rs833069	Intron 2	No association	ZNF257, ZKSCAN5, ZNF701, ZNF263, SP4, SP5	
	rs2146323	Intron 2	A	Zfp335	

Table 1. Cont.

Genes	SNPs	Location	Risk Allele	Predicted TF (JASPAR)	Expression in Placenta
	rs3025010	Intron5	No association	Ebf2, EBF3, ZNF449, ZNF682, KLF3, NFIC, ZNF324	
	rs3025039	Exon 7	T	Bach1::Mafk, Mafg, MAFG::NFE2L, MAFK, MAF::NFE2	
<i>CDKAL1</i>	rs10946398	Intron 5	C	CREB1, MAF	Y
	rs7754840	Intron 5	C	n/a	
	rs7756992	Intron 5	G	Irf1, IRF7, MEF2A, MEF2C, MEF2D	
	rs9368222	Intron 5	A	SOX4, SOX10, SOX 12, Sox 11, Sox6	
	rs7747752	Intron 5	C	MGA	
<i>MTNR1B</i>	rs1387153	Intergenic	T	NR5A1, ZBTB12, ZSCAN31, THAP1	Y
	rs10830962	Intergenic	G	MEF2B, MEF2D, Rhox11, CDX2	
	rs4753426	Promoter	C	n/a	
	rs10830963	Intron 1	G	n/a	
<i>GLO1</i>	rs1130534	Exon 4	T	n/a	Y
	rs4746	Exon 4	T	n/a	
	rs1781735	Promoter	No association	n/a	
<i>GCK</i>	rs1799884	Promoter	T	n/a	Y
	rs4607517	Intergenic	A	PBX3, SREBF1, PKNOX1, Neurod2	
<i>GCKR</i>	rs1260326	Missense	C	n/a	Y
	rs780094	Intron 16	C	NRL, TBX19, TBXT, PKNOX1	

Pancreas-specific and β -cell-specific *Tcf7l2* null mice altered glucose homeostasis by decreasing glucose tolerance, impairing insulin secretion, and reducing pancreatic β -cell volume [15,16]. TCF7L2 was bound to phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*) promoter to suppress the encoding of p38, resulting in the activation of p-Akt and an increase in insulin secretion [17]. Selective deletion of *Tcf7l2* in mice pancreatic α -cells showed a lower α -cell mass and defective counterregulatory response by increasing glucose infusion rates and decreasing plasma glucose concentration. Loss of *Tcf7l2* also suppressed the expression of glucagon (*Gcg*) and MAF BZIP transcription factor B (*Mafb*) in the islet [18]. However, no effects were found on insulin (*Ins*) gene expression in insulin-positive cells and β -cell mass [18]. A *Tcf7l2* mutant in zebrafish showed hyperglycemia, pancreatic and vascular defects, and decreasing regeneration [19]. RNAseq in zebrafish adult pancreatic cell type revealed that *Tcf7l2* exhibited the highest expression in acinar tissue and was expressed in δ -cells but not in β -cells [19].

TCF7L2 plays a role in the development and functioning of adipose tissue. Humans with impaired glucose tolerance and adipocyte insulin resistance [20], humans with obesity [12], and mice with high-fat diet-induced obesity [21] showed low *TCF7L2* levels. TCF7L2 was required for Wnt/ β -catenin signaling during adipogenesis [20]. Conditional adipocyte *Tcf7l2^{ff}* knockout mice induced adipocyte hypertrophy and impaired lipolysis response to fasting [21]. Specifically in mature adipocytes in vivo, disabling the TCF7L2 protein by eliminating the HMG-box DNA-binding domain resulted in overall glucose intolerance and insulin resistance in the liver [20]. Transcriptome-wide profiling indicated that TCF7L2 regulates the extracellular matrix, immune response, and apoptosis in the adipose progenitor [12]. However, the actions of TCF7L2 in adipose tissue remain controversial. Human adipose progenitor had the highest expression of *TCF7L2* mRNA but then decreased during differentiation [12]. In contrast, *Tcf7l2* was elevated during adipocyte differentiation in murine 3T3-L1 cells [20]. In obesity, the protein level of TCF7L2 is reduced

in whole adipose tissue but increased in adipocyte progenitor. Knockdown of *TCF7L2* in adipose progenitor showed activation of Wnt/ β -catenin signaling in a dose-dependent manner, resulting in impaired proliferation and adipogenesis, while overexpression of *TCF7L2* activated adipocyte differentiation [12]. Finally, SNP rs7903146 minor allele T increased insulin accumulation in adipose tissue by decreasing the level of *TCF7L2* in adipose progenitor but not in mature adipocytes. A luciferase assay elucidated that the risk allele T abolished the enhancer activity of *TCF7L2* [12].

Mice with liver-specific *Tcf7l2* knockout (*Alb-Cre; Tcf7l2^{ff}*) displayed elevated fasting glucose levels without alterations in body weight, plasma insulin, or insulin-like growth factor-1 levels. The deficiency of hepatic *Tcf7l2* resulted in impaired glucose and insulin tolerance, yet no changes were observed in hepatic insulin signaling or energy expenditure. Interestingly, hepatic *Tcf7l2* depletion significantly increased the expression of lipogenic genes in the liver, without affecting genes related to β -oxidation and lipolysis [22].

Notably, *TCF7L2* is also exhibited in the placenta [23]; however, the mechanism associated with GDM has never been revealed.

3. HHEX

The haematopoietically expressed homeobox (*HHEX*) gene encodes a member of the homeobox family of transcription factors. The genomic structure of human *HHEX* comprises four exons. It is mapped in the 270-kb linkage disequilibrium (LD) block of 10q23.33, containing three genes: insulin degradation enzyme (*IDE*), kinesin family member 11 (*KIF11*), and *HHEX* [24].

HHEX variants rs1111875 (T > C), rs5015480 (T > C), and rs7923837 (A > G) were associated with increased susceptibility to GDM [25–27]. All three SNPs are in the intergenic region of the *IDE-KIF11-HHEX* LD block, in which the closest gene is *HHEX* [25]. However, in silico studies, such as cis-expression quantitative trait locus (cis-eQTL), which linked SNPs to *HHEX*, have never been confirmed. Interestingly, the major alleles in all SNPs increased the risk of GDM and are mainly predicted to be the binding sites of forkhead box (FOX) transcription factors, as shown in Table 1.

HHEX plays roles during pancreas and liver embryogenic development, which may affect glucose homeostasis and insulin secretion later in life. The pancreas and liver originate from a shared pool of progenitors, and *HHEX* plays a crucial role in development by serving as a gatekeeper for pancreatic lineage specification by collaborating with pancreatic transcription factors and endodermal transcription factors like *FOXA2* and *GATA4* [28]. *HHEX* participates in the development of the pancreatic endoderm by controlling the expression of genes associated with pancreatic development, including *NKX6.1*, *PTF1A*, *ONECUT1*, and *ONECUT3* [29]. Notably, *HHEX* was not detected in the pancreatic β -cells and α -cells of adult humans and mice, while it was exhibited in adult pancreatic δ -cells and regulated somatostatin secretion [30]. Lysine-specific demethylase-1 targeted the *Hhex* locus and promoted the repression of *Hhex* by facilitating methylation at H3K4me1/2, leading to the prevention of the transition of β -cells to δ -cells [31].

Although *HHEX* is expressed in adipocytes [32] and the placenta [33], studies of mechanism and function remain limited. Knockdown of *Hhex* in preadipocyte cell line 3T3-L1 suppressed adipogenesis in a dose-dependent manner and led to the suppression of peroxisome proliferator-activated receptor gamma (*PPARG*) level [32].

4. SLC30A8

The solute carrier family 30 member 8 gene (*SLC30A8*) encodes zinc transporter 8 (ZnT8) protein, which is highly specifically expressed in insulin-producing β -cells and required for insulin biosynthesis and secretion. *SLC30A8* is located on chromosome 8q24.11 and consists of eight exons spanning a length of 37 kb and encoding a 369-amino acid protein [34].

Three *SLC30A8* SNPs have been reported to be associated with the risk of GDM (Table 1). SNP rs13266634 (C > T) is a missense variant affecting the amino acid residue

325 in the ZnT8 C-terminal. The major allele CGG at the codon results in the production of arginine (R), whereas the minor allele TGG leads to the generation of tryptophan (W), denoted as R325W. This SNP showed significant associations with GDM and ethnicity specificity. The rs13266634 C allele increased the risk of developing GDM [35–37] whereas the T allele was a protective variant against the development of GDM [36,38,39]. Loss of ZnT8 function improved glucose responsiveness and enhanced proinsulin conversion, leading to more effective insulin secretion and preservation of the function of β -cells [40,41]. Mechanistically, the protective T allele enhanced the response to the glucose challenge by increasing insulin secretion and decreasing glucagon secretion in primary islets. Additionally, there was a tendency for the T allele to lower the expression of *SLC30A8* ($p = 0.053$) and genes related to proinsulin processing [42].

The other two *SLC30A8* SNPs, rs3802177 (G > A) and rs2466293 (A > G), are both located at 3' UTR variants. *SLC30A8* rs3802177 [7] and rs2466293 [38] were significantly associated with an increased risk of GDM in the Chinese population and were predicted to be binding sites for transcription factors, as shown in Table 1. However, the molecular mechanisms governing how these SNPs affect the expression of *SLC30A8* require further investigation.

5. ADIPOQ

The adiponectin, C1Q, and collagen domain containing gene (*ADIPOQ*) is located on chromosome 3q27.3 and is major expressed in adipose tissue. It encodes adiponectin, a 30 kDa circulating protein in the plasma, which is involved in various physiological mechanisms encompassing energy metabolism and insulin sensitivity [43]. Women with GDM often experience hypoadiponectinemia, leading to insulin resistance and glucose intolerance [44].

SNPs rs17300539 (−11391G > A) and rs266729 (−11377C > G) in the promoter region, rs2241766 (+45T > G) in exon 2, and rs1501299 (+276G > T) in intron 2 have been reported as being associated with the risk of GDM development (Table 1). These four variants are situated within the two *ADIPOQ* LD blocks. Block 1 includes the promoter sequence spanning from −14,811 to −4120, while block 2 encompasses the exons within the region −450 to +4545 [45].

ADIPOQ rs266729 (C > G) allele G increased the risk of GDM in Asian and European populations [46,47], while reducing it in the American population [48]. The study of Chinese women did not show a significant difference in the genotypes and allele frequencies of rs266729 between GDM patients and the control [49]. The patient's carrier allele G had a higher adiponectin level [46] and diastolic blood pressure [49] compared to carrier allele C. In contrast, the study of Bulgarian women elucidated that the G allele had a protective effect against GDM [50]. Another SNP in the promoter region, rs17300539 (G > A) allele G, was associated with lower adiponectin [51]. Notably, the variant rs17300539, along with rs266729, has been reported as having no association with GDM in black South African women [52].

SNP rs2241766 (T > G) is a synonymous mutation (Gly15Gly) at exon 2. Although rs2241766 allele G was associated with the risk of GDM [53], the effects of this SNP on adiponectin levels in serum are still controversial in different ethnicities [45,46,54,55]. In Thai women with GDM, the study showed no significant differences in adiponectin levels between different genotypes [46]. However, in Chinese patients, allele G was associated with higher adiponectin levels compared to allele T [55]. Conversely, in Malaysian patients, the trend was reversed, with allele T linked to higher adiponectin levels [54].

Rs1501299 (G > T) showed an association with the risk of T1D, T2D, and GDM [56]; however, there are still few studies on GDM [46,49,53,57]. Tangjittipokin et al. elucidated that patients with minor allele T had higher fasting glucose levels than those with major allele G [46]. GDM patients with the rs1501299 GT genotype had lower diastolic blood pressure than those with the GG genotype [49].

Taken together, the *ADIPOQ* SNPs are important susceptibility factors for developing GDM. Nevertheless, the molecular mechanisms governing how these SNPs affect the level of adiponectin need to be investigated.

6. *FTO*

The human fat mass and obesity-related gene (*FTO*) is mapped on chromosome 16q12.2, including nine exons and eight introns. *FTO* encodes a 2-oxoglutarate-dependent nucleic acid demethylase, and its main substrate is N6-methyladenosine (m6A) in nuclear RNA, controlling several post-transcriptional regulatory processes [58]. *FTO* is widely expressed in adipose tissues and skeletal muscles in humans, playing a crucial role in the regulation of body weight and fat mass. *FTO* is also a critical regulator of adipogenesis that acts in the early stages of adipogenesis, leading to obesity [59]. *FTO* inhibits insulin secretion and contributes to pancreas islet β -cells dysfunction [60]. However, no study has investigated the role of skeletal muscles in the functioning of the *FTO* gene in GDM.

FTO rs1121980 (G > A) minor allele A was found to be significantly associated with a reduced risk of GDM [61]. Additionally, the SNP rs9939609 (T > A) showed a significant association with the risk of developing GDM, and the association was detected only in the Caucasian subgroup by meta-analysis [37]. Individuals carrying the AT genotype of rs9939609 were found to have a higher risk of exceeding excessive gestational weight gain earlier than those with the TT genotype [62]. Notably, multiple meta-analysis studies have reported an inability to detect significant associations between *FTO* polymorphisms, including rs9939609, rs8050136, rs1421085, and rs1121980, and the risk of developing GDM [63–67].

Although the *FTO* SNPs rs8050136, rs9939609, and rs1421085 did not emerge as major genetic regulators in the development of GDM, these SNPs were found to be associated with concentrations of adiponectin and TNF α in subjects with GDM [63]. SNP rs8050136 showed no significant association with GDM, but posed an increased risk of GDM in Bangladeshi multigravida women [67]. Interestingly, *FTO* SNPs are located in intron 1 (as listed in Table 1), suggesting a potential role in regulating the expression of *FTO* itself and possibly influencing nearby genes [58].

7. *VEGFA*

The vascular endothelial growth factor A (*VEGFA*) gene is located at chromosome 6p21.3 and consists of eight exons separated by seven introns with a full molecular length of 14 kb. *VEGFA* undergoes alternative mRNA splicing, resulting in the generation of different-length isoforms. These isoforms possess distinct biological properties, and each plays a specific role in the differentiation and development of the vascular system [68].

Hypervascularity is normally found with increase in placental weight in GDM [69]. However, the plasma levels of *VEGFA* are still contradictory. Troncoso et al. showed no difference in *VEGFA* levels between GDM and the control group, while Meng et al. indicated that GDM patients had lower *VEGFA* levels [70]. In contrast, other studies showed that GDM patients had elevated *VEGFA* levels [71,72]. *VEGFA* is also expressed in β -cells and controls development and function. The protein level of *VEGFA* remained constant in β -cells throughout pregnancy in mice [73]. However, when *VEGFA* signaling was disrupted in β -cells of pregnant mice, it led to a decrease in the maintenance of islet vessels and induced transient glucose intolerance without affecting the expansion of the β -cell mass [74].

Although the expression of *VEGFA* seems important in the pathogenesis of GDM, there is only one study on the association of *VEGFA* polymorphisms with GDM in Chinese women [71]. Five SNPs of the *VEGFA* gene were selected: rs2146323 (C > A), rs2010963 (G > C), rs3025039 (C > T), rs3025010 (T > C), and rs833069 (G > A) (Table 1). SNPs rs2146323 allele A (intron 2) and rs3025039 allele T (exon 7) showed a dramatically increased risk of GDM. The patients who carried the rs3025039 CT+TT genotype had a higher level of *VEGFA* than those who carried the CC genotype. Other SNPs showed no difference

in the distributions of genotypes and alleles between GDM and control. Interestingly, the frequency of haplotypes CAAC, CAAT, CACC, CACT, GACT, and GGCT for the rs2010963–rs833069–rs2146323–rs3025010 combination was found to be statistically different between women with GDM and healthy women [71].

An imbalance in the expression of various other vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) also influences the pathophysiology of the GDM [75], future studies examining susceptibility variants and the underlying biological mechanisms will likely unveil associations within this growth factor family with GDM.

8. *CDKAL1*

The CDK5 regulatory subunit associated protein 1-like 1 gene (*CDKAL1*) is in chromosome 6p22.3. This gene encodes a 65-kDa CDKAL1 protein, functioning as a methylthiotransferase. It acts as a tRNA modification enzyme, playing a role in enhancing the translation of various transcripts in pancreatic β -cells, including that of proinsulin. CDKAL1 also serves as an endogenous inhibitor of cyclin-dependent kinase 5 (CDK5). The inhibition of CDK5 by CDKAL1 plays a crucial role in preventing the translocation of PDX1, a transcription factor responsible for regulating the insulin gene. This disruption in the translocation process leads to an interruption in insulin production [76]. In adipocytes, CDKAL1 negatively regulates the adipocyte-specific genes in response to hyperglycemic and hyperlipidemic conditions [77]. CDKAL1 regulates the differentiation of adipocytes in murine 3T3-L1 cells through the Wnt/ β -catenin signaling pathway [78]. Additionally, in adipose-specific *Cdkal1* knockout mice, CDKAL1 is involved in controlling mitochondrial function [79].

The GDM-associated SNPs fall within an intronic 5 region of the *CDKAL1* locus (Table 1) and have recently been the hot spot for studying the risk with GDM. SNP rs7754840 (G > C) allele C significantly correlated with GDM risk in meta-analysis [64,80,81]; however, the associations varied across different ethnicities. No association between variations and GDM was found in Egyptian and Chinese populations [82,83]. Meanwhile, Caucasian women showed an association, and Bangladeshi women had a significant association only after adjusting for gravidity and family history of diabetes [39,84]. Meta-analysis showed that SNP rs7756992 (A > G) minor allele G increased the risk of GDM in Bangladeshi women [64,80,84]. The allele G of this SNP also showed a strong association with impaired glucose metabolism, low birth weight, and a decreased insulin secretion index later in life [85]. Interestingly, SNP rs7747752 (G > C) was reported as being associated with GDM risk without the previous report on association with T2D. The studies conducted on Chinese women elucidated that SNP rs7747752 allele C was genetically associated with elevated GDM risk and with interaction with other factors [86–88]. Another SNP, rs9368222 minor allele A, which is in the same block as rs7747752, was also associated with the risk of GDM in the Hispanic population but not in the Caucasian population [89]. For SNP rs10946398 (A > C), well known to be associated with T2D, it was recently reported that allele C was associated with GDM in Pakistani women [90]. In contrast, the CC genotype was not associated with GDM, but was associated with the need for insulin therapy in Caucasian women [91]. Notably, the *CDKAL1* locus stands out as a prominent example of ancestry-correlated heterogeneity, as multi-ancestry meta-analyses showed that the SNPs at this locus exhibited more pronounced effects on GDM in GWAS conducted on individuals of East Asian ancestry compared to other populations [92].

9. *MTNR1B*

The melatonin receptor 1B gene (*MTNR1B*), located in chromosome 11q14.3, encodes melatonin receptor MT2, which is expressed in the human brain, pancreatic β -cells, and skeletal muscle. MT2 not only regulates circadian rhythm, but is also involved in glucose metabolism. Melatonin binds with MT2 and suppresses cyclic guanosine monophosphate (cGMP) signaling, which results in a decrease in insulin secretion in pancreatic β -cells. In the skeletal muscle, the binding of melatonin to MT2 stimulates glucose transport into

cells via the insulin receptor substrate-1 (IRS-1)/phosphoinositide 3-kinase (PI-3-kinase) pathway [93]. *MTNR1B* is also expressed in the placenta, and GDM women have higher levels of MT2 compared to normal women [94]. A study of trophoblast HTR-8/SVneo cells showed that melatonin upregulates *GLU4*, *PPARG*, and *MT2* expression, leading to elevated glucose consumption [94].

Several *MTNR1B* polymorphisms were shown to be associated with GDM (Table 1). SNP rs10830963 (C > G), within the single 11.5-kb intron, is the most popular variant, and allele G showed susceptibility to increased risk of GDM from meta-analysis and different ethnicities [7,13,35,39,66,89,94–97]. The placental expression level of MT2 in GDM women carrying the GG and GC genotypes was higher than in those carrying the CC genotype [95]. SNPs rs1387153 (C > T) allele T and rs10830962 (C > G) allele G are both located in the intergenic region over 2 kb upstream from *MTNR1B* and demonstrated a significant association with an increased risk of GDM [96,98–101]. Notably, maternal rs10830963 (C > G) had an association with offspring birth weight [13,102]. SNP rs4753426 (T > C), located in the *MTNR1B* promoter, still has contradictory reports. No statistically significant differences were observed in the distribution of *MTNR1B* rs4753426 genotypes and alleles between women with GDM and healthy pregnant women in a study conducted on the Caucasian population [66]. However, rs4753426 minor allele C was associated with susceptibility to GDM [96,98], and another study demonstrated that major allele T was a protective variant for GDM development [99].

10. *GLO1*

The glyoxalase I gene (*GLO1*) is located on chromosome 6p21.2 and is predominantly expressed in the human skeleton. *GLO1* serves as a protective enzyme against dicarbonyl stress. Mechanistically, methylglyoxal (MG) is a byproduct of glycolysis, and *GLO1* plays a crucial role in detoxifying MG to D-lactate. Elevated levels of MG can directly inhibit insulin signaling by binding to IRS-1 within the skeletal muscle and by binding to circulating insulin. Conditions associated with metabolic impairment, such as obesity, insulin resistance, and T2D, have been observed to suppress the expression of *GLO1*, disrupting the MG/*GLO1* axis in skeletal muscle metabolism [103].

The association between *GLO1* polymorphisms and GDM has only one report from Zeng et al., who recently showed the effects in the Chinese population [104]. SNP rs1130534 (T > A) is a synonymous mutation at codon 124 (Gly124Gly). The AA genotype of rs1130534 was identified as a protective factor against GDM. The TA genotype increased fasting glucose levels and the risk of GDM. Furthermore, newborn weight was notably lower in individuals with the TA genotype than in those with the TT genotype. SNP rs4746 (T > G) is a missense variant affecting the amino acid residue 111 in exon 4. The codon major allele GAG generates a glutamic acid (E), while the minor allele GCG instead generates an alanine (A) (E111A). The GG genotype and the G allele were associated with a lower risk of GDM [104]. Another *GLO1* variant, rs1781735, is in the promoter, which significantly affects the transcriptional activity of *GLO1* [105]. This SNP showed no association with the risk of GDM, but the GG genotype was more associated with cumulative neonatal weight and MG levels than the TG or TT genotypes. Also, individuals with the GG genotype exhibited significantly higher MG levels than individuals with the TT genotype. The combined effects of multiple SNPs, specifically the rs1781735–rs4746–rs1130534 (T–G–T) haplotypes, were found to significantly reduce the risk of developing GDM [104]. Notably, none of the *GLO1* variants is predicted to be the binding site of the transcription factor, as shown in Table 1.

11. *GCK* and *GCKR*

The glucokinase gene (*GCK*) is situated on chromosome 7p15.3, composed of 10 coding exons, and is expressed in pancreatic β -cells, liver, and brain. On the other hand, the glucokinase regulator gene (*GCKR*) is located on chromosome 2p23.3 and encodes a glucokinase regulatory protein (GKRP), responsible for controlling the activity of *GCK*. *GCK*, in turn, plays a key role in glucose storage and disposal in the liver and modulates

insulin secretion in the pancreas. Mechanistically, GKR_P forms an inactive complex with GCK at basal glucose concentrations. Together, GCK and GKR_P work in tandem, maintaining blood glucose homeostasis. Variants in the *GCK* and *GCKR* genes can disrupt the balance of the GCK/GKR_P complex, leading to abnormal glucose concentrations and hyperglycemia [106,107]. Indeed, heterozygous inactivating mutations in *GCK* can lead to a form of diabetes known as maturity-onset diabetes of the young (GCK-MODY). This condition presents a challenge in diagnosis, especially during pregnancy, as it can easily be confused with GDM [108].

GCK SNPs rs1799884 (C > T) and rs4607517 (G > A) were both reported to be associated with T2D; however, the association was different in GDM. SNP rs1799884 (C > T) is in the *GCK* promoter without any study and prediction to be the binding site of transcription factor, as shown in Table 1. The association of this variant with GDM is still contradicted in Asian and Caucasian populations. *GCK* rs179988 minor allele T was significantly associated with GDM [39,109,110] but no association was reported [61,86,91]. GDM women showed a predominance of the T allele and more commonly required insulin treatment [91]. SNP rs4607517 (G > A), an intergenic variant between *GCK* and *YKT6*, had no report to show an association with GDM [61,86,109], except for the interaction between this SNP and sweets consumption on GDM [111]. However, fasting blood glucose was significantly lower in individuals with the rs4607517 GA genotype than in those with the GG genotype [109]. Notably, the distribution of rs4607517 was not in Hardy–Weinberg equilibrium in the Filipinos [35].

SNP rs1260326 (C > T) is a missense variant at *GCKR* exon 15, which substitutes proline to leucine at position 446 (P446L). Nevertheless, there was no difference in genotypes between cases and controls [11] and no association of rs1260326 with GDM risk was found from the meta-analysis [37,64]. Interestingly, the association between rs1260326 major allele C and GDM was shown in Chinese and Euro-Brazilian women [49,112], among whom GDM women with the CC genotype had a higher 1-h oral glucose tolerance test (OGTT) level compared to those with the TT genotype [49]. In contrast, the *GCKR* intronic rs780094 (T > C) variant was the risk factor for GDM from the meta-analysis [37,64]. However, the case-control studies showed no difference in genotypes between control and GDM women [91], and no association of the SNP with GDM risk was observed [109].

12. Conclusions

The potential to comprehend the pathophysiology of GDM through genetic polymorphisms (Figure 2) holds promise, providing insights into predicting and managing GDM patients' risks. However, the incorporation of associated SNPs into clinical practice remains a challenge, influenced by such factors as GDM detection criteria, sample size, and ethnicity in GWAS analysis. Additionally, the shared pathogenesis with T2D complicates the identification of unique GDM variants. Given the multicomplex nature of GDM involving various tissues, it is crucial to uncover the underlying mechanism of each genetic variant. Furthermore, genetic information must be considered alongside factors such as diet, lifestyle, and gut microbes that influence individual susceptibility. The continuous exploration of new SNPs, improving the genetic background of GDM, and integrating machine learning into polygenic risk score (PRS) models may have the potential to refine our understanding and offer valuable assistance in clinical practice.

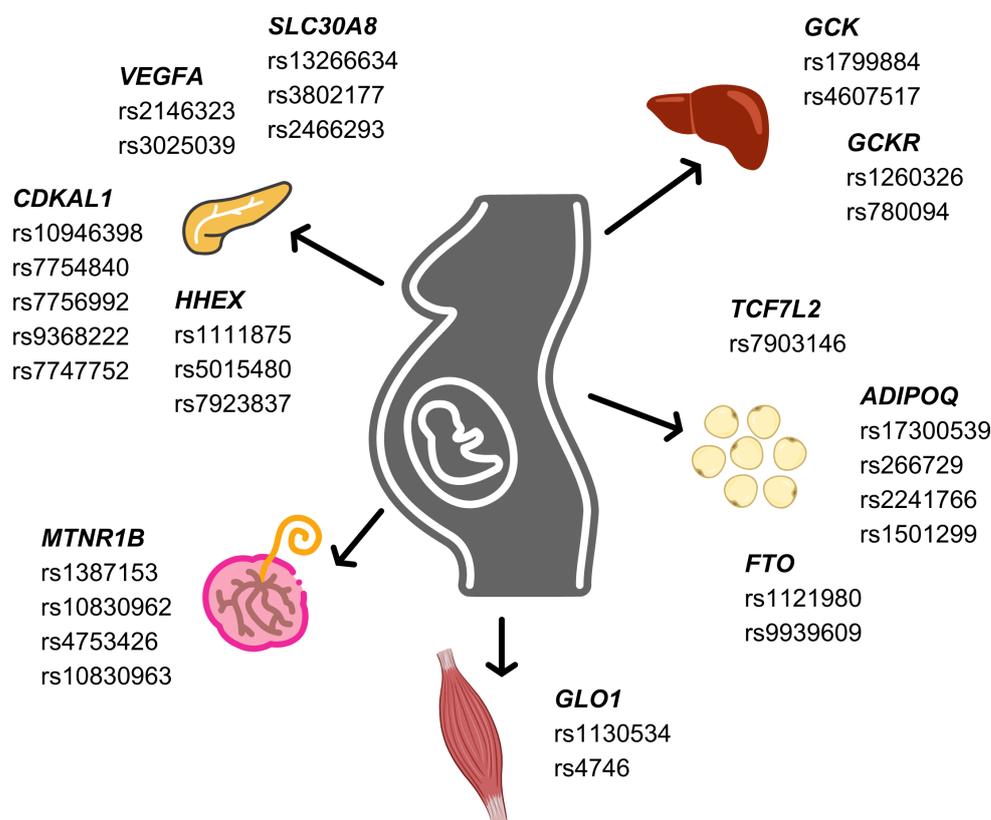


Figure 2. Associated single nucleotide polymorphisms on gestational diabetes mellitus risk in pancreas, liver, skeletal muscle, adipose tissue, and placenta.

Author Contributions: S.S. primarily wrote the manuscript. W.T. provided supervisory and editorial assistance. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Faculty of Medicine Siriraj Hospital, Mahidol University and by a Health Systems Research Institute (HSRI) (grant No. 66-138) to W.T.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. ElSayed, N.A.; Aleppo, G.; Aroda, V.R.; Bannuru, R.R.; Brown, F.M.; Bruemmer, D.; Collins, B.S.; Hilliard, M.E.; Isaacs, D.; Johnson, E.L.; et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. *Diabetes Care* **2023**, *46* (Suppl. S1), S19–S40. [[CrossRef](#)]
2. Plows, J.F.; Stanley, J.L.; Baker, P.N.; Reynolds, C.M.; Vickers, M.H. The Pathophysiology of Gestational Diabetes Mellitus. *Int. J. Mol. Sci.* **2018**, *19*, 3342. [[CrossRef](#)] [[PubMed](#)]
3. Wang, Y.; Li, L.; Li, P. Novel single nucleotide polymorphisms in gestational diabetes mellitus. *Clin. Chim. Acta* **2023**, *538*, 60–64. [[CrossRef](#)] [[PubMed](#)]
4. Rauluseviciute, I.; Riudavets-Puig, R.; Blanc-Mathieu, R.; Castro-Mondragon, J.A.; Ferenc, K.; Kumar, V.; Lemma, R.B.; Lucas, J.; Cheneby, J.; Baranasic, D.; et al. JASPAR 2024: 20th anniversary of the open-access database of transcription factor binding profiles. *Nucleic Acids Res.* **2024**, *52*, D174–D182. [[CrossRef](#)] [[PubMed](#)]
5. Kent, W.J.; Sugnet, C.W.; Furey, T.S.; Roskin, K.M.; Pringle, T.H.; Zahler, A.M.; Haussler, D. The human genome browser at UCSC. *Genome Res.* **2002**, *12*, 996–1006. [[CrossRef](#)] [[PubMed](#)]
6. Del Bosque-Plata, L.; Martinez-Martinez, E.; Espinoza-Camacho, M.A.; Gragnoli, C. The Role of TCF7L2 in Type 2 Diabetes. *Diabetes* **2021**, *70*, 1220–1228. [[CrossRef](#)] [[PubMed](#)]
7. Ding, M.; Chavarro, J.; Olsen, S.; Lin, Y.; Ley, S.H.; Bao, W.; Rawal, S.; Grunnet, L.G.; Thuesen, A.C.B.; Mills, J.L.; et al. Genetic variants of gestational diabetes mellitus: A study of 112 SNPs among 8722 women in two independent populations. *Diabetologia* **2018**, *61*, 1758–1768. [[CrossRef](#)]
8. Chang, S.; Wang, Z.; Wu, L.; Lu, X.; Shangguan, S.; Xin, Y.; Li, L.; Wang, L. Association between TCF7L2 polymorphisms and gestational diabetes mellitus: A meta-analysis. *J. Diabetes Investig.* **2017**, *8*, 560–570. [[CrossRef](#)]

9. Fang, C.; Wu, S.; Zhang, J.; Tian, Q.; Zhang, Z.; Wu, L. Impaired glucolipid metabolism in gestational diabetes mellitus with T variation of TCF7L2 rs7903146: A case–control study. *Int. J. Diabetes Dev. Ctries.* **2023**, 1–8. [[CrossRef](#)]
10. Zhang, P.; Deng, M.; Li, W.; Dai, Q.; He, H.; Zheng, W.; She, L.; Xiang, B.; Zeng, J.; Zhou, F.; et al. The correlation between transcription factor 7-like 2 gene polymorphisms and susceptibility of gestational diabetes mellitus in the population of central China: A case-control study. *Front. Endocrinol.* **2022**, *13*, 916590. [[CrossRef](#)]
11. Franzago, M.; Fraticelli, F.; Nicolucci, A.; Celentano, C.; Liberati, M.; Stuppia, L.; Vitacolonna, E. Molecular Analysis of a Genetic Variants Panel Related to Nutrients and Metabolism: Association with Susceptibility to Gestational Diabetes and Cardiometabolic Risk in Affected Women. *J. Diabetes Res.* **2017**, *2017*, 4612623. [[CrossRef](#)]
12. Verma, M.; Loh, N.Y.; Sabaratnam, R.; Vasan, S.K.; van Dam, A.D.; Todorovic, M.; Neville, M.J.; Toledo, E.; Karpe, F.; Christodoulides, C. TCF7L2 plays a complex role in human adipose progenitor biology, which might contribute to genetic susceptibility to type 2 diabetes. *Metabolism* **2022**, *133*, 155240. [[CrossRef](#)] [[PubMed](#)]
13. Beaumont, R.N.; Warrington, N.M.; Cavadino, A.; Tyrrell, J.; Nodzenski, M.; Horikoshi, M.; Geller, F.; Myhre, R.; Richmond, R.C.; Paternoster, L.; et al. Genome-wide association study of offspring birth weight in 86 577 women identifies five novel loci and highlights maternal genetic effects that are independent of fetal genetics. *Hum. Mol. Genet.* **2018**, *27*, 742–756. [[CrossRef](#)]
14. Tangjittipokin, W.; Chongjarean, N.; Plengvidhya, N.; Homsanit, M.; Yenichitsomanus, P.T. Transcription factor 7-like 2 (TCF7L2) variations associated with earlier age-onset of type 2 diabetes in Thai patients. *J. Genet.* **2012**, *91*, 251–255. [[CrossRef](#)] [[PubMed](#)]
15. da Silva Xavier, G.; Mondragon, A.; Sun, G.; Chen, L.; McGinty, J.A.; French, P.M.; Rutter, G.A. Abnormal glucose tolerance and insulin secretion in pancreas-specific Tcf7l2-null mice. *Diabetologia* **2012**, *55*, 2667–2676. [[CrossRef](#)] [[PubMed](#)]
16. Mitchell, R.K.; Mondragon, A.; Chen, L.; McGinty, J.A.; French, P.M.; Ferrer, J.; Thorens, B.; Hodson, D.J.; Rutter, G.A.; Da Silva Xavier, G. Selective disruption of Tcf7l2 in the pancreatic beta cell impairs secretory function and lowers beta cell mass. *Hum. Mol. Genet.* **2015**, *24*, 1390–1399. [[CrossRef](#)] [[PubMed](#)]
17. Wu, H.H.; Li, Y.L.; Liu, N.J.; Yang, Z.; Tao, X.M.; Du, Y.P.; Wang, X.C.; Lu, B.; Zhang, Z.Y.; Hu, R.M.; et al. TCF7L2 regulates pancreatic beta-cell function through PI3K/AKT signal pathway. *Diabetol. Metab. Syndr.* **2019**, *11*, 55. [[CrossRef](#)] [[PubMed](#)]
18. da Silva Xavier, G.; Mondragon, A.; Mourougavelou, V.; Cruciani-Guglielmacci, C.; Denom, J.; Herrera, P.L.; Magnan, C.; Rutter, G.A. Pancreatic alpha cell-selective deletion of Tcf7l2 impairs glucagon secretion and counter-regulatory responses to hypoglycaemia in mice. *Diabetologia* **2017**, *60*, 1043–1050. [[CrossRef](#)] [[PubMed](#)]
19. Facchinello, N.; Tarifeno-Saldivia, E.; Grisan, E.; Schiavone, M.; Peron, M.; Mongera, A.; Ek, O.; Schmitner, N.; Meyer, D.; Peers, B.; et al. Tcf7l2 plays pleiotropic roles in the control of glucose homeostasis, pancreas morphology, vascularization and regeneration. *Sci. Rep.* **2017**, *7*, 9605. [[CrossRef](#)]
20. Chen, X.; Ayala, I.; Shannon, C.; Fourcaudot, M.; Acharya, N.K.; Jenkinson, C.P.; Heikkinen, S.; Norton, L. The Diabetes Gene and Wnt Pathway Effector TCF7L2 Regulates Adipocyte Development and Function. *Diabetes* **2018**, *67*, 554–568. [[CrossRef](#)]
21. Geoghegan, G.; Simcox, J.; Seldin, M.M.; Parnell, T.J.; Stubben, C.; Just, S.; Begaye, L.; Lusic, A.J.; Villanueva, C.J. Targeted deletion of Tcf7l2 in adipocytes promotes adipocyte hypertrophy and impaired glucose metabolism. *Mol. Metab.* **2019**, *24*, 44–63. [[CrossRef](#)] [[PubMed](#)]
22. Lee, D.S.; An, T.H.; Kim, H.; Jung, E.; Kim, G.; Oh, S.Y.; Kim, J.S.; Chun, H.J.; Jung, J.; Lee, E.W.; et al. Tcf7l2 in hepatocytes regulates de novo lipogenesis in diet-induced non-alcoholic fatty liver disease in mice. *Diabetologia* **2023**, *66*, 931–954. [[CrossRef](#)] [[PubMed](#)]
23. Kuzmicki, M.; Telejko, B.; Wawrusiewicz-Kurylonek, N.; Kalejta, K.; Lemancewicz, A.; Zdrodowski, M.; Grabiec, M.; Pryszczepko-Wawreszuk, A.M.; Kretowski, A.; Gorska, M.; et al. The expression of transcription factor 7-like 2 (TCF7L2) in fat and placental tissue from women with gestational diabetes. *Diabetes Res. Clin. Pract.* **2011**, *94*, e43–e46. [[CrossRef](#)] [[PubMed](#)]
24. Qian, Y.; Lu, F.; Dong, M.; Lin, Y.; Li, H.; Chen, J.; Shen, C.; Jin, G.; Hu, Z.; Shen, H. Genetic variants of IDE-KIF11-HHEX at 10q23.33 associated with type 2 diabetes risk: A fine-mapping study in Chinese population. *PLoS ONE* **2012**, *7*, e35060. [[CrossRef](#)] [[PubMed](#)]
25. Xie, W.; Zhang, L.; Wang, J.; Wang, Y. Association of HHEX and SLC30A8 Gene Polymorphisms with Gestational Diabetes Mellitus Susceptibility: A Meta-analysis. *Biochem. Genet.* **2023**, *61*, 2203–2221. [[CrossRef](#)] [[PubMed](#)]
26. Wang, X.; Ding, Y.; Zhang, X.; Rao, J.; Yu, H.; Pan, H. The association between HHEX single-nucleotide polymorphism rs5015480 and gestational diabetes mellitus: A meta-analysis. *Medicine* **2020**, *99*, e19478. [[CrossRef](#)] [[PubMed](#)]
27. Tarnowski, M.; Malinowski, D.; Safranow, K.; Dziedziejko, V.; Czerewaty, M.; Pawlik, A. Hematopoietically expressed homeobox (HHEX) gene polymorphism (rs5015480) is associated with increased risk of gestational diabetes mellitus. *Clin. Genet.* **2017**, *91*, 843–848. [[CrossRef](#)] [[PubMed](#)]
28. Yang, D.; Cho, H.; Tayyebi, Z.; Shukla, A.; Luo, R.; Dixon, G.; Ursu, V.; Stransky, S.; Tremmel, D.M.; Sackett, S.D.; et al. CRISPR screening uncovers a central requirement for HHEX in pancreatic lineage commitment and plasticity restriction. *Nat. Cell Biol.* **2022**, *24*, 1064–1076. [[CrossRef](#)]
29. Ito, R.; Kimura, A.; Hirose, Y.; Hatano, Y.; Mima, A.; Mae, S.I.; Keidai, Y.; Nakamura, T.; Fujikura, J.; Nishi, Y.; et al. Elucidation of HHEX in pancreatic endoderm differentiation using a human iPSC differentiation model. *Sci. Rep.* **2023**, *13*, 8659. [[CrossRef](#)]
30. Zhang, J.; McKenna, L.B.; Bogue, C.W.; Kaestner, K.H. The diabetes gene Hhex maintains delta-cell differentiation and islet function. *Genes Dev.* **2014**, *28*, 829–834. [[CrossRef](#)]

31. Liang, X.; Duan, H.; Mao, Y.; Koestner, U.; Wei, Y.; Deng, F.; Zhuang, J.; Li, H.; Wang, C.; Hernandez-Miranda, L.R.; et al. The SNAG Domain of Insm1 Regulates Pancreatic Endocrine Cell Differentiation and Represses beta- to delta-Cell Transdifferentiation. *Diabetes* **2021**, *70*, 1084–1097. [[CrossRef](#)]
32. Evseeva, M.N.; Dyikanov, D.T.; Karagyaur, M.N.; Prikazchikova, T.A.; Sheptulina, A.F.; Balashova, M.S.; Zatsepin, T.S.; Rubtsov, Y.P.; Kulebyakin, K.Y. Hematopoietically-expressed homeobox protein HHEX regulates adipogenesis in preadipocytes. *Biochimie* **2021**, *185*, 68–77. [[CrossRef](#)] [[PubMed](#)]
33. Rajaraman, G.; Murthi, P.; Quinn, L.; Brennecke, S.P.; Kalionis, B. Homeodomain protein HLX is expressed primarily in cytotrophoblast cell types in the early pregnancy human placenta. *Reprod. Fertil. Dev.* **2008**, *20*, 357–367. [[CrossRef](#)] [[PubMed](#)]
34. Chimienti, F.; Devergnas, S.; Favier, A.; Seve, M. Identification and cloning of a beta-cell-specific zinc transporter, ZnT-8, localized into insulin secretory granules. *Diabetes* **2004**, *53*, 2330–2337. [[CrossRef](#)] [[PubMed](#)]
35. Benny, P.; Ahn, H.J.; Burlingame, J.; Lee, M.J.; Miller, C.; Chen, J.; Urschitz, J. Genetic risk factors associated with gestational diabetes in a multi-ethnic population. *PLoS ONE* **2021**, *16*, e0261137. [[CrossRef](#)] [[PubMed](#)]
36. Dereke, J.; Palmqvist, S.; Nilsson, C.; Landin-Olsson, M.; Hillman, M. The prevalence and predictive value of the SLC30A8 R325W polymorphism and zinc transporter 8 autoantibodies in the development of GDM and postpartum type 1 diabetes. *Endocrine* **2016**, *53*, 740–746. [[CrossRef](#)] [[PubMed](#)]
37. Lin, Z.; Wang, Y.; Zhang, B.; Jin, Z. Association of type 2 diabetes susceptible genes GCKR, SLC30A8, and FTO polymorphisms with gestational diabetes mellitus risk: A meta-analysis. *Endocrine* **2018**, *62*, 34–45. [[CrossRef](#)] [[PubMed](#)]
38. Zeng, Q.; Tan, B.; Han, F.; Huang, X.; Huang, J.; Wei, Y.; Guo, R. Association of solute carrier family 30 A8 zinc transporter gene variations with gestational diabetes mellitus risk in a Chinese population. *Front. Endocrinol.* **2023**, *14*, 1159714. [[CrossRef](#)] [[PubMed](#)]
39. Rosta, K.; Al-Aissa, Z.; Hadarits, O.; Harreiter, J.; Nadasdi, A.; Kelemen, F.; Bancher-Todesca, D.; Komlosi, Z.; Nemeth, L.; Rigo, J.; et al. Association Study with 77 SNPs Confirms the Robust Role for the rs10830963/G of MTNR1B Variant and Identifies Two Novel Associations in Gestational Diabetes Mellitus Development. *PLoS ONE* **2017**, *12*, e0169781. [[CrossRef](#)]
40. Zhang, Y.; Jian, W.; He, L.; Wu, J. ZnT8 in T2D: A novel therapeutic target for maintaining insulin secretion capacity. *Acta Biochim. Biophys. Sin.* **2020**, *52*, 1050–1051. [[CrossRef](#)]
41. Ma, Q.; Xiao, Y.; Xu, W.; Wang, M.; Li, S.; Yang, Z.; Xu, M.; Zhang, T.; Zhang, Z.N.; Hu, R.; et al. ZnT8 loss-of-function accelerates functional maturation of hESC-derived beta cells and resists metabolic stress in diabetes. *Nat. Commun.* **2022**, *13*, 4142. [[CrossRef](#)] [[PubMed](#)]
42. Dwivedi, O.P.; Lehtovirta, M.; Hastoy, B.; Chandra, V.; Krentz, N.A.J.; Kleiner, S.; Jain, D.; Richard, A.M.; Abaitua, F.; Beer, N.L.; et al. Loss of ZnT8 function protects against diabetes by enhanced insulin secretion. *Nat. Genet.* **2019**, *51*, 1596–1606. [[CrossRef](#)] [[PubMed](#)]
43. Moyce Gruber, B.L.; Dolinsky, V.W. The Role of Adiponectin during Pregnancy and Gestational Diabetes. *Life* **2023**, *13*, 301. [[CrossRef](#)] [[PubMed](#)]
44. Tangjittipokin, W.; Thanatummat, B.; Wardati, F.; Narkdontri, T.; Teerawattanapong, N.; Boriboonthirunsarn, D. The genetic polymorphisms and levels of adipokines and adipocytokines that influence the risk of developing gestational diabetes mellitus in Thai pregnant women. *Gene* **2023**, *860*, 147228. [[CrossRef](#)] [[PubMed](#)]
45. Takhshid, M.A.; Haem, Z.; Aboualzadeh, F. The association of circulating adiponectin and +45 T/G polymorphism of adiponectin gene with gestational diabetes mellitus in Iranian population. *J. Diabetes Metab. Disord.* **2015**, *14*, 30. [[CrossRef](#)] [[PubMed](#)]
46. Tangjittipokin, W.; Narkdontri, T.; Teerawattanapong, N.; Thanatummat, B.; Wardati, F.; Sunsaneevithayakul, P.; Boriboonthirunsarn, D. The Variants in ADIPOQ are Associated with Maternal Circulating Adipokine Profile in Gestational Diabetes Mellitus. *J. Multidiscip. Healthc.* **2023**, *16*, 309–319. [[CrossRef](#)] [[PubMed](#)]
47. Pawlik, A.; Teler, J.; Maciejewska, A.; Sawczuk, M.; Safranow, K.; Dziedziejko, V. Adiponectin and leptin gene polymorphisms in women with gestational diabetes mellitus. *J. Assist. Reprod. Genet.* **2017**, *34*, 511–516. [[CrossRef](#)]
48. Bai, Y.; Tang, L.; Li, L.; Li, L. The roles of ADIPOQ rs266729 and MTNR1B rs10830963 polymorphisms in patients with gestational diabetes mellitus: A meta-analysis. *Gene* **2020**, *730*, 144302. [[CrossRef](#)]
49. Zhu, M.; Lv, Y.; Peng, Y.; Wu, Y.; Feng, Y.; Jia, T.; Xu, S.; Li, S.; Wang, W.; Tian, J.; et al. GCKR and ADIPOQ gene polymorphisms in women with gestational diabetes mellitus. *Acta Diabetol.* **2023**, *60*, 1709–1718. [[CrossRef](#)]
50. Beltcheva, O.; Boyadzhieva, M.; Angelova, O.; Mitev, V.; Kaneva, R.; Atanasova, I. The rs266729 single-nucleotide polymorphism in the adiponectin gene shows association with gestational diabetes. *Arch. Gynecol. Obstet.* **2014**, *289*, 743–748. [[CrossRef](#)]
51. Hivert, M.F.; Scholtens, D.M.; Allard, C.; Nodzenski, M.; Bouchard, L.; Brisson, D.; Lowe, L.P.; McDowell, I.; Reddy, T.; Dastani, Z.; et al. Genetic determinants of adiponectin regulation revealed by pregnancy. *Obesity* **2017**, *25*, 935–944. [[CrossRef](#)]
52. Dias, S.; Adam, S.; Rheeder, P.; Pheiffer, C. No Association Between ADIPOQ or MTHFR Polymorphisms and Gestational Diabetes Mellitus in South African Women. *Diabetes Metab. Syndr. Obes.* **2021**, *14*, 791–800. [[CrossRef](#)] [[PubMed](#)]
53. Huang, L.T.; Wu, S.L.; Liao, X.; Ma, S.J.; Tan, H.Z. Adiponectin gene polymorphisms and risk of gestational diabetes mellitus: A meta-analysis. *World J. Clin. Cases* **2019**, *7*, 572–584. [[CrossRef](#)] [[PubMed](#)]
54. Low, C.F.; Mohd Tohit, E.R.; Chong, P.P.; Idris, F. Adiponectin SNP45TG is associated with gestational diabetes mellitus. *Arch. Gynecol. Obstet.* **2011**, *283*, 1255–1260. [[CrossRef](#)]

55. Feng, Y.; Jiang, C.D.; Chang, A.M.; Shi, Y.; Gao, J.; Zhu, L.; Zhang, Z. Interactions among insulin resistance, inflammation factors, obesity-related gene polymorphisms, environmental risk factors, and diet in the development of gestational diabetes mellitus. *J. Matern. Fetal. Neonatal. Med.* **2019**, *32*, 339–347. [[CrossRef](#)] [[PubMed](#)]
56. Howlader, M.; Sultana, M.I.; Akter, F.; Hossain, M.M. Adiponectin gene polymorphisms associated with diabetes mellitus: A descriptive review. *Heliyon* **2021**, *7*, e07851. [[CrossRef](#)] [[PubMed](#)]
57. Cakina, S.; Ulu, S.; Beyazit, F.; Özen, E.; Postacı, E.S. Association between adiponectin and gene polymorphism in gestational diabetes mellitus patients. *Rev. Romana De Med. De Lab.* **2023**, *31*, 119–124.
58. Lan, N.; Lu, Y.; Zhang, Y.; Pu, S.; Xi, H.; Nie, X.; Liu, J.; Yuan, W. FTO—A Common Genetic Basis for Obesity and Cancer. *Front. Genet.* **2020**, *11*, 559138. [[CrossRef](#)]
59. Merkestein, M.; Laber, S.; McMurray, F.; Andrew, D.; Sachse, G.; Sanderson, J.; Li, M.; Usher, S.; Sellayah, D.; Ashcroft, F.M.; et al. FTO influences adipogenesis by regulating mitotic clonal expansion. *Nat. Commun.* **2015**, *6*, 6792. [[CrossRef](#)]
60. Fan, H.Q.; He, W.; Xu, K.F.; Wang, Z.X.; Xu, X.Y.; Chen, H. FTO Inhibits Insulin Secretion and Promotes NF-kappaB Activation through Positively Regulating ROS Production in Pancreatic beta cells. *PLoS ONE* **2015**, *10*, e0127705.
61. Cao, M.; Zhang, L.; Chen, T.; Shi, A.; Xie, K.; Li, Z.; Xu, J.; Chen, Z.; Ji, C.; Wen, J. Genetic Susceptibility to Gestational Diabetes Mellitus in a Chinese Population. *Front. Endocrinol.* **2020**, *11*, 247. [[CrossRef](#)]
62. Santos, K.D.; Rosado, E.L.; da Fonseca, A.C.P.; Belfort, G.P.; da Silva, L.B.G.; Ribeiro-Alves, M.; Zembrzuski, V.M.; Martinez, J.A.; Saunders, C. FTO and ADRB2 Genetic Polymorphisms Are Risk Factors for Earlier Excessive Gestational Weight Gain in Pregnant Women with Pregestational Diabetes Mellitus: Results of a Randomized Nutrigenetic Trial. *Nutrients* **2022**, *14*, 1050. [[CrossRef](#)] [[PubMed](#)]
63. Saucedo, R.; Valencia, J.; Gutierrez, C.; Basurto, L.; Hernandez, M.; Puello, E.; Rico, G.; Vega, G.; Zarate, A. Gene variants in the FTO gene are associated with adiponectin and TNF-alpha levels in gestational diabetes mellitus. *Diabetol. Metab. Syndr.* **2017**, *9*, 32. [[CrossRef](#)] [[PubMed](#)]
64. Guo, F.; Long, W.; Zhou, W.; Zhang, B.; Liu, J.; Yu, B. FTO, GCKR, CDKAL1 and CDKN2A/B gene polymorphisms and the risk of gestational diabetes mellitus: A meta-analysis. *Arch. Gynecol. Obstet.* **2018**, *298*, 705–715. [[CrossRef](#)] [[PubMed](#)]
65. He, H.; Cao, W.T.; Zeng, Y.H.; Huang, Z.Q.; Du, W.R.; Guan, N.D.; Zhao, Y.Z.; Wei, B.R.; Liu, Y.H.; Jing, C.X.; et al. Lack of associations between the FTO polymorphisms and gestational diabetes: A meta-analysis and trial sequential analysis. *Gene* **2018**, *677*, 169–175. [[CrossRef](#)] [[PubMed](#)]
66. Tarnowski, M.; Bujak, J.; Kopytko, P.; Majcher, S.; Ustianowski, P.; Dziedziejko, V.; Safranow, K.; Pawlik, A. Effect of FTO and IGF2BP2 gene polymorphisms on duration of pregnancy and Apgar scores in women with gestational diabetes. *J. Obstet. Gynaecol.* **2019**, *39*, 151–156. [[CrossRef](#)] [[PubMed](#)]
67. Amin, U.S.M.; Rahman, T.A.; Hasan, M.; Tofail, T.; Hasanat, M.A.; Seraj, Z.I.; Salimullah, M. Type 2 diabetes linked FTO gene variant rs8050136 is significantly associated with gravidity in gestational diabetes in a sample of Bangladeshi women: Meta-analysis and case-control study. *PLoS ONE* **2023**, *18*, e0288318. [[CrossRef](#)] [[PubMed](#)]
68. Melincovici, C.S.; Bosca, A.B.; Susman, S.; Marginean, M.; Mihu, C.; Istrate, M.; Moldovan, I.M.; Roman, A.L.; Mihu, C.M. Vascular endothelial growth factor (VEGF)—Key factor in normal and pathological angiogenesis. *Rom. J. Morphol. Embryol.* **2018**, *59*, 455–467.
69. Troncoso, F.; Acurio, J.; Herlitz, K.; Aguayo, C.; Bertoglia, P.; Guzman-Gutierrez, E.; Loyola, M.; Gonzalez, M.; Rezgaoui, M.; Desoye, G.; et al. Gestational diabetes mellitus is associated with increased pro-migratory activation of vascular endothelial growth factor receptor 2 and reduced expression of vascular endothelial growth factor receptor 1. *PLoS ONE* **2017**, *12*, e0182509. [[CrossRef](#)]
70. Meng, Q.; Shao, L.; Luo, X.; Mu, Y.; Xu, W.; Gao, L.; Xu, H.; Cui, Y. Expressions of VEGF-A and VEGFR-2 in placentae from GDM pregnancies. *Reprod. Biol. Endocrinol.* **2016**, *14*, 61. [[CrossRef](#)]
71. Dong, P.P. Association of vascular endothelial growth factor expression and polymorphisms with the risk of gestational diabetes mellitus. *J. Clin. Lab. Anal.* **2019**, *33*, e22686. [[CrossRef](#)]
72. Sirico, A.; Rossi, E.D.; Degennaro, V.A.; Arena, V.; Rizzi, A.; Tartaglione, L.; Di Leo, M.; Pitocco, D.; Lanzone, A. Placental diabetes: Placental VEGF and CD31 expression according to pregestational BMI and gestational weight gain in women with gestational diabetes. *Arch. Gynecol. Obstet.* **2023**, *307*, 1823–1831. [[CrossRef](#)]
73. Yang, W.; Jiang, Y.; Wang, Y.; Zhang, T.; Liu, Q.; Wang, C.; Swisher, G.; Wu, N.; Chao, C.; Prasad, K.; et al. Placental growth factor in beta cells plays an essential role in gestational beta-cell growth. *BMJ Open Diabetes Res. Care* **2020**, *8*, e000921. [[CrossRef](#)] [[PubMed](#)]
74. Staels, W.; Heremans, Y.; Leuckx, G.; Van Gassen, N.; Salinno, C.; De Groef, S.; Cools, M.; Keshet, E.; Dor, Y.; Heimberg, H.; et al. Conditional islet hypovascularisation does not preclude beta cell expansion during pregnancy in mice. *Diabetologia* **2017**, *60*, 1051–1056. [[CrossRef](#)] [[PubMed](#)]
75. Bolatai, A.; He, Y.; Wu, N. Vascular endothelial growth factor and its receptors regulation in gestational diabetes mellitus and eclampsia. *J. Transl. Med.* **2022**, *20*, 400. [[CrossRef](#)] [[PubMed](#)]
76. Ghosh, C.; Das, N.; Saha, S.; Kundu, T.; Sircar, D.; Roy, P. Involvement of Cdkal1 in the etiology of type 2 diabetes mellitus and microvascular diabetic complications: A review. *J. Diabetes Metab. Disord.* **2022**, *21*, 991–1001. [[CrossRef](#)] [[PubMed](#)]

77. Okamura, T.; Yanobu-Takanashi, R.; Takeuchi, F.; Isono, M.; Akiyama, K.; Shimizu, Y.; Goto, M.; Liang, Y.Q.; Yamamoto, K.; Katsuya, T.; et al. Deletion of CDKAL1 affects high-fat diet-induced fat accumulation and glucose-stimulated insulin secretion in mice, indicating relevance to diabetes. *PLoS ONE* **2012**, *7*, e49055. [[CrossRef](#)] [[PubMed](#)]
78. Take, K.; Waki, H.; Sun, W.; Wada, T.; Yu, J.; Nakamura, M.; Aoyama, T.; Yamauchi, T.; Kadowaki, T. CDK5 Regulatory Subunit-Associated Protein 1-like 1 Negatively Regulates Adipocyte Differentiation through Activation of Wnt Signaling Pathway. *Sci. Rep.* **2017**, *7*, 7326. [[CrossRef](#)] [[PubMed](#)]
79. Palmer, C.J.; Bruckner, R.J.; Paulo, J.A.; Kazak, L.; Long, J.Z.; Mina, A.I.; Deng, Z.; LeClair, K.B.; Hall, J.A.; Hong, S.; et al. Cdkal1, a type 2 diabetes susceptibility gene, regulates mitochondrial function in adipose tissue. *Mol. Metab.* **2017**, *6*, 1212–1225. [[CrossRef](#)] [[PubMed](#)]
80. Yu, X.Y.; Song, L.P.; Wei, S.D.; Wen, X.L.; Liu, D.B. CDK5 Regulatory Subunit-Associated Protein 1-Like 1 Gene Polymorphisms and Gestational Diabetes Mellitus Risk: A Trial Sequential Meta-Analysis of 13,306 Subjects. *Front. Endocrinol.* **2021**, *12*, 722674. [[CrossRef](#)]
81. Mahdizade, A.H.; Bahreiny, S.S.; Bastani, M.-N.; Dabbagh, M.R.; Aghaei, M.; Ali Malayeri, F.; YousefiFard, A.; Taghizadeh, E. The influence of CDKAL1 (rs7754840) gene polymorphism on susceptibility to gestational diabetes mellitus in pregnant women: A systematic review and meta-analysis. *Int. J. Diabetes Dev. Ctries.* **2023**, 1–10. [[CrossRef](#)]
82. Noury, A.E.; Azmy, O.; Alsharnoubi, J.; Salama, S.; Okasha, A.; Gouda, W. Variants of CDKAL1 rs7754840 (G/C) and CDKN2A/2B rs10811661 (C/T) with gestational diabetes: Insignificant association. *BMC Res. Notes* **2018**, *11*, 181. [[CrossRef](#)] [[PubMed](#)]
83. Wang, Y.; Nie, M.; Li, W.; Ping, F.; Hu, Y.; Ma, L.; Gao, J.; Liu, J. Association of six single nucleotide polymorphisms with gestational diabetes mellitus in a Chinese population. *PLoS ONE* **2011**, *6*, e26953. [[CrossRef](#)] [[PubMed](#)]
84. Amin, U.S.M.; Parvez, N.; Rahman, T.A.; Hasan, M.R.; Das, K.C.; Jahan, S.; Hasanat, M.A.; Seraj, Z.I.; Salimullah, M. CDKAL1 gene rs7756992 A/G and rs7754840 G/C polymorphisms are associated with gestational diabetes mellitus in a sample of Bangladeshi population: Implication for future T2DM prophylaxis. *Diabetol. Metab. Syndr.* **2022**, *14*, 18. [[CrossRef](#)] [[PubMed](#)]
85. Sun, X.F.; Xiao, X.H.; Zhang, Z.X.; Liu, Y.; Xu, T.; Zhu, X.L.; Zhang, Y.; Wu, X.P.; Li, W.H.; Zhang, H.B.; et al. Positive Association Between Type 2 Diabetes Risk Alleles Near CDKAL1 and Reduced Birthweight in Chinese Han Individuals. *Chin. Med. J.* **2015**, *128*, 1873–1878. [[CrossRef](#)] [[PubMed](#)]
86. Wang, K.; Chen, Q.; Feng, Y.; Yang, H.; Wu, W.; Zhang, P.; Wang, Y.; Ko, J.; Zhao, F.; Du, W.; et al. Single Nucleotide Polymorphisms in CDKAL1 Gene Are Associated with Risk of Gestational Diabetes Mellitus in Chinese Population. *J. Diabetes Res.* **2019**, *2019*, 3618103. [[CrossRef](#)] [[PubMed](#)]
87. Wang, H.; Yang, W.; Liu, J.; Leng, J.; Li, W.; Yu, Z.; Li, J.; Ma, R.C.W.; Hu, G.; Fang, Z.; et al. Serum concentrations of SFAs and CDKAL1 single-nucleotide polymorphism rs7747752 are related to an increased risk of gestational diabetes mellitus. *Am. J. Clin. Nutr.* **2021**, *114*, 1698–1707. [[CrossRef](#)]
88. Wang, H.; Li, J.; Leng, J.; Li, W.; Liu, J.; Yan, X.; Yu, Z.; Hu, G.; Ma, R.C.W.; Fang, Z.; et al. The CDKAL1 rs7747752-Bile Acids Interaction Increased Risk of Gestational Diabetes Mellitus: A Nested Case-Control Study. *Front. Endocrinol.* **2022**, *13*, 808956. [[CrossRef](#)]
89. Ramos-Levi, A.; Barabash, A.; Valerio, J.; Garcia de la Torre, N.; Mendizabal, L.; Zulueta, M.; de Miguel, M.P.; Diaz, A.; Duran, A.; Familiar, C.; et al. Genetic variants for prediction of gestational diabetes mellitus and modulation of susceptibility by a nutritional intervention based on a Mediterranean diet. *Front. Endocrinol.* **2022**, *13*, 1036088. [[CrossRef](#)]
90. Asghar, A.; Firasat, S.; Afshan, K.; Naz, S. Association of CDKAL1 gene polymorphism (rs10946398) with gestational diabetes mellitus in Pakistani population. *Mol. Biol. Rep.* **2023**, *50*, 57–64. [[CrossRef](#)]
91. Tarnowski, M.; Malinowski, D.; Pawlak, K.; Dziedziczko, V.; Safranow, K.; Pawlik, A. GCK, GCKR, FADS1, DGKB/TMEM195 and CDKAL1 Gene Polymorphisms in Women with Gestational Diabetes. *Can. J. Diabetes* **2017**, *41*, 372–379. [[CrossRef](#)]
92. Pervjakova, N.; Moen, G.H.; Borges, M.C.; Ferreira, T.; Cook, J.P.; Allard, C.; Beaumont, R.N.; Canouil, M.; Hatem, G.; Heiskala, A.; et al. Multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes. *Hum. Mol. Genet.* **2022**, *31*, 3377–3391. [[CrossRef](#)]
93. Zhu, H.; Zhao, Z.J.; Liu, H.Y.; Cai, J.; Lu, Q.K.; Ji, L.D.; Xu, J. The melatonin receptor 1B gene links circadian rhythms and type 2 diabetes mellitus: An evolutionary story. *Ann. Med.* **2023**, *55*, 1262–1286. [[CrossRef](#)]
94. Wei, L.; Jiang, Y.; Gao, P.; Zhang, J.; Zhou, X.; Zhu, S.; Chen, Y.; Zhang, H.; Du, Y.; Fang, C.; et al. Role of melatonin receptor 1B gene polymorphism and its effect on the regulation of glucose transport in gestational diabetes mellitus. *J. Zhejiang Univ. Sci. B* **2023**, *24*, 78–88. [[CrossRef](#)] [[PubMed](#)]
95. Li, C.; Zhou, Y.; Qiao, B.; Xu, L.; Li, Y.; Li, C. Association Between a Melatonin Receptor 1B Genetic Polymorphism and Its Protein Expression in Gestational Diabetes Mellitus. *Reprod. Sci.* **2019**, *26*, 1382–1388. [[CrossRef](#)] [[PubMed](#)]
96. Jia, Y.; Shen, Y.; Shi, X.; Gu, X.; Zhang, P.; Liu, Y.; Zhu, A.; Jiang, L. MTNR1B gene on susceptibility to gestational diabetes mellitus: A two-stage hospital-based study in Southern China. *Mol. Genet. Genom.* **2020**, *295*, 1369–1378. [[CrossRef](#)] [[PubMed](#)]
97. Chen, F.; Fei, X.; Li, M.; Zhang, Z.; Zhu, W.; Zhang, M.; Chen, X.; Xu, J.; Zhang, M.; Shen, Y.; et al. Associations of the MTNR1B rs10830963 and PPARG rs1801282 variants with gestational diabetes mellitus: A meta-analysis. *Int. J. Diabetes Dev. Ctries.* **2023**, *43*, 1029–1042. [[CrossRef](#)]
98. Zhang, Y.; Zhao, K.; Jin, L.; Zhou, Y.; Shang, X.; Wang, X.; Yu, H. MTNR1B gene variations and high pre-pregnancy BMI increase gestational diabetes mellitus risk in Chinese women. *Gene* **2023**, *894*, 148023. [[CrossRef](#)] [[PubMed](#)]

99. Liu, J.; Li, W.; Liu, B.; Dai, A.; Wang, Y.; She, L.; Zhang, P.; Zheng, W.; Dai, Q.; Yang, M. Melatonin Receptor 1B Genetic Variants on Susceptibility to Gestational Diabetes Mellitus: A Hospital-Based Case-Control Study in Wuhan, Central China. *Diabetes Metab. Syndr. Obes.* **2022**, *15*, 1207–1216. [[CrossRef](#)]
100. Shan, D.; Wang, A.; Yi, K. MTNR1B rs1387153 Polymorphism and Risk of Gestational Diabetes Mellitus: Meta-Analysis and Trial Sequential Analysis. *Public Health Genom.* **2023**, *26*, 201–211. [[CrossRef](#)]
101. Xie, K.; Chen, T.; Zhang, Y.; Wen, J.; Cui, X.; You, L.; Zhu, L.; Xu, B.; Ji, C.; Guo, X. Association of rs10830962 polymorphism with gestational diabetes mellitus risk in a Chinese population. *Sci. Rep.* **2019**, *9*, 5357. [[CrossRef](#)]
102. Liang, Z.; Liu, H.; Wang, L.; Chen, Y.; Zhou, T.; Heianza, Y.; Li, W.; Leng, J.; Wang, J.; Gao, R.; et al. Maternal MTNR1B genotype, maternal gestational weight gain, and childhood obesity. *Am. J. Clin. Nutr.* **2020**, *111*, 360–368. [[CrossRef](#)] [[PubMed](#)]
103. Mey, J.T.; Haus, J.M. Dicarbonyl Stress and Glyoxalase-1 in Skeletal Muscle: Implications for Insulin Resistance and Type 2 Diabetes. *Front. Cardiovasc. Med.* **2018**, *5*, 117. [[CrossRef](#)] [[PubMed](#)]
104. Zeng, Q.; Yang, T.; Wei, W.; Zou, D.; Wei, Y.; Han, F.; He, J.; Huang, J.; Guo, R. Association between GLO1 variants and gestational diabetes mellitus susceptibility in a Chinese population: A preliminary study. *Front. Endocrinol.* **2023**, *14*, 1235581. [[CrossRef](#)] [[PubMed](#)]
105. Gale, C.P.; Futers, T.S.; Summers, L.K. Common polymorphisms in the glyoxalase-1 gene and their association with pro-thrombotic factors. *Diab. Vasc. Dis. Res.* **2004**, *1*, 34–39. [[CrossRef](#)] [[PubMed](#)]
106. Matschinsky, F.M.; Magnuson, M.A.; Zelent, D.; Jetton, T.L.; Doliba, N.; Han, Y.; Taub, R.; Grimsby, J. The network of glucokinase-expressing cells in glucose homeostasis and the potential of glucokinase activators for diabetes therapy. *Diabetes* **2006**, *55*, 1–12. [[CrossRef](#)] [[PubMed](#)]
107. Matschinsky, F.M.; Wilson, D.F. The Central Role of Glucokinase in Glucose Homeostasis: A Perspective 50 Years After Demonstrating the Presence of the Enzyme in Islets of Langerhans. *Front. Physiol.* **2019**, *10*, 148. [[CrossRef](#)] [[PubMed](#)]
108. Chakera, A.J.; Steele, A.M.; Gloyn, A.L.; Shepherd, M.H.; Shields, B.; Ellard, S.; Hattersley, A.T. Recognition and Management of Individuals With Hyperglycemia Because of a Heterozygous Glucokinase Mutation. *Diabetes Care* **2015**, *38*, 1383–1392. [[CrossRef](#)]
109. She, L.; Li, W.; Guo, Y.; Zhou, J.; Liu, J.; Zheng, W.; Dai, A.; Chen, X.; Wang, P.; He, H.; et al. Association of glucokinase gene and glucokinase regulatory protein gene polymorphisms with gestational diabetes mellitus: A case-control study. *Gene* **2022**, *824*, 146378. [[CrossRef](#)]
110. Popova, P.V.; Klyushina, A.A.; Vasilyeva, L.B.; Tkachuk, A.S.; Bolotko, Y.A.; Gerasimov, A.S.; Pustozerov, E.A.; Kravchuk, E.N.; Predeus, A.; Kostareva, A.A.; et al. Effect of gene-lifestyle interaction on gestational diabetes risk. *Oncotarget* **2017**, *8*, 112024–112035. [[CrossRef](#)]
111. Ao, D.; Zhao, Q.; Song, J.Y.; Liu, Z.; Wang, Y.; Wang, H.J.; Yang, H.X. The association of the glucokinase rs4607517 polymorphism with gestational diabetes mellitus and its interaction with sweets consumption in Chinese women. *Public Health Nutr.* **2021**, *24*, 2563–2569. [[CrossRef](#)]
112. Anghebem-Oliveira, M.I.; Webber, S.; Alberton, D.; de Souza, E.M.; Klassen, G.; Picheth, G.; Rego, F.G. The GCKR Gene Polymorphism rs780094 is a Risk Factor for Gestational Diabetes in a Brazilian Population. *J. Clin. Lab. Anal.* **2017**, *31*, e22035. [[CrossRef](#)]

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