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Review Article

Updated review of genetic variants influencing gestational diabetes mellitus in women: current knowledge and future perspectives

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Abstract: Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy, is characterized by underlying maternal defects in β-cell response to insulin during pregnancy. Genetic predisposition to GDM has been associated with certain genetic variants. The present review summarizes the findings of previous studies regarding incidence and genetic variant risk factors of GDM. Common variants in several candidate genes have been demonstrated to increase the risk of GDM. Additionally, miRNA-binding sites, long noncoding RNA variants, and incidence risk of GDM are discussed. This review provides an overview of genetic variant factors that may contribute to prevention of GDM. These insights may lead to more effective strategies for prevention and treatment of GDM.

Keywords: Gestational diabetes, genetic variants, type 2 diabetes mellitus

Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy [1]. The spread of obesity and diabetes worldwide, increases in incidence of GDM during recent years, and short-term and long-term adverse health outcomes, for both women and offspring associated with GDM, highlight the significance of preventing GDM among high risk women. Strong association between maternal obesity during pregnancy and metabolic syndrome in childhood is of particular concern since almost two-thirds of American women now enter pregnancy either overweight or obese [2]. Prevalence of GDM has increased in recent decades and depends on the prevalence of same population to type 2 diabetes mellitus (ranging from 1.7 to 11.6%) [3, 4]. Gestational diabetes mellitus (GDM) and type 2 diabetes share common pathophysiological backgrounds, including beta cell dysfunction and insulin resistance. In addition, women with GDM are at increased risk of developing type 2 diabetes later in life. Well-documented risk factors for GDM include pre-pregnancy obesity, family history of diabetes, and advanced maternal age. Poor diet and low physical activity before or during pregnancy may also represent risk factors of GDM [5]. The present study summarizes current knowledge of genetic variants related to insulin secretion and resistance, immunity factors and adipocytokines, and future perspectives related to noncoding RNAs.

Genetic variants influencing gestational diabetes mellitus in women

Insulin secretion and GDM prevalence

Metabolic dysregulation of glucose clearance and production, together with defects in pancreatic beta-cell function, are fundamental features of GDM [6].

Potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11) encodes an integral membrane protein and inward-rectifier type potassium channel. ATP-sensitive potassium (K_{ATP}) channels in pancreatic β-cells comprise two sub-units: a pore-forming K^+ inward rectifier

Kir6.2 (KCNJ11) and a sulfonylurea receptor SUR1 (ABCC8), a target of sulfonylurea drugs [7]. The encoded protein, which has a greater tendency to allow potassium to flow into a cell rather than out of a cell, is controlled by G-proteins. It has been found to be associated with sulfonylurea receptor SUR [8]. Mutations in this gene are a cause of familial persistent hyperinsulinemic hypoglycemia of infancy (PHHI), an autosomal recessive disorder characterized by unregulated insulin secretion. Defects in this gene may also contribute to autosomal dominant non-insulin-dependent diabetes mellitus type II (NIDDM), transient neonatal diabetes mellitus type 3 (TNDM3), and permanent neonatal diabetes mellitus (PNDM) [9].

Whether mutations of KCNJ11 confer susceptibility to GDM remains under investigation. A survey conducted in Scandinavia gestational women identified KCNJ11 as a susceptibility gene of GDM. EE, EK, and KK genotype frequencies of KCNJ11 E23K polymorphism differed significantly between GDM and control women (31.5, 52.7, and 15.8% vs 37.3, 48.8, and 13.9%, respectively; p=0.050). In addition, frequency of the K allele was increased in women with GDM (odds ratio [OR]=1.17, 95% CI 1.02-1.35; p=0.027) and this effect was greater under a dominant model (KK/EK vs EE) (OR=1.3, 95% CI 1.05-1.60; p=0.016) [10]. However, three independent investigations conducted respectively in Korea, Greece, and Denmark, found no relevance of E23K to prevalence of GDM [11-13]. A systematic review revealed that T allele of rs5219 was found to be associated with an increased risk of GDM (95% CI 1.06-1.26, P=0.002) [14]. These results, however, verify that the association between rs5219 (also known as E23K) and GDM is modest.

Detection of KNCJ11 genetic variants can offer directions for clinical therapy and implications for offspring health. Many patients with KCNJ11 mutations can be successfully treated for years with sulfonylurea medications, permitting insulin secretion through closure of the channel. Diagnosing someone with a KCNJ11 mutation may allow a change in treatment with patients changing from insulin therapy to sulfonylurea medications [15]. An affected person's child is more likely to inherit the mutation and develop diabetes. Further validation in different ethnic backgrounds and biological function analyses are necessary.

Sulfonylureas promote insulin secretion by binding to a membrane receptor expressed in pancreatic β-cells, sulfonylurea receptor type 1 (SUR1), a member of the ATP-binding cassette (ABC) superfamily [16]. SUR1 is a functional subunit of the ATP-sensitive potassium channel (K_{ATP}) of pancreatic β-cells and plays a key role in glucose-induced insulin secretion by linking signals derived from glucose metabolism to cell membrane depolarisation and insulin exocytosis [7]. Polymorphisms of the SUR1 gene (1273AGA allele) caused a conversion from impaired glucose tolerance to type 2 diabetes in Finnish subjects with impaired glucose tolerance [17]. According to a Finnish study, a tag-GCC allele of exon 16 splice acceptor site and an AGG allele of the R1273R polymorphism were more common in subjects with GDM than in normoglycemic subjects. Variants were not associated with altered first-phase insulin secretion [18]. However, the polymorphism C49620T in the SUR1 gene was not associated with GDM incidence risk and development of glucose intolerance in that Polish population [19].

KCNQ1, encoding the pore-forming subunit of a voltage-gated K^+ channel that is essential for the repolarization phase of the action potential in insulin-secreting cells, has been confirmed as a susceptibility gene for type 2 diabetes in multiple transethnic groups [20]. Regardless of ethnic background, KCNQ1 mutation has been associated with higher GDM occurrence risk [21-27]. rs2074196 and rs2234895 polymorphisms in KCNQ1 have been associated weight gain, impaired glucose metabolism, insulin resistance, and risk of GDM.

TCF7L2, a gene encoding a transcription factor of the canonical Wnt signaling pathway, plays a key role in glucose homeostasis. Genetic variants in TCF7L2 have been associated with type 2 diabetes (T2D) and impaired beta cell function [28]. Wnt pathways are important for normal lipid and glucose metabolism. Hence, the pathophysiology of metabolic disorders and CT/TT genotypes of SNP rs7903146 have been associated with impaired insulin secretion, incretin effects, and enhanced rate of hepatic glucose production [28]. T allele of TCF7L2 rs7903146 and rs7901695 polymorphisms are

among the most powerful SNPs, associated with susceptibility of GDM in overall populations in White, Hispanic/Latino, and Asian subgroups [29, 30]. The relationship between rs12255372 and GDM varies depending on ethnicity [30].

CAPN10, which encodes the cysteine protease calpain 10, is the first type 2 diabetes mellitus (T2DM) susceptibility gene identified through a genome-wide scan. CAPN10 genetic variants have been reported to be associated with T2DM in a wide range of populations [31-33]. Asian Indians carrying the CAPN10 (rs2975760) have a susceptibility to GDM and T2DM [34]. Although CAPN10 genetic variant distribution in the GDM population doesn't meet the Hardy-Weinberg-Equilibrium, variation in the calpain-10 gene has been found to be not correlated with GDM in populations with other ethnic backgrounds [35, 36].

Common variants in MTNR1B (melatonin receptor 1B) have been strongly associated with increased risk of type 2 diabetes and impaired early insulin secretion [37]. Melatonin influences insulin secretion through inhibition of the cAMP-pathway and decrease of insulin release [38]. Gene polymorphism rs10830963/G of MTNR1B gene variants plays a robust role in developing GDM or glycemic traits, such as acute insulin response, disposition index, and glucose effectiveness [39-41]. This result has been confirmed in multiple country populations. It is noteworthy that risk allele G prevents GDM high risk populations from benefiting from lifestyle interventions, including diet, physical activity, and weight control [42]. Also, rs4753426 in MTNR1B may be a susceptibility gene locus of a higher GDM development risk, while the C allele results in increased fasting plasma glucose levels and impaired pancreatic β-cell function [43].

Insulin resistance and GDM prevalence

Insulin resistance is the condition in which target tissues fail to respond appropriately to circulating insulin [44]. Insulin resistance during gestation is a physiologic phenomenon and adaptation in normal pregnancy, but GDM predisposed individuals with other risk factors, such as morbigenous genetic variants, are prone to suffering pathologic processes [45]. Insulin resistance increases in severity during gestation and becomes prominent in the late second and third trimesters [46, 47]. GDM women suffer from metabolic syndrome, characterized by the presence of hypertension, insulin resistance, glucose intolerance, dyslipidemia, and central obesity [48]. The common link between these diverse insults and insulin resistance has been widely considered to involve impaired insulin signaling [49].

Activation of insulin receptor substrate-1 (IRS1) is a key initial step in the insulin signaling pathway [50]. IRS1 (rs1801278) has been associated with type 2 diabetes mellitus in the high-risk population of India [51]. However, in lean Mexican diabetic subjects with a BMI less than 25 kg/m^2, Gly972Arg has been strongly associated with diabetes risk. Its contribution to overall risk in the general population could be minimal. This evidence supports the line of research seeking to clarify the roles of IRS1 in lean patients with diabetes [52]. In the Greek population, with 148 women with GDM and 107 control subjects, results indicated that the G972R polymorphism of IRS-1 gene was strongly associated with increased susceptibility to GDM [12]. Research results in the Saudi population are in complete agreement [53]. However, prevalence of genotype Gly/Arg in Brazilian pregnant women groups has not been statistically significant [54]. According to a systematic meta-analysis review, rs1801278 in IRS1 was associated with increased risk of developing GDM [55]. This indicates that further studies with large sample sizes, accounting for the interaction of genetic and environmental risk factors, are needed to understand associations between IRS1 genetic polymorphisms and risk of GDM.

Insulin-like growth factor II (IGF2) variations in fetal imprinted genes regulate the maternal availability of nutrients [56, 57]. In Caucasian women, insulin receptor and IGF2 alleles interact to confer additional risk for GDM. Increased risk for GDM has been associated with insulin receptor and IGF2 restriction fragment length polymorphisms [58]. Polymorphic variations (rs6578987, rs680, rs10770125, and rs792-4316) in paternally transmitted fetal IGF2 have been associated with increased maternal glucose concentrations in pregnancy, potentially altering the risk of gestational diabetes in the mother [59].

Insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) gene on chromosome 3q27 is a paralog of IGF2BP1, a known regulator of IGF2 gene expression. Multiple research cases have shown that IGF2BP2 polymorphism is associated with type 2 diabetes [60]. IGF2BP2 (rs4402960,) has been identified to be highly associated with GDM occurrence risk and weight gain in a Korean, Chinese, and Danish population [61-64]. However, IGF2BP2 rs147-0579 and rs4402960 in a Sweden population were found to not be correlated with GDM incidence risk [65]. s11705701 in IGF2BP2 has been associated in the Mexican population with body fat accumulation, GDM incidence risk, and alteration of insulin sensitivity [66].

β-adrenergic receptors (ADRBs) are G protein-coupled receptors contributing to lipolysis and thermogenesis in visceral adipose tissue to modulate metabolic rates. They are activated by the specific binding of their endogenous ligands, the catecholamines [67, 68]. Trp64Arg polymorphisms have also been associated with increased body weight, type 2 diabetes mellitus, insulin resistance, and obesity [69, 70]. Trp64Arg polymorphisms were more frequent in the European Caucasian GDM women than the control group, displaying a clear-cut association with increased weight gain during pregnancy and increased postload glucose value [71]. However, there was no association between Trp64Arg polymorphisms and GDM in the Taiwanese population [72, 73]. It remains intriguing that there is a possible synergistic effect of IRS-1 (Gly972Arg) and ADRB3 Trp-64Arg polymorphisms, as participants carrying both mutant genes are prone to developing GMD [74].

Adipocytokine-related GDM prevalence

Adipokines are proteins secreted from the adipocytes, believed to have metabolic influence. Adiponectin, a protein derived from adipose tissue, has been thought to play a role in the regulation of energy homeostasis, systemic inflammation, vascular function, cell growth, and even bone metabolism [75, 76]. Adiponectin is present in the circulation of healthy individuals at very high concentrations, accounting for approximately 0.05% of total plasma proteins, with levels ranging from 3 to 30 μg/mL [77]. Mothers with obesity or gestational diabetes mellitus have low circulating levels of adiponectin and frequently deliver large babies with increased fat mass. They are susceptible to perinatal complications and to development of metabolic syndrome later in life [78]. Maternal adiponectin supplementation prevents fetal overgrowth caused by maternal obesity, mediated by inhibition of placental insulin and mTORC1 signaling, indicating the clinical potential of adiponectin [79]. Circulating adiponectin levels have been found to be associated with + 45 T/G polymorphism of adiponectin genes in Iranian GDM populations [80]. Malaysian gestational diabetic patients that carried TG/GG genotype in adiponectin SNP45 have lowered levels of plasma adiponectin, compared to other groups, indicating a role of adiponectin SNP45 in circulating plasma adiponectin levels and subsequent risk of GDM [81]. It's noteworthy that SNP + 45T/G polymorphisms of adiponectin genes are not associated with GDM in the Chinese population [82]. However, according to new IADPSG (International Diabetes in Pregnancy Consensus Group) criteria, adiponectin gene polymorphism 45TG is associated with GDM, plasma adiponectin levels, and adverse pregnancy outcomes [83]. The promoter polymorphism rs266729 has been strongly associated with GDM and the minor G allele at position-11377, 5' from the adiponectin gene appears to confer protection against pregnancy-related diabetes mellitus. This effect is probably due to the influence of rs266729 on adiponectin transcription regulation during pregnancy [84]. While studies have yielded many conflicting findings pertaining to adiponectin in pregnancy, further investigation in this area is essential. Ultimately, elucidation of adiponectin physiology in the setting of both normal pregnancy and its pathologic conditions may provide unique insight into fundamental processes relevant to health and disease in mothers and children.

Initially considered an antiobesity hormone, leptin has subsequently been proposed to exert potent anti-diabetic actions that are independent of its effects on body weight and food intake [85]. Long-term leptin-replacement therapy has been well tolerated, dramatically improving glycemic control, insulin sensitivity, and plasma triglycerides in patients with severe insulin resistance [86]. A significantly higher risk for Czech GDM patients has been observed in the presence of an allele (AA and AG genotypes) against carriers of GG genotype [87]. Another report showed that leptin G2548A

polymorphisms were significantly associated with BMI, but not with GDM risk and plasma leptin levels [88]. Polymorphisms rs7799039 and rs13266634 are not associated with GDM in Euro-Brazilian populations [89].

Immunity-associated genes and GDM prevalence

GDM is an inflammatory condition and, as such, immunity-associated genetic variants have been implicated in its physiopathology. T2DM is currently regarded as a chronic inflammatory disease, due to the similarity between T2DM and GDM and the clear relationship between T2DM and inflammation. It has been hypothesized that immunity could be also implicated in the pathophysiology of GDM [90].

The HLA class II region encodes the strongest genetic contribution to insulin-dependent diabetes mellitus (IDDM) and women with a DR3 or DR4 genotype have a higher risk of developing IDDM after pregnancy, compared to non-DR3/non-DR4 patients [91]. However, increased prevalence of IDDM-associated HLA-DR3 and HLA-DR4 genotypes have only been found in women with GDM that had islet autoantibodies at delivery or that developed insulin-dependent diabetes within a few years after pregnancy. Frequency of type 1 diabetes high-risk HLA-DQ alleles (DQB1*0201, B1*0302) did not differ between GDM mothers and controls, but type 1 diabetes protective HLA DQB1*0602 allele was less frequent in GDM [92]. In a Swedish population, autoimmune diabetes with onset during pregnancy has been highly associated with type 1 diabetes-associated genotypes (DR3-DQ2/x and DR4-DQ8/x) and with MICA5.0/5.1. DR7-DQ2/y, DR9-DQ9/y, and DR14-DQ5/y. To some extent, MICA5.0/z are risk factors for nonautoimmune GDM [93]. DQB1*02 and DRB1*1302 have been firmly associated with increased risk of developing GDM, while DQB1*0602 acts in a protective role against GDM [94]. More studies are required to elucidate how these variants contribute to GDM susceptibility.

MBL2 encodes mannose-binding lectin. Elevated MBL levels during (early) pregnancy might be an essential condition for maintaining pregnancy and for protecting the mother against infections during pregnancy. MBL2 has recently been found to play a role in insulin resistance and development of type 1 diabetes and GDM. Functional variants in MBL2 contribute to type 2 diabetes susceptibility in both Native Americans and the Old Order Amish [95]. Genetic studies have revealed that GDM shares common genetic variants with type 2 diabetes [96]. However, it remains to be investigated whether the same set of MBL2 variants contribute to the pathogenesis of GDM. Anna Megia et al. found that Spanish pregnant women bearing the G54D MBL allele had a greater risk for developing GDM and having heavier infants. Additionally, polymorphism G54D of the gene MBL2 had no effect in the need for additional treatment associated with diet-based therapy and in occurrence of large newborns for gestational age in the Portuguese population [97].

Interleukin-10 (IL-10) is an anti-inflammatory cytokine associated with hyperglycemia, type 2 diabetes mellitus (DM), obesity, and metabolic syndrome [98]. Tumor necrosis factor-alpha (TNF α), a pro-inflammatory cytokine, is one of the key cytokines implicated in mediating insulin resistance [98]. Association has been indicated between SNP in the human promoter of the IL-10 gene, as well as TNF α gene, and development of GDM in Malaysia [99]. GDM mothers carrying the homozygous mutant alleles (AA) at position-597 in the promoter region of the human IL-10 gene had lower levels of plasma IL-10 at 32 and 36 weeks of pregnancy, compared to the control group [99]. SNP at position-597 promoter gene of IL-10 was significantly associated with development of GDM. Also, the G/G genotype of the TNF-α-308G/A polymorphism increased insulin levels and insulin resistance in women with GDM. AG haplotype is a genetic risk factor for GDM in the Mexican population [100].

Future perspectives

Genetic variants of non-coding RNAs may contribute to incidence risk of GDM. This part of the review focuses on the recent emergence of microRNAs (miRNAs) as metabolic and developmental regulators in pregnancy and their role in the development of gestational diabetes mellitus (GDM). Dicer and Drosha are two indispensable enzymes in the miRNA biogenesis process and DGCR8 is the essential component of Drosha in the microprocessor complex [101]. Dysregulation of Drosha, Dicer, and

DGCR8 expression was found in pregnant and GDM patients when compared to healthy control participants [102]. MicroRNAs play a role in the development of GDM. A study from Li et al. identified a cohort of miRNAs differentially concentrated in full-term placenta from women with GDM, compared to those showing normoglycemia [103]. Several studies also explored the potential of microRNAs contributing to the pathogenesis and development of GDM [104]. Objectively, the interest in miRNAs and GDM is rather new, with only a few studies published so far. Many are of small sample size but are of interest because they are supported by replication and/or functional (*in vitro*) studies. Large studies are now needed to confirm the role of miRNAs in metabolic regulation in pregnancy, identifying miRNAs implicated as well as their maternal or placental origin.

Recently, two studies provided evidence that SNPs in miRNA-binding sites are a novel source of human GDM susceptibility loci. CDKN2B rs1063192, within the hsa-miR-323b-5p binding site, was associated with increased risk of GDM in pregnant Chinese Han women. rs1063192 genotype CC was associated with increased 60 and 180 minute glucose levels and higher insulin levels at 180 minutes of oral glucose tolerance test, compared with the TT genotype [105]. Wang et al. recently identified C allele of SLC30A8 rs2466293 and INSR rs1366600 contributing to increased GDM susceptibility in Chinese Han women. The allele C of SNP rs2466293 was also associated with reduced beta cell function and fasting insulin levels [106].

LncRNAs have a role in the development and function of pancreatic β cells, white and brown adipose tissue, and other endocrine organs. They are involved in the pathogenesis and development of diabetes mellitus [107, 108]. Although lncRNAs have been investigated in diabetes mellitus, few studies have focused on GDM. lncRNA MALAT1 has been identified as a potential serum biomarker of GDM, with expression levels of lncRNA MALAT1 higher among GDM cases than controls [109]. Pregnancy-related lncRNAs and GDM-associated lncRNA genetic variants have not been reported.

MicroRNAs and binding site variants add the benefit of furthering understanding of the pathophysiological processes behind GDM development. MicroRNAs during pregnancy and GDM have been of rising interest in the ever-expanding field of epigenetics. They may represent a promising avenue for genetic factor attribution, expanding the understanding of GDM pathophysiology. Apparently, miR-binding SNPs of candidate genes in GDM have not been extensively elucidated. The discovery of pregnancy-related miRNAs and GDM-associated binding sites will provide us with important information regarding their function in maternal and placental metabolic regulation. Although they show potential contributing to the pathogenesis of GDM, their utility is still under investigation and remains unproven. However, current studies have supported the importance of miRNAs in development of GDM.

Conclusion

GDM is increasing in prevalence around the world. It is associated with increased risk of obesity and diabetes in offspring, affecting the health of current and future generations. It is now part of an international growing concern, according to the WHO, and needs to be tackled using innovative strategies. This study summarized accumulating evidence regarding the role of genetic factors in the aetiology of GDM. Some research cases came up with conclusions based on relatively large pooled sample sizes. For others, the sample size was too small. Therefore, regarding SNPs, a systematic meta-analysis is necessary. Their association with GDM risk warrants further evaluation as more evidence becomes available.

In summary, this review compiled evidence for significant association of GDM with SNPs from genes related to insulin secretion and resistance. Adipocytokine-related and immunity-related genetic variants were also discussed. Moreover, miRNA-binding sites, long noncoding RNA variants, and incidence risk of GDM were reviewed. Genetic studies of GDM considering fetal and/or paternal genomes, gene-gene, and gene-environmental interactions among non-Caucasian populations are sparse. Future studies in these areas are warranted to better understand the etiology of GDM.

Disclosure of conflict of interest

None.

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