Genes Associated with Metabolism in Gestational Diabetes Mellitus: A New Categorization According to Risk Factors

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Abstract: Gestational Diabetes Mellitus (GDM) is a rising public health concern with a highly increased prevalence over the last decade. Previous genetic studies on GDM mainly focused on identifying genes associated with the shared genetic architecture between Type 2 Diabetes Mellitus (T2DM) and GDM. There is a relative lack of research on the unique genetic architecture of GDM. Thus, to shed light on the traits of GDM, this review provided a new categorization of genes with determined association with GDM based on their correspondence to some important risk factors, through combining out the related references. It was concluded that most genetic evidence concentrated in a history of GDM and a strong family history of diabetes. Evidence in obesity, polycystic ovary syndrome (PCOS), and ethnicity gave insights on other underlying mechanisms of GDM that are worth exploration.

1 INTRODUCTION

Diabetes Mellitus is one of most significant public health concerns because of its wide age range and diverse complications. As one of the three essential classifications of Diabetes Mellitus, although GDM experiences a similar increase in the prevalence as T2DM, this medical complication did not receive as much exclusive research.

To date, most genetic studies on GDM were extended research based on genes previously demonstrated to be associated with T2DM. Therefore, it cannot be denied that there may be a focus bias leading to the much higher number of genes related to the shared metabolic mechanisms with T2DM compared to genes uniquely related to GDM. In short, research on genetics about exclusive traits of GDM is insufficient. This review introduced genes associated with GDM and categorized these genes according to their corresponding risk factors—history of GDM and a strong family history of diabetes, obesity, PCOS, and ethnicity. New insights on the underlying genetic mechanisms of GDM and further identification of more genes unique for GDM are in hope. Such identification could contribute to the personalization of therapy and created new drugs to target specific mechanisms. (Rosik 2020) What is more, even though clinical genetic testing procedure for GDM is not available yet, this review could offer references for the range of genes considered in future genetic testing of GDM.

2 THE CONCEPTION OF GDM

GDM is the type of diabetes developed or first recognized during pregnancy, in which glucose intolerance results in different severities of hyperglycemia. The prevalence of GDM has a noticeable rise during last decade. Because of its obvious regional difference and inconsistency in the diagnostic criteria, the prevalence of GDM is varied all over the world, ranging from 1 to 20%. (Alfadhli 2015) There's no sign that the trend will stop worsening. Thus, inventing procedures for the prevention, diagnosis, and treatment of GDM is of urgency.

Typically, GDM doesn't have overt symptoms. Even at present, it's difficult to distinguish them from normal pregnancy symptoms, making a uniform and sound screening for GDM crucial. However, currently, a global standard strategy for screening and diagnosing GDM is not available. The most adopted diagnostic criterion is the one recommended by WHO in 2013. An oral glucose tolerance test (OGTT) is usually required for diagnosis, during which the plasma glucose concentrations are measured regularly after ingesting 75 grams of glucose.

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(Alfadhli 2015) GDM is diagnosed when blood sugar levels range from 92 mg/dl fasting, ≥180 mg/dl in the 60th minute of the OGTT, or ≥153 mg/dl in the 120th minute of OGTT. (Rosik 2020) Once GDM is diagnosed, lifestyle management like dietary changes and physical exercise should be initiated. Long-term self-monitoring of blood glucose levels is another necessary part of GDM management. When these interventions fail to control the patient's blood glucose level within an acceptable range, medical therapies with insulin, glyburide, and metformin will be introduced. (Alfadhli 2015) In general, GDM is a disease requiring a lot of individual effort. This trait leads to a relatively low-costing treatment for GDM as well as some uncontrollability in its treatment because of the huge variation in people's self-discipline.

Undiagnosed GDM increases the risk for gestational hypertension, pre-eclampsia, macrosomia, birth defects, and polyhydramnios. (Metzger 2008) Also, evidence show that women with GDM have six times higher possibility to develop diabetes after pregnancy, which accordingly makes GDM a significant predictor for T2DM (Damm 2016). Furthermore, children of patients with GDM are two to eight times more likely to develop obesity, metabolic syndrome, and T2DM, compared to children of mothers without GDM (Damm 2016). If the worsening trend of GDM continues, a widespread deterioration in blood glucose control is in expectation due to the impact from generation to generation.

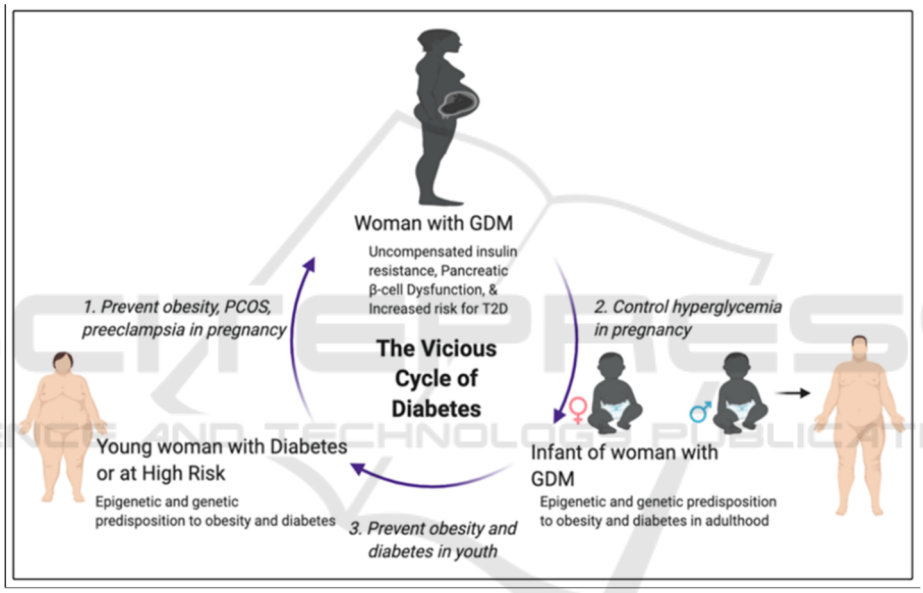

Figure 1: A vicious cycle of obesity and diabetes from generation to generation (Alejandro 2020).

A vicious cycle of obesity and diabetes from generation to generation exists. As evidence show, obesity, a history of GDM and a strong family history of diabetes are all strong factors leading to the occurrence of GDM. Then, children of patients with GDM are two to eight times more likely to develop obesity and T2DM. However, there are still three major windows of opportunities to take interventions to break the vicious cycle. First, prevent risk factors for GDM, like obesity and PCOS. Second, manage and control blood sugar levels during pregnancy. Third, control weight gain and prevent obesity during adolescence. A break of the vicious cycle is critical as the prevalence of diabetes including GDM continues to increase over years.

3 THE NORMAL PREGNANCY METABOLISM AND PATHOPHYSIOLOGY OF GDM

During pregnancy, maternal metabolism changes greatly to provide and store enough nutrients for different stages of pregnancy. For instance, an increased lipid storage often occurs. The key metabolic alteration is a substantial increase in insulin resistance. Placenta and other hormones, including human placental lactogen, placental growth hormone, progesterone, leptin, cortisol, prolactin, human chorionic gonadotropin, and estradiol, are possible factors leading to increased insulin resistance. [6-9]

Other factors include tumor necrosis factor-alpha (TNF-α) and other inflammatory mediators which are produced by the placenta and other tissues. (Lowe 2014)

To compensate for the pregnancy-induced insulin resistance, an enhancement in insulin secretion is initiated. GDM develops when beta cells fail to secrete as much insulin as needed in pregnancy. Another possible mechanism leading to GDM is that pregnancy-induced insulin resistance triggers a genetic predisposition of impairment of beta cell function. (Lambrinoudaki 2010)

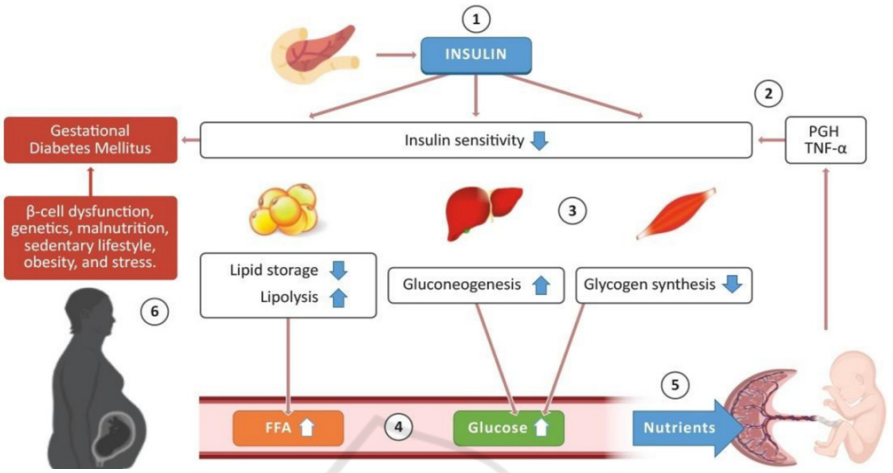

Figure 2: Normal glucose-insulin metabolism during pregnancy. (Lizárraga 2021)

Part 1. The pancreas produces insulin which can act on multiple organs, adipose tissue, and muscle to control blood glucose levels. Part 2. Placenta and other hormones, proinflammatory cytokines like TNF-α cause increased insulin resistance/decreased insulin sensitivity. Part 3&4. Then, there's an accordingly decrease in lipid storage and an increase in lipolysis activity, resulting in higher amounts of free fatty acids (FFA) in the bloodstream. Meanwhile, promoted gluconeogenesis occurs in the liver and depressed glycogen synthesis occurs in skeletal muscles, leading to higher amounts of glucose in the bloodstream. Part 5. FFA and glucose are transported into the placenta to provide enough nutrients to support fetal growth. Part 6. GDM develops when factors like beta-cell dysfunction and genetics lead to insufficient insulin secretion that fails to compensate for the increased insulin resistance.

4 GENETICS IN VARIOUS RISK FACTORS

Common GDM risk factors include a history of GDM, a strong family history of diabetes, obesity, PCOS, ethnicity, and advanced maternal age. (Alfadhli 2015) Except for advanced maternal age, other risk factors are all supported with genetic evidence. This study aims to achieve a new categorization of genes that have been identified to be related to GDM according to their correspondence to different risk factors. Because of an uneven distribution of efforts in studies on these risk factors, a ranking of the importance of the risk factors cannot be safely concluded. Based on current evidence, a history of GDM and a strong family history of diabetes are the biggest risk factors. The following ordering of risk factors is primarily according to the amount of available evidence.

4.1 A History of GDM & a Strong Family History of Diabetes

A history of GDM and a strong family history of diabetes are two risk factors that share many physiological traits. Previous studies achieved most findings of genes responsible for glucose metabolism and mechanisms regarding insulin like beta cell function. It provides a sound explanation for why a history of GDM and a strong family history of diabetes, which contribute to progressive dysfunctions of these mechanisms, are significant risk factors of GDM. Interestingly, GDM has a similar impact on the risk of T2DM.

4.1.1 Transcription Factor 7–like 2 (TCF7L2)

Many TCF7L2 polymorphisms have threatening

effects on the risk of GDM. In their study, Zhang et al. showed that rs7903146 (OR=1.44, p < 0.001) and rs12255372 (OR=1.46, P = 0.002) are strongly correlated with increased GDM risk. (Zhang 2021) Reducing insulin secretion is the potential pathway.

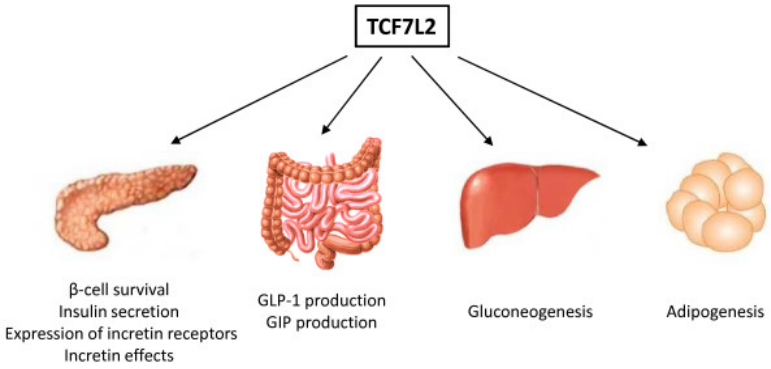

Figure 3. Potential metabolic pathways that TCF7L2 may contribute to. (Chiang 2012).

TCF7L2 is an important protein involved in Wnt signaling pathway by contributing to the formation of a key effector in this pathway. Wnt pathway impacts glucose homeostasis by controlling the gene expression and functioning of some hormones, like GLP-1, GIP, and insulin. This pathway also affects adipogenesis negatively. Even though the mechanism of how TCF7L2 polymorphisms leads to increased GDM risk is unclear, this finding has been successfully replicated several times. Insulin down-regulates the gene expression of TCF7L2 in adipocytes. People with insulin resistance are observed to have higher levels of TCF7L2 in adipose tissue.

4.1.2 Melatonin Receptor 1B (MTNR1B)

MTNR1B has the potential effect of antagonizing insulin release. (Dalfrà 2020) Its polymorphism rs10830963 was more frequently found in GDM patients compared to the controls (48.4% vs. 42.3%). (Zhang 2014) The G allele carriers were observed to increase the risk of GDM risk (OR=1.24, p < 0.00001). (Zhang 2014) A similar association was found between rs1387153 single-nucleotide polymorphism (SNP) and GDM risk. (Zhang 2014)

4.1.3 Glucokinase (GCK)

GCK amplifies the secretion when a rise in blood glucose is detected to manage insulin secretion. (Dalfrà 2020) A meta-analysis of recent studies found a significant association between rs1799884 and enhanced GDM risk with an OR of 1.29 (p < 0.001). (Zhang 2021)

4.1.4 Glucokinase Regulatory Protein (GCKR)

GCKR encodes regulatory proteins that exert an inhibiting effect on GCK in the liver and pancreatic islet cells. (Dalfrà 2020) The polymorphism rs780094 C/T SNP was found to be associated with a decrease in GDM risk in all populations in its dominance, recessive, and allelic models. (Lin 2018)

4.1.5 Potassium Channel Inwardly Rectifying Subfamily J member 11 (KCNJ11)

KCNJ11 contributes to the regulation of insulin secretion. (Dalfrà 2020) A meta-analysis conducted by Zhang et al. demonstrated a modest correlation between KCNJ11 rs5219 (E23K) and increased GDM risk (OR=1.15, P=0.002). (Zhang 2021)

4.1.6 CDK5 Regulatory Subunit Associated Protein 1 Like 1 (CDKAL1)

CDKAL1 is involved in beta cell function and insulin release. (Rosik 2020) Guo et al. demonstrated that rs7754840 and rs7756992 were all significantly correlated with GDM risk. (Guo 2018)

4.1.7 Solute Carrier Family 30, Member 8 (SLC30A8)

SLC30A8 is only expressed in the pancreas and is responsible for insulin secretion. (Dalfrà 2020) In their study, Lin et al. demonstrated a protective effect of rs13266634 C/T SNP on GDM development. (Lin 2018)

4.1.8 Insulin Receptor Substrate 1 (IRS1)

IRS1 encodes insulin receptor substrate 1 which impacts insulin signaling. (Dalfrà 2020) A meta-analysis determined that the T allele of IRS1 rs1801278 was discovered more frequently in GDM patients than in the control group (8.7% vs. 5.1%). It leads to the conclusion that rs1801278 is strongly correlated with GDM risk. (Zhang 2014)

4.1.9 Insulin Like Growth Factor 2 MRNA Binding Protein 2 (IGF2BP2)

IGF2BP2 encodes proteins which play a role in insulin secretion. Zhang et al. identified the effect of rs4402960 on increasing GDM risk (OR=1.21, P<0.001). (Zhang 2021)

Many of the recent studies were testing the association between T2DM susceptibility genes with GDM, based on the assumption that there is a shared genetic architecture between GDM and T2DM. (Lowe 2014) Also, there is a potential bias because the references this review relies on only included a relatively limited number of women with GDM, compared to a large number of patients with T2DM involved in these references. Among tested genes, the nine genetic loci listed are demonstrated to be also associated with GDM and are supported with the most evidence. However, many T2DM susceptibility genes failed to show any evidence for their correlation with GDM. (Lowe 2014) Therefore, although further examination of the association between other T2DM susceptibility genes and GDM is of great significance to understand GDM, exploration of other underlying genetic mechanisms is still necessary.

4.2 Obesity

As a rising public health crisis aggravated by the widespread sedentary lifestyles, obesity leads to many life-threatening diseases, including GDM. It is shown that the prevalence of GDM in normal-weight women, defined as women whose pre-pregnancy BMI is 18.5-24.9, is 3.6%, whereas that in women with BMI over 40.0 is 13.9%. (Deputy 2018) Some genes related to lipid metabolism showed evidence for association with increased GDM risk.

FTO contributes to regulating fat mass, adipogenesis and body weight. FTO rs9939609 T/A SNP had an identified association with increased GDM risk. (Dalfrà 2020) Moreover, according to Yang et al.'s study, there were associations between FTO gene rs11075995, rs3826169, rs74245270, rs74018601, rs7205009 and rs9888758 and the enhancement of the risk of GDM. (Yang 2020)

Furthermore, an enhancement in the gene expression of the adipokines TNFα, IL-1β and or leptin was investigated to increase in adipose tissue from obese and GDM women. On the other hand, the gene expression of LPL, FATP2, FATP6, ASCL1, PNPLA2, PPARδ, PPARγ and RXRα was observed to decrease in GDM patients. (Lappas 2014)

As findings of the association between FTO and GDM risk are inconsistent, further studies are in need to determine the association. Still, the association between other genes involved in lipid metabolism and GDM risk is worth examination.

4.3 PCOS

PCOS is a health condition characterized by hyperandrogenism, anovulation, and insulin resistance. Similar to the relationship between T2DM and GDM, PCOS may contribute to an increase of the risk of GDM.

Fibroblast growth factor (FGF) 19 & 21. FGF 19 and FGF 21, encoding adipokines which are involved in insulin resistance and serum levels of adiponectin, were identified to be correlated with GDM risk. (Wang 2013) Moreover, GDM patients with PCOS history were observed to have much lower levels of FGF 19 than GDM patients without PCOS history and controls without PCOS history. (Wang 2013) Wang et al. indicated that a decrease in serum FGF19 level was a possible part of the pathophysiology of GDM. (Wang 2013) On the other hand, increased serum FGF 21 was potentially involved in a compensatory response to GDM. (Wang 2013)

Even though only limited genes are found to prove the association between PCOS and GDM genetically, evidence for such genes' involvement in the pathophysiology of GDM is encouraging, providing potential research directions of the pathophysiology of GDM.

4.4 Ethnicity

Many statistics show that the prevalence of GDM varies among different ethnic groups, even though the genetic evidence is not obvious yet. Non-Hispanic Asian women had the highest prevalence (11.1%). (Deputy 2018) In general, GDM has higher frequency among African, Hispanic, Indian, and Asian women than among Caucasian women. (Alfadhli 2015) PPARG is a gene that demonstrated some association

with ethnicity.

Peroxisome proliferator-activated receptor γ (PPARG). PPARG plays a role in the regulation of adipocyte differentiation and glucose homeostasis. Its polymorphism rs1801282 was demonstrated to be associated with GDM risk only in the Asian population. However, the association was not identified in the Caucasian population. (Metzger 2008)

The lack of genetic evidence for this association could be because many previous studies contained groups of mixed ancestry or participants from a single ethnic group. Further findings of such genes require research incorporating and comparing various ethnic groups.

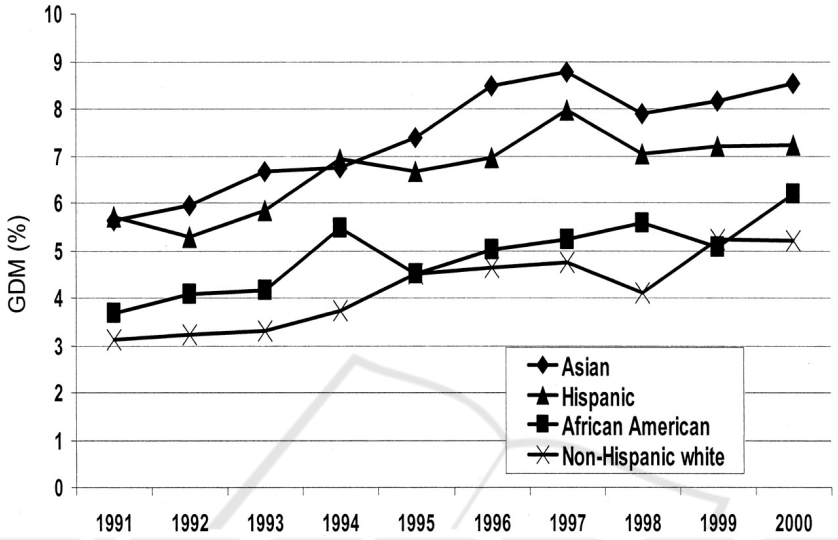

Figure 4: Age-adjusted prevalence of GDM by ethnicity and years: Northern California Kaiser Permanente, 1991-2000 (Ferrara 2007).

All ethnic groups were investigated to have a similar increasing trend in their prevalence of GDM in the Northern California Kaiser Permanente study from 1991-2000. Asian and Hispanic women had higher prevalence of GDM than other ethnic groups.

5 DISCUSSIONS

Clinical genetic testing is already available for monogenic forms of diabetes, especially Maturity Onset Diabetes of the Young (MODY). The mutations of 14 genes are identified to be individually associated with the occurrence of MODY. (Firdous 2018) Currently, the genetic diagnosis of MODY is usually done through next-generation sequencing (NGS), which analyzes the mutations in DNA isolated from blood sample. This method usually diagnoses MODY with almost 100% sensitivity. (Firdous 2018)

However, in terms of polygenic forms of diabetes like T2DM and GDM, the genetic etiology is much more complicated. What further extends the difficulty of clinical genetic testing for polygenic forms of diabetes is the interactive impacts of environmental and lifestyle factors on such diabetes.

Nonetheless, the application of genetic diagnosis of MODY is still inspiring for the development of a genetic diagnosis procedure of GDM in the future. There could be a huge step forward if some genes unique to the etiology of GDM are identified. This is also in accordance with the aim of this review—to provide insights on underlying mechanisms (other than the shared genetic architecture with T2DM) that have the potential to find genes associated with GDM exclusively.

6 CONCLUSIONS

In this paper, through the combining of related references, a new classification of genes that influence GDM was made and based on their correspondence to various risk factors. The underlying mechanisms that are associated with obesity (lipid metabolism), PCOS, and race were also revealed in this paper. Finally, it was concluded that except for advanced maternal age, other risk factors such as history of GDM, a strong family history of diabetes, obesity, PCOS, ethnicity were identified to

have genetic evidence associated with an increase in GDM risk. Among them, history of GDM and a strong family of history combined (due to their similarity in physiological mechanism) had the highest number of genes with a demonstrated association with GDM. This trend could be attributed to the concentrated research on the similarity between the genetic architecture of T2DM and GDM. However, this paper could be further improved with more research on obesity, PCOS, race and other related genes, as well as an in-depth explanation of their metabolic mechanisms. In the future, with more samplings and diverse ethnic groups, more associated genes may be found by related researchers and may contributing to the genetic testing for GDM.

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