Genetics of gestational diabetes mellitus

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Abstract

Gestational diabetes mellitus (GDM) has now become a major public health problem because of its prevalence and its associated complications during pregnancy. Earlier studies have suggested that type 2 diabetes mellitus (T2DM) and GDM might have similar pathophysiology, such as increased insulin resistance, decreased insulin secretion resulting in hyperglycaemia. Evidence for a genetic basis of GDM has been poorly understood. To some extent, the current advancement in genomic techniques has thrown better light on the genetics of GDM. Based on the candidate gene approach and genome wide association studies, genetic loci in several genes that are responsible for insulin secretion, insulin resistance, lipid and glucose metabolism and other pathways have shown association with the GDM susceptibility. Understanding the possible underlying genetic factors of GDM would help us in gaining knowledge on the pathophysiologic mechanism of the disease.

Keywords: GDM, ***CDKAL1***, ***HKDC1***, ***HMG20A***, ***HNF4A***.

Introduction

Gestational diabetes mellitus (GDM) is defind as any degree of glucose intolerance with onset or detected for the first time during the gestational period.[1] In India alone, there are about 62.4 million with diabetes and about 4 million women with gestational diabetes mellitus.[2] Earlier studies have suggested that type 2 diabetes mellitus (T2DM) and GDM might have similar pathophysiology, such as increased insulin resistance, decreased insulin secretion resulting in hyperglycaemia.

An overview of glucose metabolism in pregnancy is very important and will give better understanding of GDM. During pregnancy there could be changes in maternal metabolism.[1] There is a progressive increase in insulin resistance with an increase in maternal adiposity and decrease in insulin sensitivity due to the effect of hormones from the placenta. Changes in insulin sensitivity is accompanied by changes in glucose levels. This condition rapidly reverses upon delivery in normal women. The glycaemic control in the mother is dependent on the balance between pancreatic β-cell secretion of insulin, clearance of insulin and action of insulin in liver, muscle and fat.[3] Women who are unable to respond properly to the changes of pregnancy, such as increase in insulin resistance, become hyperglycaemic leading to gestational diabetes mellitus. The diagnostic criteria for GDM have changed over years and in 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommended criteria for screening pregnant women with a 75-g oral glucose tolerance test (OGTT), which has been widely accepted. The IADPSG criteria states that, diagnosis of GDM is done, if any one of the following values: FPG $\geq$ 92 mg/dl (5.1mmol/l), 1-h plasma glucose $\geq$ 180 mg/dl (10.0mmol/l) and 2 hour plasma glucose $\geq$ 153 mg/dl (8.5 mmol/l), after a 75g glucose load.

The genetic basis of GDM is poorly understood. Twin concordance rates, familial risk estimates and the contribution of genetic factors to a phenotype which is measured as heritability have been very few. Propective studies have been extremely daunting since studying related individuals presenting with GDM have been tough to find. Retrospective studies have been even more difficult since the diagnostic criteria for GDM have changed over the years thus making retrospective identification of GDM cases next to impossible. Compounded by lack of screening for GDM in routine medical practice, the situation leads to poor heritability estimates and small sample sizes for genetic studies. To some extent, the current advancement in genomic techniques has thrown better light on the genetics of GDM.

GDM could develop when a genetic predisposition to pancreatic islet β-cell impairment is unmasked by the increased insulin resistance during pregnancy. Initial genetic studies were focused largely on candidate genes with genes selected largely based on their biological role, such as insulin secretion and insulin resistance. These studies have successfully identified the association of some of the previously implicated T2DM genes with GDM. However, the association with GDM was not demonstrated by all the T2DM associated loci. Genetic mechanisms leading to GDM are not yet fully understood

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and it is therefore questionable whether the genetic factors for T2DM and GDM are the same.[4]

Understanding the possible underlying genetic factors of GDM would help us in gaining knowledge on the pathophysiologic mechanism of the disease. Till date, the genetic basis of GDM and its potential clinical significance are not well understood. This review focuses on the findings of the genetic studies on GDM.

Genetic studies on GDM based on candidate gene approach

Early studies on genetics of GDM selected candidate genes were based on certain biochemical pathways and then based on SNPs which showed association with T2DM. Candidate susceptibility gene variants related to insulin secretion and insulin resistance such as glucokinase (***GCK***), potassium inwardly rectifying channel subfamily J, member 11 (***KCNJ11***), HLA antigens, insulin receptor (INSR), insulin-like growth factor-2 (***IGF2***), insulin (***INS***-VNTR), plasminogen activator inhibitor 1 (***PAI-1***), hepatocyte nuclear factor-4a (***HNF4A***) have been reported to be associated with increased risk for GDM.[4]

Various candidate gene approach studies have shown a number of genetic variants to be associated with GDM in different ethnic populations. Genetic variants in ***MTNR1B***, ***TCF7L2*** and ***GCKR*** genes have shown association with GDM among European ancestry women. ***TSPAN8*** gene variants showed increased risk for GDM in African-American. Among Finnish GDM women, ***MTNR1B*** gene variants showed strong association with GDM while the variants in the ***ADCY5***, ***ANK1***, ***G6PC2***, ***GCKR***, ***FTO***, ***TCF7L2***, ***TLE1*** and ***ZMIZ1*** genes showed nominal association with GDM.[3]

A recent study on 115 loci among the Mexican pregnant women that were related to T2DM, GDM, traits like BMI or poor pregnancy outcomes with GDM reported significant association with GDM were shown by SNPs in ***TCF7L2*** and ***KCNQ1*** genes and nominal association with GDM was shown by variants in loci that were previously associated with T2DM (***KLF14***, ***HHEX***, ***GRB14***, ***DUSP9*** and ***PEPD***), increased BMI (***FAIM2***) or GDM (***FTSJD1***/ ***CALB2***). In Korean population, the ***FTSJD1/CALB2***, showed association with GDM while in Mexican-American women, it was only nominally associated and did not show any association with T2DM.[5] Hence, this gene may be considered as a potential candidate for GDM.[3]

Genetics of GDM based on GWA Studies

Genome wide association study (GWAS) is a hypothesis free, powerful strategy to find novel genes or gene variations as it investigates genetic variations across the entire genome. GWAS has been instrumental in dissecting out the genetics of complex diseases such as diabetes.

GWA and meta-analyses studies have lead to identification of numerous T2DM associated variants. These genetic variants are now being studied for the association with GDM. Genetic variants such as ***CDKAL1***, encoding a protein of unknown function but having high sequence homology with proteins regulating cyclin-dependent kinase 5 and two genes involved in cell cycle regulation namely, ***CDKN2A*** and ***CDKN2B*** showed strong evidence for association with GDM in the Korean population.[4] Other loci such as ***HHEX***, ***IGF2BP2***, ***SLC30A8*** and ***TCF7L2*** showed modest evidence for association with GDM. In the Danish population, a strong evidence for association with GDM was shown by ***TCF7L2***, while, marginal association with GDM were demonstrated by ***CDKAL1*** and ***HNF1B***.[3]

Meta-analyses on early candidate gene studies and GWAS showed significant associations of SNPs in or near the ***TCF7L2***, ***GCK***, ***KCNJ11***, ***KCNQ1***, ***CDKAL1***, ***IGF2BP2***, ***MTNR1B*** and ***IRS1*** genes. All these eight loci were previously related to the risk of T2DM. Most of these genes (***TCF7L2***, ***GCK***, ***KCNJ11***, ***KCNQ1***, ***CDKAL1***, ***IGF2BP2***, ***MTNR1B***) have shown to modulate pancreatic islet beta cell function or development, while IRS1 gene plays a role in insulin signaling.[4] These findings support the shared genetic basis between GDM and T2DM, as both insulin resistance and defects in insulin secretion plays a major role in the etiology of both GDM and T2DM.

In our recent study done at the Madras Diabetes Research Foundation (MDRF), Chennai, India, CDK5 regulatory subunit associated protein 1-like 1 (***CDKAL1***) gene variants showed association with GDM among the 11 T2DM associated variants such as ***CDKAL1***, ***GCK***, ***IGF2BP2***, ***KCNJ11***, ***MTNR1A***, ***MTNR1B***, ***SRR*** and ***TCF7L2*** were investigated on Asian Indian population. The function of ***CDKAL1*** gene is not completely understood. Studies have shown that ***CDKAL1*** inhibits the activity of cyclin-dependent kinase 5 (CDK5), thereby affecting the function of beta cells. ***CDKAL1*** also acts as a tRNA modification enzyme. Hence, the presence of risk alleles might alter the protein translation affecting the conversion of proinsulin to insulin in beta cells.[6]

An earlier, genome wide association study (GWAS) on T2DM among south Asians, showed a strong association of six novel genes namely, ***AP3S2*** (rs2028299), ***GRB14*** (rs3923113), ***HMG20A*** (rs7178572), ***HNF4A*** (rs4812829), ***ST6GAL1*** (rs16861329) and ***VPS26A*** (rs1802295) with T2DM. These SNPs did not show any association with T2DM among Europeans. Among these six variants,

Table: Summary of the association of GDM susceptible genes.

S No	Gene	Function	Variants	Asian Indians	Other ethnic groups
1	CDK5 regulatory subunit associated protein 1 like-1 (*CDKAL1*) 6p22.3	A tRNA methylthiotransferase	rs7754840	Associated with GDM (6)	Associated with GDM in Korean population and not associated in Chinese (3)
2	Glucokinase (*GCK*) 7p15.3-p15.1	Phosphorylates glucose in pancreatic β-cells and Hepatocytes	rs1799884	Not associated with GDM (6)	Associated with GDM in Caucasian and Thailand populations (3)
3	Insulin-like growth factor 2 mRNA binding protein 2 (*IGF2BP2*) 3q27.2	Binds insulin-like growth factor-2 mRNA and may regulate protein translation	rs4402960	Not associated with GDM (6)	Associated with GDM in Caucasian, Korean and Chinese populations (3)
4	Insulin receptor substrate 1 (*IRS1*) 2q36	Substrate of insulin receptor tyrosine kinase	rs1801278	-	Associated with GDM in Caucasian population (3)
5	Potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) 11p15.1	Integral membrane protein, controlled by G-proteins and associated with the sulfonylurea receptor	rs5219	Not associated with GDM (6)	Associated with GDM in Caucasian and Korean populations (3)
6	Potassium voltage-gated channel, KQT-like subfamily, member 1 (*KCNQ1*) 11p15.5-p15.4	Voltage-gated potassium channel	rs2237895	-	Associated with GDM in Korean and Chinese populations (7)
7	Melatonin receptor 1B (MTNR1B) 11q21-q22	G-protein coupled receptor that is expressed on β-cells, binds melatonin	rs10830963 rs1387153	Not associated with GDM (6)	Associated with GDM in Caucasian and Korean and not associated in Chinese population (3)
8	Transcription factor 7-like 2 (*TCF7L2*) 10q25.3	Transcription factor and member of the Wnt signaling pathway	rs12255372	Nominal association with GDM (6)	Associated with GDM in Caucasian and Korean populations (3)
9	Adaptor-related protein complex (*AP3S2*) 15q26	Involved in vesicle transport and sorting in these tissues	rs2028299	Not associated with GDM (Unpublished data)	Not associated with GDM in Mexican population (5)
10	Growth factor receptor-bound protein (*GRB14*) 2q24	Adapter protein that binds to insulin and insulin-like growth factor receptors inhibiting tyrosine kinase signaling	rs3923113	Not associated with GDM (Unpublished data)	Nominal association with GDM in Mexican population (5)
11	High-mobility group protein 20A (*HMG20A*) 15q24	Regulatory protein controlling gene expression by histone modification and involved in neuronal development	rs7178572	Associated with GDM (Unpublished data)	Not associated with GDM in Mexican population (5)
12	Hepatocyte nuclear factor (*HNF4A*) 20q13	Transcription factor strongly expressed in liver	rs4812829	Associated with GDM (Unpublished data)	-
13	Sialyltransferase 6 galactosidase 1 protein (*ST6GAL1*) 3q27	Enzyme located in the Golgi apparatus	rs16861329	Not associated with GDM (Unpublished data)	Not associated with GDM in Mexican population (5)
14	Vacuolar protein sorting-associated protein (*VPS26A*) 10q22	Multimeric protein complex involved in transport to trans-Golgi complex	rs1802295	Not associated with GDM (Unpublished data)	-
15	Hexokinase domain containing 1 (*HKDC1*) 10q22.1	Function unclear; may have cellular hexokinase activity	rs10762264 rs4746822	Associated with GDM (10)	-

AP3S2 (rs2028299), ***GRB14*** (rs3923113), ***HMG20A*** (rs7178572) and ***ST6GAL1*** (rs16861329) were studied in Mexican population and found that all the four variants did not show any association with GDM. However, a weak association with GDM was observed with ***GRB14*** variant (rs3923113).[5] In a more recent study on Asian Indian population, the genetic variants such as ***HMG20A*** (rs7178572) and ***HNF4A*** (rs4812829) have shown association with GDM (Kanthimathi et al., Unpublished data). High mobility group 20A (***HMG20A***) gene encodes a widely expressed non-histone chromosomal protein and may be involved in neuronal differentiation. Although these studies have given evidence of the association of ***HMG20A*** with diabetes, the probable mechanism is still unknown. While, Hepatocyte nuclear factor 4A (***HNF4A***) is a nuclear transcription factor that regulates the expression of various genes involved in glucose metabolism and insulin secretion.

Although several GWA studies on T2DM have been published, only one study on GWAS in GDM is available till

date. Kwak et al.,[7] performed a GWAS in a South Korean cohort and reported that SNPs in ***CDKAL1*** and ***MTNR1B*** gene variants showed a strong association with GDM at a genome-wide significance level ($p<5\times10^{-8}$) with GDM and a near genome-wide significant association was observed with ***IGF2BP2***. These are already known T2DM susceptibility genes which have demonstrated association with GDM as well. These findings also support the hypothesis that both GDM and T2DM share a similar genetic background.

Understanding the biological effects of genetic variations may help us in gaining knowledge on the pathogenesis of GDM and T2DM. Earlier studies have shown associations between some T2DM susceptibility loci and T2DM related quantitative traits and have also shown that these associations are modified by factors such as adiposity and other gene variants.

In a GWA study conducted in a multi-ethnic pregnant women cohort to identify genetic loci associated with measures of maternal metabolism, Hayes et al.[8] identified a strong association of ***HKDC1*** with 2-h glucose and BACE2 loci with fasting C-peptide. ***HKDC1***, a novel human hexokinase gene encodes hexokinase domain containing 1. The variant in ***HKDC1*** that showed association with 2-h glucose in pregnant women, showed only nominal association in non-pregnant individuals. This shows that ***HKDC1*** may play a role in glucose metabolism during pregnancy than in nongravid state. Guo et al.[9] demonstrated the possible role of the novel hexokinase gene in the development of GDM as they observed increased levels of maternal 2-hour glucose to be associated with lower levels of ***HKDC1*** expression. Our recent study showed association of HKDC1 genetic variants with susceptibility to GDM among south Asian population.[10] These studies (summarised in Table) suggest that, in addition to studying T2DM and metabolic traits associated genes, understanding the genetic architecture underlying maternal metabolism during pregnancy may provide additional insights into the genetic contribution to risk for GDM and foetal outcomes.

Conclusions

Studies on the genetic background of GDM have significantly lagged behind compared to other forms of diabetes like T2DM. However, knowledge gained in understanding the genetic basis of T1DM and T2DM have important implications for GDM. Testing of T2DM susceptibility loci among study group with GDM, has provided evidence that, at a small level, GDM and T2DM share common susceptibility loci. Further studies are needed to establish GDM specific loci. These GDM susceptibility loci, could have implications on the offspring as well. In summary, identification of loci underlying GDM and its related traits will help us in understanding the biological background of GDM and thereby facilitate an improved intervention.

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