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Genetics of Gestational Diabetes Mellitus and Maternal Metabolism

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Abstract Gestational diabetes mellitus (GDM) is defined as abnormal glucose tolerance with onset or first recognition during pregnancy. Women with a history of GDM are at long-term risk for developing type 2 diabetes (T2DM), raising the question to what extent GDM and T2DM share a common genetic architecture. Meta-analysis of candidate gene studies and genome-wide association analysis (GWAS) have identified a number of genes which are reproducibly associated with GDM, including *TCF7L2*, *GCK*, *KCNJ11*, *KCNQ1*, *CDKAL1*, *IGF2BP2*, *MTNR1B*, and *IRS1*. These genes are also associated with T2DM. Candidate gene and GWAS have also identified genes associated with maternal metabolic traits, most of which are also associated with metabolic traits in the general population. Two genes, *BACE2* and *HKDC1*, are uniquely associated with maternal metabolic traits. These studies suggest that there are similarities and differences between the genetic architecture of GDM and T2DM and metabolic quantitative traits in pregnant and non-pregnant populations.

Keywords Gestational diabetes · Genetics · Pregnancy · Candidate gene · Genome-wide association study

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Introduction

Gestational diabetes mellitus (GDM) is defined as abnormal glucose tolerance with onset or first recognition during pregnancy [1–4]. The prevalence of GDM varies among different ancestry groups, typically in direct proportion to the prevalence of hyperglycemia within an ancestry group outside of pregnancy [1, 3]. It is also impacted by the diagnostic criteria used [1, 3], with a higher prevalence when lower diagnostic values are used and vice versa [3, 4]. With all of those considerations, the prevalence of GDM varies from 7 to 17 % in different populations and, commensurate with the increase in obesity and type 2 diabetes (T2DM) in the general population, the prevalence of GDM appears to be increasing [4–6]. Moreover, new guidelines proposed recently by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) based upon adverse fetal outcomes recommend lower diagnostic values [7], and, if adopted, the prevalence of GDM would approximately double [4].

A number of risk factors for GDM have been identified. These include advanced maternal age, ancestry, higher parity, prior history of GDM, or prior delivery of a macrosomic infant, short stature, obesity, multiple pregnancy, high blood

pressure during pregnancy, and a family history of diabetes [1]. Ancestry as a risk factor could represent genetic, cultural, or environmental differences between groups. In this review, we describe genetic factors that impact the risk of GDM.

Pregnancy is accompanied by a number of changes in metabolism which are designed to allow the mother to meet both her own and the growing fetus's energy needs [8–10]. Key among these changes is a substantial decrease in insulin sensitivity during pregnancy. In early gestation, there is a slight enhancement of insulin sensitivity, but by 12–14-weeks gestation, insulin sensitivity begins to decrease with a progressive decline in the second and third trimesters [8, 9, 11]. During the third trimester of pregnancy, insulin sensitivity has been reported to be 30–70 % of prepregnant values, reaching values similar to those see in T2DM [2, 8, 9]. Pregnancy-induced insulin resistance is rapidly reversed upon delivery [12] and is thought to be secondary to both greater maternal adiposity as well as placental and other hormones, including human placental lactogen, placental growth hormone, progesterone, leptin, cortisol, prolactin, human chorionic gonadotropin, and estradiol as well as tumor necrosis factor-alpha (TNF-α) and other inflammatory mediators which are produced by placental and other tissues [8, 9, 11–13]. Enhanced insulin secretion during pregnancy is an important compensatory mechanism for the insulin resistance; compared to the non-gravid state, basal insulin levels double by the third trimester [8]. An increase in beta cell mass induced by pregnancy contributes to but does not fully account for the increase in insulin secretion [9, 14].

Similar to most causes of hyperglycemia, GDM is a result of inadequate beta cell compensation to the increased insulin requirements of late pregnancy [4]. In a minority of cases, the hyperglycemia is secondary to evolving type 1 diabetes characterized by the presence of autoantibodies or undiagnosed monogenic diabetes, e.g., maturity onset diabetes of the young (MODY); however, in the majority of cases, the inadequate beta cell composition reflects a chronic beta cell defect that becomes apparent during pregnancy [4]. Although women with GDM typically exhibit increased insulin secretion compared to the non-gravid state, the increase is insufficient to compensate for the acquired insulin resistance characteristic of pregnancy [4]. This is similar to the defect in insulin secretion characteristic of T2DM.

Not surprisingly, women with a history of GDM are at risk for progressive beta cell dysfunction and the development of T2DM over time post-partum [4]. The incidence of T2DM following GDM reported in different studies varies widely depending upon length of follow-up, ancestry, diagnostic criteria used for the diagnosis of GDM, and other factors [15, 16]. In general, after 5 years of follow-up, the cumulative incidence of T2DM in women with a history of GDM varied between 20 to 70 % in different studies [15].

The clear higher risk for T2DM in women with a history GDM, the risk for GDM conferred by a family history of T2DM, the clustering of T2DM and impaired glucose tolerance in families of women with a history of GDM [17], and the similarity of the underlying pathophysiology of GDM and T2DM raise the question to what degree the underlying genetic architecture of T2DM and GDM are similar. With improved understanding of the genetics of T2DM and related quantitative traits, this question has been addressed over the last several years.

Candidate Gene Analyses

The initial and, to date, most commonly used approach to identify genetic variants associated with GDM has been genotype variants in candidate genes, i.e., genes predicted to have an impact on the biology of GDM. A major limitation of candidate gene studies is that they use this directed approach in the selection of the genes to be studied, as opposed to the unbiased approach of genome-wide association studies (GWAS). It has become apparent that the candidate gene approach has been of limited utility for identifying genes associated with complex diseases and traits. Many of the susceptibility genes identified through GWAS were not necessarily strong biological candidates, and, in turn, most of the candidate genes studied to date are not among the most strongly associated genes identified in GWAS. Moreover, as the early candidate gene studies were undertaken prior to the improved definition of the genetic architecture of complex traits and diseases provided by GWAS, they have typically suffered from inherent limitations, including small sample sizes and inclusion of a limited number of variants in the genetic loci being studied [18].

Early on, candidate genes for GDM were chosen based largely on biological plausibility. The results of these early studies have been the subject of previous reviews [18, 19]. Many of these early candidate gene studies contained a relatively small number of women in the control and GDM groups and, in some cases, groups of mixed ancestry. Moreover, uniform criteria for the diagnosis of gestational diabetes were not necessarily used across different studies. Thus, robust and reproducible association of many of the genetic variants with GDM was not demonstrated in individual studies. Given the relationship between GDM and T2DM described above, more recent studies have been based on the underlying assumption that the genetic architecture of GDM and T2DM are similar. A large number of genetic variants associated with T2DM have been identified through GWAS together with meta-analyses that have included increasingly large numbers of individuals with T2DM [20–22]. A number of these variants have now been tested for their association with GDM.

GWAS have provided insight into the genetic architecture of complex diseases and traits, but much remains uncertain. Multiple models have been proposed for the architecture of complex diseases and traits, including the following: (i) A large number of small effect common variants across the spectrum of allele frequency account for disease risk and quantitative trait variation; (ii) a large number of large effect rare variants underlie observed associations; or (iii) a combination of genotypic, environmental, and epigenetic interactions accounts for the association [23, 24]. It is likely that some combination of those different potential mechanisms accounts for the underlying architecture of complex diseases and traits as common, low frequency, and rare variants have all now been shown to be associated with complex diseases and traits [25, 26]. To date, in GDM, most studies have focused on the association of common variants with disease risk. Sequencing and other studies designed to explore the impact of rare variants on disease risk have not been undertaken.

As noted, early studies largely focused on candidate gene analyses with genes chosen initially based upon biological plausibility and subsequently based on a demonstrated association with T2DM. Many of these studies included only a small number of participants, so results were often variable. Recently, two different meta-analyses which included many of these early studies have been performed [27, 28••]. One examined association of 12 SNPs in ten genes which included results from 29 studies, while the other examined 9 SNPs in eight genes reported in 22 studies. Sixteen of the studies were common between the two meta-analyses. Given the overlap between the two studies, variants in six genes demonstrated evidence for association in both meta-analyses, with each study reporting a significant association of variants in one additional gene. The eight genes demonstrating association with GDM were as follows: *TCF7L2*, *GCK*, *KCNJ11*, *KCNQ1*, *CDKAL1*, *IGF2BP2*, *MTNR1B*, and *IRS1* (Table 1) [27, 28••]. All of these loci are also associated with risk of T2DM [20–22]. The majority of these genes encode proteins important for beta cell function or development, including *GCK*, *KCNJ11*, *KCNQ1*, *MTNR1B*, *IGF2BP2*, *CDKAL1*, and *TCF7L2* [21, 22, 29–35]. In contrast, variants in *IRS1*, which is a docking protein that plays a critical role in insulin signaling, impact insulin sensitivity [35].

The meta-analyses did not find evidence for association of variants in peroxisome proliferator-activated receptor gamma (*PPARG*) and adrenoreceptor beta 3 (*ADRB3*) with GDM [27, 28••]. *ADRB3* has been shown to be associated with BMI in some, but not all, ancestry groups but has not been identified as a susceptibility gene for T2DM [36]. In contrast, *PPARG*, which encodes a transcription factor with an important role in adipogenesis [21, 22, 37], has been identified as a T2DM susceptibility gene [21, 22].

More recently, the overlap between the genetic architecture of GDM and T2DM was more directly tested by examining the association of a number of T2DM susceptibility genes with GDM [38, 39]. Stuebe et al. examined the association of T2DM susceptibility genes with GDM in 899 European ancestry and 386 African-American women; 6.2 % of women in each cohort had been diagnosed with GDM [39]. They tested 38 SNPs in 35 different loci. Among European ancestry women, association of a variant in *MTNR1B*, *TCF7L2*, and *GCKR* with GDM was demonstrated. *GCKR* encodes glucokinase regulatory protein and is abundantly expressed in liver where it binds to glucokinase resulting in a loss of enzymatic activity [33]. In the African-American cohort, an increased risk of GDM was present in women homozygous for the risk allele of *TSPAN8*, while a lower risk of GDM was found in women carrying the T allele of *JAZF1* [39]. As there were only 24 African-American women with GDM, these results must be interpreted with caution. A second similar study examined the association of T2DM risk alleles with GDM in a cohort of 940 Finnish women (533 women with GDM and 407 controls) [38]. A total of 69 SNPs in 64 loci were examined. Two different SNPs in *MTNR1B* were significantly associated with GDM. Otherwise, SNPs in *GCKR*, *TCF7L2*, *ANK1*, *FTO*, *TLE1*, *ZMIZ1*, *G6PC2*, and *ADCY5* demonstrated nominal association with GDM [38]. Finally, Huerta-Chagoya et al. examined the association of 176 SNPs in 115 loci associated with T2DM, GDM, BMI, or adverse pregnancy outcomes with GDM in 750 pregnant Mexican women (408 GDM and 342 controls) [40]. SNPs in *TCF7L2* and *KCNQ1* were significantly associated with GDM, while variants in *KLF14*, *FAIM2*, *HHEX*, *GRB14*, *DUSP9*, *FTSJD1*/*CALB2*, and *PEPD* showed nominal association with GDM. The failure to demonstrate significant associations with GDM in the above studies is not surprising. Most T2DM susceptibility alleles confer only a small increase in the risk for T2DM and were identified in GWAS and meta-analyses that included, in some studies, more than 20,000 cases and controls which increased the power to detect association with small effect sizes (odds ratios for susceptibility to T2DM) [20–22]. Thus, these studies of GDM likely lacked power to demonstrate significant associations. While most of these T2DM loci have failed to demonstrate association with GDM, many of these loci represent potential drug targets and may ultimately be of use in personalizing treatment of GDM. For example, *KCNJ11* encodes a potassium channel which associates with the sulfonylurea receptor and helps regulate insulin secretion. Association of a specific variant in *KCNJ11* with response to sulfonylurea treatment has been reported in some but not all studies [41, 42]. Sulfonylureas have been used to treat GDM [43], although the potential role of *KCNJ11* variants in regulating the response to sulfonylureas in GDM has not been examined.

Table 1 Candidate genes demonstrating association with GDM in meta-analyses

Gene	Chromosome	Encoded protein	Protein function
IRS1	2	Insulin receptor substrate 1	Substrate of insulin receptor tyrosine kinase; key molecule in the insulin signaling pathway
IGF2BP2	3	Insulin-like growth factor 2 mRNA-binding protein 2	Binds insulin-like growth factor-2 mRNA and may regulate protein translation; risk allele associated with decreased insulin secretion
CDKAL1	6	CDK5 regulatory subunit associated protein 1 like-1	A tRNA methylthiotransferase; non-pregnant carriers of the risk alleles have impaired oral and intravenous glucose stimulated insulin secretion
GCK	7	Glucokinase	Phosphorylates glucose in pancreatic β-cells and hepatocytes; involved in the regulation of insulin secretion
TCF7L2	10	Transcription factor 7-like 2	Transcription factor and member of the Wnt signaling pathway; risk allele associated with reduced insulin secretion
MTNR1B	11	Melatonin receptor 1B	G-protein coupled receptor that is expressed on β-cells, binds melatonin and may antagonize insulin release
KCNJ11	11	Potassium inwardly rectifying channel, subfamily J, member 11	Integral membrane protein and inward-rectifier type potassium channel which is controlled by G-proteins and associated with the sulfonylurea receptor; involved in the regulation of insulin secretion
KCNQ1	11	Potassium voltage-gated channel, KQT-like subfamily, member 1	Voltage-gated potassium channel; involved in the regulation of insulin secretion

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Beyond the studies described above, a number of generally small and unreplicated studies have reported other candidate loci which show evidence for association with GDM. These studies await replication in larger populations.

Genome-Wide Association Studies

The above studies examined the association of specific candidate genes with GDM based upon biologic plausibility or known association with T2DM. This approach will not necessarily allow for identification of genetic variation that is uniquely associated with GDM. Although there are apparent similarities between the genetic architecture of GDM and T2DM, it is not known whether there are genes uniquely associated with GDM. A second approach which can be used to address that question is GWAS [44]. GWAS interrogate genetic variants across the genome for association with a trait or disease in an unbiased, hypothesis-free manner. This approach has been successful in identifying genetic variation associated with complex diseases and traits and in beginning to define the genetic architecture of complex traits or diseases. As noted, one observation is that many of the variants associated with complex diseases or traits are relatively common and have only a modest effect on disease risk [23, 44] but that low frequency and rare variants with potentially larger effects on disease risk may also contribute [45]. Recent studies suggest that low frequency and rare variants contribute to T2DM risk [22]. Identification of both common variants with a modest effect and low frequency and rare variants requires a large number of subjects for significant associations to be demonstrated. This has presented a problem in GDM as potential cases are limited to women who have been pregnant, and GDM, itself, is relatively uncommon.

To date, there has been a single GWAS performed for GDM. The study was performed in a South Korean cohort that included 468 cases and 1242 controls [46••]. The controls were women over age 50 who did not have a history of diabetes or a family history of diabetes; however, no information on parity or glycemic status during pregnancy was available. A second cohort that included an additional 931 women with GDM as well as 783 women without a personal or family history of diabetes was used to replicate the top 11 genetic variants associated with GDM in the first discovery cohort. In a joint meta-analysis of the results from the two cohorts, SNPs in *CDKAL1* and *MTNR1B* demonstrated genome-wide significant association (defined as $p < 5 \times 10^{-8}$ to correct for multiple testing of millions of variants across the genome) with GDM. *IGF2BP2* demonstrated near genome-wide significant association. All of these genes demonstrated association

with GDM in candidate gene studies and are known T2DM susceptibility genes [21, 22, 47]. The next two most highly associated loci with GDM, *FTSJD1*/*CALB2* and *LBXCOR1*, fell short of demonstrating genome-wide significant association with GDM. Neither of these loci has been shown to be associated with T2DM, although *FTSJD1*/*CALB2* was also nominally associated with GDM in Mexican-American women [40], and represent potential candidates for genes uniquely associated with GDM. Future studies with larger cohorts will be needed to address this question.

Beyond examining the association of individual SNPs with GDM, the investigators also further examined the hypothesis that the genetic architecture of GDM and T2DM is similar [46••]. To do that, they examined the association of 34 known T2DM risk alleles with GDM. This demonstrated an excess of small *p* values compared to what would be expected under the null hypothesis. Further, when the effect sizes of the known T2DM variants in GDM and T2DM were compared, there was, in general, a significant positive correlation between the two. Together, these findings lend further support for similarities between the underlying genetic architecture of GDM and T2DM.

Genetics of Maternal Metabolic Quantitative Traits

An alternative approach to gain insight into the genetics of GDM is to examine genetic variation that contributes to maternal quantitative traits during pregnancy, since quantitative trait studies are better powered than discrete trait studies (e.g., GDM cases vs. controls). Studies in non-pregnant populations have demonstrated substantial overlap between genetic variation associated with T2DM and various metabolic quantitative traits [47, 48]. Among the traits that have been examined are glucose, C-peptide, and insulin levels, typically measured at fasting, 30 min, 1 h, and 2 h during an OGTT. Beyond these directly measured values, calculated measurements to model insulin sensitivity and resistance have also been considered, for example, the Matsuda Insulin Sensitivity Index (Matsuda ISI), insulin disposition (Matsuda ISI multiplied by an insulinogenic index defined as the ratio of changes in insulin and glucose from fasting to 30 min), insulin resistance (HOMA-IR or HOMA2), and area under the curve (AUC) for insulin using the trapezoidal method for insulin measurements over time. The continuous nature of these measures affords increased statistical power, avoids selection of a specific definition for GDM, and allows insight into multiple contributors to altered glucose metabolism during pregnancy. In several cases, loci known to be associated with T2D and/or metabolic traits in the general population have demonstrated association in pregnant populations. Several unique associations that appear to be most relevant during pregnancy have also been reported.

Several candidate gene studies for maternal metabolic traits in pregnant populations of various ancestries have focused on loci known to be associated with T2DM, GDM, and metabolic traits in the general population. For example, the methylthiotransferase *CDKAL1* and the G-protein-coupled receptor *MTNRB1* are both expressed in beta cells and associated with both T2DM and GDM (21,22,46). In pregnant South Korean women with GDM, *CDKAL1* was also associated with fasting insulin, while *MTNR1B* demonstrated nominal association with fasting insulin [46••]. In a study of ~1150 pregnant Chinese women, *CDKAL1* was associated with insulin sensitivity (Matsuda ISI), insulin disposition, and 2-h proinsulin conversion measured by AUC, with another gene important for cell cycle regulation, *CDKN2A*/*2B*, also demonstrating association with insulin sensitivity and disposition [49]. A study with an expanded set of candidate genes in the same cohort of pregnant Chinese women confirmed association of *MTNRB1* with maternal metabolic traits, including Matsuda ISI, early-phase insulin release, and fasting insulin conversion, while variants in *HNF1B* and *KCNJ11* were associated with Matsuda ISI, HOMA-IR, insulin disposition, and/or fasting and 2-h insulin conversion [50]. In the study of 750 pregnant Mexican women from Huerta-Chagoya et al. described above, *MTNR1B* was associated with the HOMA2 measure of insulin resistance [40]. Associations of *CENTD2* with 1-h glucose, and *TCF7L2* and *KCNQ1* haplotypes with glucose levels during the OGTT and AUC for insulin were also observed in this population [40].

TCF7L2, which is a transcription factor and member of the Wnt signaling pathway, has demonstrated associations with GDM as well as T2DM and fasting glucose in the general population [48, 51]. In a candidate gene study in European ancestry and Thai women who participated in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, marginal association of *TCF7L2* with fasting glucose and strong associations with 1- and 2-h glucose in HAPO participants of European ancestry was observed [52]. Interestingly, in a large meta-analysis, *TCF7L2* was not reported to have a strong association with 2-h glucose in the general population [47] suggesting the possibility of pregnancy-specific association with 2-h glucose for this trait.

Studies of a specific variant in the promoter of *GCK* that encodes glucokinase have also demonstrated associations with GDM, T2DM and fasting glucose in the general population [21, 22, 27, 28••, 48]. This same variant was associated with fasting glucose in pregnant women of European ancestry [53], and in analyses of HAPO data, with fasting and 1-h glucose in women of European ancestry and 2-h glucose in Thais [52].

One mechanism underlying pregnancy-induced insulin resistance is the production of inflammatory mediators [12, 13, 54], and association of higher levels of various inflammatory mediators with higher levels of fasting, 1-h, and 2-h glucose

Table 2 Genetic loci demonstrating genome-wide significant association with maternal metabolic traits

Gene	Chromosome	Encoded Protein	Protein Function	Associated maternal trait	Associated metabolic traits in non-gravid populations
G6PC2	2	Glucose-6-phosphatase, catalytic, 2	Component of an integral membrane system that catalyzes glucose-6-phosphate hydrolysis	Fasting glucose	Fasting glucose
GCKR	2	Glucokinase regulator	Regulatory protein that inhibits glucokinase by forming an inactive complex with the enzyme	Fasting C-peptide, fasting glucose	Lipid phenotypes, fasting glucose, 2-h glucose, fasting insulin, type 2 diabetes
PCSK1	5	Proprotein convertase subtilisin/kexin type 1	Calcium-dependent serine endoprotease involved in proteolytic activation of several precursor proteins including proinsulin, pro-glucagon-like peptide 1 and pro-opiomelancortin, among others	Fasting glucose	Findings not consistent but associated with obesity-related traits, fasting plasma glucose, 2-h plasma glucose, and fasting and post-glucose proinsulin levels
PPP1R3B	8	Protein phosphatase 1, regulatory subunit 3B	Facilitates interaction of protein phosphatase 1 with enzymes of glycogen metabolism	Fasting C-peptide, fasting glucose	Lipid phenotypes, fasting glucose, C-reactive protein, type 2 diabetes
HKDC1	10	Hexokinase domain containing 1	Structure consistent with a hexokinase but function not yet defined	2-h glucose	Nominal association with 2-h glucose in a meta-analysis of over 40,000 individuals
MTNR1B	11	Melatonin receptor 1B	G-protein coupled receptor that is expressed on β-cells, binds melatonin and may antagonize insulin release	Fasting glucose, 1-h glucose	Fasting glucose, impaired fasting glucose, type 2 diabetes, altered β-cell function, including decreased insulin release following oral and IV glucose
BACE2	21	β-site amyloid polypeptide cleaving enzyme 2	Not defined	Fasting C-peptide	None reported

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levels in HAPO mothers of European ancestry has been demonstrated [12, 13, 54]. Candidate gene studies examining the association of genetic variation within loci important in inflammatory pathways have been undertaken and shown association with maternal metabolic traits. In a study of HAPO mothers of European and Thai ancestry, variants in the inflammatory pathway genes *RETN*, *IL8*, *ADIPOR8*, *LEPR*, *IL6*, and *TNFA* demonstrated associations with maternal metabolic traits with effects in consistent directions for both ancestry groups [55]. A polymorphism in the *TNFA* promoter region also demonstrated association with insulin resistance (HOMA-IR) in a small study of pregnant Mexican women with GDM [56].

The above candidate gene studies for maternal metabolic traits have largely focused on genes with previously reported associations with GDM and T2DM and metabolic traits in the general population. Similar to the South Korean GWAS for GDM, a comprehensive GWAS using HAPO data provided an opportunity to examine in an unbiased way associations with maternal metabolic traits with the goal of defining overlap between associations observed in non-pregnant populations as well as identifying loci with potentially pregnancy-specific associations [57••]. In analyses of pregnant women of European, Thai, Afro-Caribbean, and Mexican-American ancestry, loci in *MTNR1B*, *PPP1R3B*, *PCSK1*, *GCKR*, and *G6PC2* were associated with fasting glucose, fasting C-peptide, 1-h glucose, and/or 2-h glucose, consistent with observations from non-gravid populations (Table 2) [48, 57••]. However, genome-wide significant associations of 2-h glucose with *HKDC1* and fasting C-peptide with *BACE2* loci were also observed in HAPO women [48]. *BACE2*, which encodes β-site amyloid polypeptide cleaving enzyme 2, is expressed in human pancreatic beta cells where its protein product is located in endocytic vesicles, and has been shown to both augment and inhibit insulin secretion and/or production in human islets [58, 59]. It has not been previously reported to be associated with metabolic traits in non-pregnant populations. The same SNP in *HKDC1* that was highly associated with 2-h glucose in pregnant women was shown to be only nominally associated with 2-h glucose in a large meta-analysis of non-pregnant individuals [47]. *HKDC1* encodes hexokinase domain containing 1 and is a member of the hexokinase family [33]. We have recently demonstrated that hexokinase domain containing 1 has hexokinase activity and that lower levels of *HKDC1* expression are associated with higher levels of maternal 2-h glucose [60•]. Together, these studies suggest that the genetic architecture underlying maternal metabolism during pregnancy has unique features in addition to including genes associated with T2DM and metabolic traits in the general population.

Similar to studies of the genetics of GDM, many of the above studies had a limited number of participants and, in all cases, were substantially smaller than large meta-analyses examining the genetic architecture of metabolic traits in non-pregnant populations [47, 51]. Thus, in some cases, the results await replication. However, many of the above associations were replicated across studies and/or the same locus demonstrated association with GDM, while the GWAS findings were replicated [57••].

Impact of Fetal Genotype on Maternal Metabolism

Maternal genetic variation clearly impacts maternal metabolism [61]. More recently, the potential impact of fetal genotype on maternal metabolism has become an area of interest [62]. Available data are still limited, but an effect of variants in *IGF2*, which encodes insulin-like growth factor-II (IGF-II), on maternal glucose levels has been reported [63]. *IGF2* is imprinted, i.e., only one of the two inherited alleles is expressed. In the case of *IGF*, the paternal allele is expressed. Petry et al. demonstrated that variation in the paternal but not the maternal allele of the fetal *IGF2* gene is associated with maternal glucose levels [63]. These same variants in *IGF2* were associated with increased IGF-II protein content in the placenta. The mechanism by which variation in the paternal allele of the fetal *IGF2* gene impacts maternal metabolism is yet to be elucidated, but this finding provides new insight into the regulation of maternal metabolism and suggests that other imprinted fetal genes may also affect maternal metabolism.

Conclusions

With the advent of new approaches to study the genetics of complex traits and diseases over the last 10 to 15 years, new progress has been made in defining the genetic architecture of GDM and maternal metabolism during pregnancy. Genetic variation in a number of different genes has now been shown to be clearly associated with GDM and maternal metabolic traits. In many cases, these same genetic variants were initially shown to be associated with T2DM or other metabolic traits in non-gravid populations, suggesting clear similarities between the genetic architecture of GDM and T2DM and of maternal metabolism during pregnancy and metabolism in the non-gravid population. To date, the overwhelming majority of genetic variants associated with T2DM or metabolic quantitative traits in non-pregnant populations have failed to show association with GDM or maternal metabolic traits. The extent to which these represent differences in genetic architecture versus limited power of the studies in pregnant women has not been determined, but the latter issue no doubt accounts to some extent for the limited findings in pregnant women. There are numerous challenges in recruiting women with GDM and controls, including the frequency of the condition in the population, use of different diagnostic criteria, differences in

screening, and others. Over time and with increased collaboration between groups, some of these barriers should be overcome. Beyond the clear similarities between the genetic architecture of metabolism in pregnant and non-pregnant populations, there are also indications that some genes may be uniquely associated with metabolic traits during pregnancy or GDM. Further elucidation of these genes will provide new insight into maternal metabolism during pregnancy and the pathogenesis of GDM.

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Compliance with Ethical Standards

Conflict of Interest William L. Lowe, Jr., Denise M. Scholtens, Victoria Sandler, and M. Geoffrey Hayes declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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