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Genetic Studies of Gestational Diabetes and Glucose Metabolism in Pregnancy

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Abstract

Purpose of Review—In this review, we summarize studies investigating genetics of gestational diabetes mellitus (GDM) and glucose metabolism in pregnancy. We describe these studies in the context of the larger body of literature on type 2 diabetes (T2D) and glycemic trait genomics.

Recent Findings—We reviewed 23 genetic association studies for GDM and performed a meta-analysis, which revealed variants at eight T2D loci significantly associated with GDM after the Bonferroni correction. These studies suggest that GDM and T2D share a number of genetic risk loci. Only two unbiased genome-wide association studies (GWASs) have successfully revealed genetic associations for GDM and related glycemic traits in pregnancy. A GWAS for GDM in Korean women identified two loci (near *CDKAL1* and *MTNR1B*) known to be associated with T2D, though the association of the *MTNR1B* locus with GDM appears to be stronger than that for T2D. A multi-ethnic GWAS for glycemic traits in pregnancy identified two novel loci (near *HKDC1* and *BACE2*) which appear to be associated with post-load glucose and fasting c-peptide specifically in pregnant women. There are ongoing efforts to use this genetic information, in the form of polygenic scores, to predict risk of GDM and postpartum T2D.

Summary—The body of literature examining genetic associations with GDM is limited, especially when compared to the available literature on T2D and glycemic trait genomics. Additional genetic discovery for glucose metabolism in pregnant women will require larger pregnancy cohorts and international collaborative efforts. Studies on the clinical implications of these findings are also warranted.

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Keywords

Genetics; Genome-wide association study; Gestational diabetes mellitus; Pregnancy; Type 2 diabetes mellitus

Introduction

Just as type 2 diabetes (T2D) is the most common diagnosis given to hyperglycemia outside of pregnancy, gestational diabetes (GDM) is the most common diagnosis given to newly discovered hyperglycemia in pregnant women. Hyperglycemia in pregnancy is associated with a number of pregnancy complications, including fetal overgrowth (and attendant birth injury, shoulder dystocia, and cesarean section risk), preterm labor, preeclampsia, as well as neonatal hypoglycemia, and respiratory distress syndrome [1–3]. Thus, it is typically recommended that all pregnant women undergo screening for hyperglycemia at 24–30 weeks gestation [4, 5].

Some have suggested that GDM represents a “forme fruste” of T2D, brought to clinical light because of universal screening and dramatic changes in glycemic physiology that occur during pregnancy [6, 7]. Indeed, seminal studies have demonstrated that at the time of usual GDM diagnosis in the late 2nd or early 3rd trimester, insulin resistance has increased by approximately 50% [8–11]. By this point in gestation, insulin secretory response has also dramatically increased and in many pregnancies is adequate to maintain glycemia below GDM diagnostic thresholds [8, 9, 11, 12]. Women with GDM, by virtue of having hyperglycemia, have inadequate insulin secretory response for the degree of insulin resistance present. Some studies suggest that beta-cell dysfunction in GDM is chronic but only comes to clinical attention in the second half of pregnancy [6, 7]. In this conceptual model, women with GDM are destined to develop T2D later in life with aging and weight gain [6, 7]. Epidemiologic studies support GDM as a strong risk factor for T2D, with approximately 50% of affected women having developed T2D by 10 years after pregnancy [13, 14]. Yet, other observations call into question that GDM is solely a chronic maternal disease, namely that GDM recurrence risk is less than 50% [15, 16], that GDM is more common in multiple gestation [17], and that not all women with GDM develop T2D.

If GDM and T2D represent the same disease at different stages of the life course, genetic determinants of T2D risk should overlap with that of GDM. To date, over 560 genetic loci associated with T2D have been discovered in studies of over 1,400,000 individuals [18]. Here, we review studies of the common genetic variations associated with GDM and related glycemic traits in pregnant women. We describe these studies in the context of the larger body of literature on T2D and glycemic trait genomics.

Type 2 Diabetes-Associated Genetic Loci and GDM

Based on the hypothesis that GDM shares genetic risk factors with T2D, many genetic studies of GDM have attempted to reproduce the genetic association results for T2D with GDM. The initial genetic studies on GDM focused on positional and functional candidate genes for T2D and monogenic diabetes, which included *CAP10*, *KCNJ11*, *GCK*, *HNFI1A*,

and *HNF4A* [19–21]. Some of the common variants in these regions were nominally ($P < 0.05$) associated with risk of GDM. However, the strength of association was not great enough to make a sound conclusion with the available sample size. One of the major advances in genetic studies of T2D was the identification of the *TCF7L2* locus on chromosome 10q25.3, which has a robust and reproducible effect on risk of T2D [22]. This was followed by efforts to investigate variants in the *TCF7L2* locus for a potential role in GDM [23, 24]. In a Scandinavian GDM case-control study by Shaat et al., which involved 1881 women, an intronic variant in *TCF7L2*, rs7903146:C>T, was significantly associated with increased risk of GDM with an odds ratio (OR) of 1.49 (95% confidence interval (CI) 1.28–1.75; $P = 4.9 \times 10^{-7}$) [23]. This variant is the most strongly associated single nucleotide polymorphism (SNP) for T2D in Europeans. Watanabe et al. investigated 15 tagging SNPs in the *TCF7L2* locus and found that rs12255372:G>T was associated with increased risk of GDM in 537 Mexican-Americans (OR 2.49, 95% CI 1.17–5.31, $P = 0.018$) [24]. However, they were not able to replicate the association of rs7903146 with GDM ($P = 0.601$) likely due to limited statistical power (only 94 GDM cases were included).

With the advent of genome-wide association studies (GWASs) in 2007, the number of confirmed genetic risk loci for T2D increased rapidly [25–28]. These GWASs and their meta-analyses discovered that genetic variants in/near *CDKAL1*, *CDKN2A/2B*, *FTO*, *GCKR*, *HHEX*, *IGF2BP2*, *KCNJ11*, *PPARG*, *SLC30A8*, and *TCF7L2* were associated with T2D at genome-wide significance ($P < 5 \times 10^{-8}$). Soon after, these variants were tested for association with GDM. A study by Lauenborg et al. was one of the first to evaluate these variants [29•]. They investigated 11 variants in 283 women with previous history of GDM and 2446 control women in Denmark. The study found that four variants in/near *TCF7L2*, *CDKAL1*, *TCF2*, and *FTO* that raise the risk of T2D were significantly associated with GDM when allele frequencies were compared. In addition, among the 11 variants studied, 10 had the same direction of association for T2D and GDM (even if the association was not statistically significant). Concurrently, there was another report from South Korea by Cho et al. testing 18 variants discovered by T2D GWAS for their association with GDM in 869 cases and 632 controls [30•]. Variants in/near *CDKAL1*, *CDKN2A/2B*, *HHEX*, *IGF2BP2*, *SLC30A8*, and *TCF7L2* were significantly associated with increased risk of GDM; two variants in *CDKAL1* even reached genome-wide significance. Variants in *CDKAL1*, *CDKN2A/2B*, and *HHEX* were associated with decreased insulin secretion estimated by area under the curve (AUC) of plasma insulin level during an oral glucose tolerance test (OGTT) used to diagnose GDM. This implied that at least some genetic risk loci for GDM impair insulin secretory response during pregnancy. These two studies clearly showed that a number of genetic variants associated with T2D are also associated with GDM.

Subsequent genetic studies on GDM attempted to replicate these associations in independent populations and expand the variants investigated to those discovered by the latest large-scale meta-analysis of GWAS for T2D. By literature review, we identified 23 studies that investigated genetic associations with GDM since 2009. A total of 11 studies were from European populations [29•, 31–40], seven were from East Asian populations [30•, 41, 42•, 43–46], two from Latin American populations [31, 47], two were from South Asian populations [48, 49], and one from a Middle Eastern population [50]. We retrieved 502 variant level association test results (Supplementary Table 1). For some variants, genetic

association results (direction and significance of association) for GDM were not consistent. This may be attributable to the fact that most of the studies had limited sample size and statistical power. In order to have a better understanding of the true genetic associations with GDM, we performed a fixed-effects inverse-variance weighted meta-analysis of associations reported by these studies. There were 100 variants that were reported at least in two different studies. The overall effective sample size, which takes into account the balance between the number of cases and controls, for each variant ranged from 2373 to 24,237. After applying a Bonferroni correction ($P < 5 \times 10^{-4}$, 0.05/100) to adjust for multiple comparisons, there were 16 variants in eight loci (in/near *IGF2BP2*, *CDKAL1*, *GLIS3*, *CDKN2A/2B*, *HHEX/IDE*, *TCF7L2*, *MTNR1B*, and *HNFI1A*) that were significantly associated with GDM (Table 1). Among these, two variants in *CDKAL1* (rs7754840:G>C, rs7756992:A>G, $r^2 = 0.75$ in Europeans), two variants in *TCF7L2* (rs4506565:A>T, rs7903146:C>T, $r^2 = 0.88$ in Europeans), and two variants in *MTNR1B* (rs1387153:C>T, rs10830963:C>G, $r^2 = 0.73$ in Europeans) reached genome-wide significance for association. The ORs ranged from 1.09 to 1.24, and rs10830963:C>G in *MTNR1B* had the largest effect size for association with GDM (OR 1.24, 95% CI 1.19–1.29, $P = 4.1 \times 10^{-26}$). All the significant variants for GDM had the same direction of association for T2D. These findings again suggest that GDM and T2D share genetic risk factors. However, it does not answer whether there are any genetic risk loci that are specific to GDM.

GWAS for GDM and MTNR1B

The strengths of a GWAS are that it uses an unbiased and hypothesis-free approach, and provides a systematic view of the genetic risk factors for a disease of interest or a quantitative trait. A GWAS for GDM does not require the selection of candidate variants from T2D genetic loci and provides an opportunity to test whether GDM and T2D share common genetic risk factors in an unbiased way. In addition, it might uncover genetic risk loci that are specific to GDM. We published the first GWAS of GDM in 2012 [42•], 5 years after the first publication of a GWAS in T2D. In this study, we used a two-stage approach, involving 468 women with GDM and 1242 control women for a stage 1 genome-wide scan and 931 women with GDM and 783 controls for stage 2 replication in a Korean population. Two variants known to be associated with T2D had genome-wide significant associations with GDM. These variants were rs7754840:G>C (OR 1.52, 95% CI 1.37–1.68, $P = 6.65 \times 10^{-16}$) in an intron of *CDKAL1* and rs10830962:C>G (OR 1.45, 95% CI 1.32–1.61, $P = 2.49 \times 10^{-13}$) which was 4.36 kb upstream of *MTNR1B*. The two variants were also associated with lower fasting insulin levels during pregnancy. As part of this investigation, we also compared the association effect size for GDM and T2D in 37 known T2D-associated variants and found a significant positive linear correlation as shown in Fig. 1 (Pearson's correlation 0.442, $P = 0.0062$). As our unbiased genome-wide approach found significant associations confined to known T2D loci, and there was a linear relationship between the effect size in GDM and T2D, it is likely that GDM and T2D share similar genetic risk factors. However, it should be noted that at least two variants (rs10830963 of *MTNR1B* and rs11708067 of *ADCY5*) had considerably different effect sizes in GDM as compared to T2D (with the *MTNR1B* variant having a greater effect for GDM and the *ADCY5* variant having an opposing direction of association for T2D). Considering that the

sample size in this study was modest for a GWAS, there is a possibility that genetic loci specific to GDM but with smaller effect size are yet to be discovered. In our stage 1 genome-wide scan for GDM-associated variants, we detected six loci that were not known to be associated with T2D but did not replicate in stage 2. Among these variants, at least two have had independent follow-up after our publication. One, rs6499500:C>G near *FTSJDI1/CALB2*, was reported to have a nominally significant ($P < 0.05$) association with GDM in a Mexican population [51]. However, the direction of association was opposite to that reported in the original GWAS. Another variant, rs12898654:C>G near *SKORI*, was strongly ($P < 5 \times 10^{-8}$) associated with body mass index and waist-hip ratio in individuals of European ancestry from the general population [52].

To our knowledge, other than our own, there is only one additional GWAS on GDM. This study included only 103 cases and 115 controls; thus, it is not surprising that no genome-wide significant loci were discovered [53]. Currently, there is an ongoing international effort to perform a trans-ethnic meta-analysis of GDM GWAS through the GENetics of Diabetes In Pregnancy (GENDIP) consortium; the case sample size is expected to exceed 5000.

One of the consistently replicated findings from genetic studies of GDM is the association between rs10830963:C>G ($r^2 = 0.98$ with rs10830962:C>G noted in the GDM GWAS paper) in *MTNR1B* and increased risk of GDM. This variant has the strongest known association with GDM and its OR is 1.24 (1.19–1.29, $P = 4.1 \times 10^{-26}$) in our meta-analysis of 14 studies displayed in Table 1. This variant is well known for its association with increased fasting glucose and increased risk of T2D [54–56]. In addition, it has a large effect on impaired early phase insulin secretion during oral or intravenous glucose tolerance test outside of pregnancy [57, 58]. However, in the latest GWAS involving 433,540 East Asians, the OR for T2D was much smaller than that for GDM (OR 1.04, 95% CI 1.02–1.05, $P = 4.49 \times 10^{-8}$) [59]. Thus, it is possible that this variant plays a more prominent role in GDM. Interestingly, rs10830963:C>G is also reported to be one of the maternal variants that has the strongest association with offspring birth weight (25 g increase in birth weight per allele) in recent GWAS [60], likely reflective of its strong effect on maternal hyperglycemia.

The GDM-associated variant is in the intron between exon 1 and exon 2 of the *MTNR1B* gene, which encodes melatonin receptor MT₂. Melatonin plays a major role in regulating circadian rhythm and is thought to be involved in metabolic regulation of body mass and glucose metabolism [61]. It is also known as a potent antioxidant [62]. Melatonin receptor MT₂ is a G protein-coupled receptor overexpressed in the brain, especially in the retina and hypothalamic suprachiasmatic nuclei. In peripheral tissues, it is expressed in adipose tissues and pancreatic islets, even though its expression is low [63]. Melatonin is relatively safe and available over the counter in the USA. As the GDM risk-associated rs10830963:C>G variant is associated with increased *MTNR1B* mRNA expression in human pancreatic islets, it could be suggested that the strategy to prevent or treat diabetes would be to inactivate MT₂ signaling [56]. On the other hand, rare loss-of-function mutations of *MTNR1B* in humans are associated with 5-fold increased risk of T2D, suggesting inactivation of MT₂ signaling would not prevent or treat diabetes [64]. These controversial findings make it unclear whether it would be beneficial to activate or inactivate the melatonin system to prevent or treat either GDM or T2D [61]. Further mechanistic and clinical investigations are required.

Genetic Determinants of Glycemic Traits in Pregnancy

Outside of pregnancy, investigators have undertaken large-scale GWAS to illuminate the genetic architecture underlying continuous traits related to glucose metabolism (glycemic traits). In one of the larger efforts, the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) has conducted GWAS meta-analyses and discovered loci that influence fasting glucose, fasting insulin, and post-load glucose [65–67]. Additional analyses by this consortium and others examined genetic determinants of insulin secretory response and insulin resistance as measured using fasting measurements or glucose tolerance tests (both oral and intravenous) [58, 68–70]. In sum, these studies have highlighted some shared genetic architecture of continuous glycemic traits and T2D as well as some loci that appear to affect glycemic traits without a strong effect on the risk of T2D.

In pregnancy, there has been just one successful published GWAS of continuous glycemic traits performed by Hayes et al. in 2013 [71••]. This was a multi-ethnic GWAS, along with replication in two independent cohorts of women of European ancestry, searching for genetic variants associated with fasting glucose, fasting c-peptide, and glucose levels 1 and 2 h after an OGTT (1-h OGTT glucose and 2-h OGTT glucose). Among 4437 pregnant women, these investigators identified five loci known to be associated with glycemic traits in non-pregnant individuals (in/near *GCKR*, *G6PC2*, *PCSK1*, *PPP1R3B*, and *MTNR1B*). The associations observed between glycemic traits in pregnancy appeared largely consistent with effects outside of pregnancy. Of note, Hayes et al. also identified two novel loci that appeared to be uniquely associated with glycemic traits in pregnancy (near *HKDC1* and *BACE2*). These associations were replicated in an independent study of Chinese women [72]. A more recent GWAS for fasting glucose and 2-h OGTT glucose in pregnancy did not identify any associations at genome-wide significance, likely because of limited power [73].

One of the novel loci identified by Hayes et al. was in *HKDC1*. This locus was found to be associated with 2-h OGTT glucose in pregnancy and was not known to be associated with glycemia outside of pregnancy. Subsequent investigations confirmed that the implicated variant lowers the expression of *HKDC1* [71••]. Prior to this study, the tissue expression pattern and function of the HKDC1 protein product had not been investigated. In subsequent investigations, *HKDC1* was found to be most heavily expressed in the liver, intestine, and kidney [74]. The HKDC1 protein product has hexokinase activity in vitro, relevant because other human hexokinases are involved in glucose metabolism [74]. In mouse models, an *HKDC1* total body knockout was found to be embryonic lethal [75]. Mice expressing one copy of *HKDC1* (50% expression levels) had impaired glucose tolerance only in older age and during pregnancy [75]. The mechanism of reduced glucose tolerance appeared to be reduced glucose uptake by peripheral tissues, in particular the small intestine and to a lesser extent the kidney and liver; in addition, hepatic triglycerides appeared to be reduced [75]. In experimental mouse models that manipulated *HKDC1* expression in the liver in pregnancy, higher levels of hepatic *HKDC1* enhanced glucose tolerance and insulin sensitivity [76]. The second locus newly identified by the Hayes et al. GWAS was in a region of pancreatic islet-specific open chromatin in the first intron of *BACE2* and was associated with fasting c-peptide in pregnant women [71••]. The BACE2 protein product has previously been identified as involved in beta-cell function [77–79]. Yet, to our knowledge, the specific locus

identified by Hayes et al. has not been linked explicitly to *BACE2* expression and investigations of physiologic implications of variants at this locus have not yet been performed.

Polygenic Scores in GDM and T2D after GDM Pregnancy

Discovery of multiple loci associated with GDM leads to the question of whether this genetic information has clinical implications. As most common disease-associated genetic variants have small effect size, they likely will only explain a limited fraction of the heritability. Thus, there have been attempts to aggregate information of multiple variants into polygenic scores and test their association with the risk of GDM [29••, 32, 80••, 81, 82] or postpartum T2D [82–85]. Polygenic scores are usually built by summing the number of risk (or quantitative trait increasing) alleles (zero, one, or two) for variants known to be associated with a trait (unweighted polygenic score) [86]. Each risk allele can be weighted by the corresponding effect size (weighted polygenic score).

We used polygenic scores to evaluate the association between variants known to be associated with glycemic traits outside of pregnancy with the same traits in pregnancy in two cohorts of women of predominantly European ancestry (Table 2) [80••]. We found a strong relationship between genetic determinates of fasting glucose and fasting glucose in pregnant women, with a fasting glucose polygenic score made up of variants discovered outside of pregnancy explaining 7% of the variation in this trait. Similarly, Moen et al. found that a similar polygenic score explained 5% of the variation in this trait in their Norwegian pregnancy cohort (Table 2) [73]. We also identified a correlation between genetic determinates of insulin secretory response and insulin secretory response in pregnancy, with the polygenic score explaining 1.3% of variation in this trait [80••]. In contrast, determinants of fasting insulin and insulin sensitivity outside of pregnancy, in aggregate, explained less of the variation in fasting insulin, fasting c-peptide, and insulin sensitivity in pregnant women [80••]. These findings suggest that the physiology and underlying genetic architecture during gestation may differ from outside pregnancy, though the size of available pregnancy cohorts continues to limit our ability to make this comparison. Of note, each of the polygenic glycemic trait scores we examined was associated with GDM.

Outside of pregnancy, polygenic scores based on tens to hundreds of variants have shown some utility for prediction of chronic diseases such as T2D, obesity, and cardiovascular disease, though in T2D it is unclear whether they add additional information beyond clinical risk factors and they have not yet been integrated into clinical practice [86–88]. Table 2 summarizes the results of studies that have investigated polygenic scores for associations with GDM and postpartum T2D. Most of the studies, including our own, built polygenic scores using variants known to be associated with T2D. Studies showed that polygenic scores consisting of these known T2D variants are significantly associated with increased risk of GDM, with odds ratios ranging from 1.03 to 1.18 per unit increase in polygenic score (Table 2). If polygenic scores prove to be valuable for prediction of GDM, this could be used in the selection of high-risk groups of women that might benefit from risk reduction programs prior to conception or in early gestation.

Women with a history of GDM are at increased risk of future development of T2D. About half of women who had pregnancies complicated by GDM progress to T2D within 10 years of parturition [14]. Accurate prediction of progression to T2D in this high-risk population might enable targeted preventive measures. At least four studies used prospective cohorts of women with a history GDM to investigate whether T2D polygenic scores predict postpartum T2D [82–85]. Three studies showed that polygenic scores are significantly associated with risk of postpartum T2D. In addition, two studies showed that adding polygenic scores to a clinical risk model increased the AUC of the receiver operating characteristic curve by 4% [82, 84]. Even though this improvement was modest, it was statistically significant despite including a limited number of variants. It should be noted that predicting T2D using genetic information in postpartum women might have greater utility than in older populations, as clinical risk factors might not yet manifest. Further research is warranted regarding the clinical utility of polygenic scores in predicting GDM and postpartum T2D.

Conclusions

Genetic studies of GDM and glucose metabolism in pregnancy have largely focused on testing common variants known to be associated with T2D and glycemic traits outside of pregnancy. These studies suggest a shared genetic architecture between GDM and T2D, supporting the epidemiologic observations linking these two conditions. Several lines of evidence suggest that there are also genetic factors that affect glucose metabolism specifically during gestation. These include the discovery of the *HKDC1* and *BACE2* loci in a pregnancy glycemic trait GWAS and the disparate effect sizes of a variant in *MTNR1B* on the risk of GDM and T2D. A potential clinical application of genetic discoveries in GDM is the use of polygenic scores in risk assessment for GDM during pregnancy or T2D after pregnancy. Findings outside of pregnancy suggest that identification of a larger number of variants may improve the ability of such polygenic scores to predict both GDM and T2D. Experiences in other common diseases suggest that discovery of more variants will require development of large, ethnically diverse cohorts of pregnant women with genomic data. The existence of near universal screening for glucose intolerance in pregnant women in many parts of the world provides an opportunity to assemble such resources. Only by doing so will we gain a more complete picture of the genetic architecture underlying GDM and gestational glucose metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Comparison of effect size of known type 2 diabetes variants in GDM and type 2 diabetes. Effect size (β coefficient) of the known type 2 diabetes variants in GDM (y axis) and type 2 diabetes (x axis) is plotted with their corresponding P values: $P < 0.0001$, red; $0.0001 < P < 0.01$, orange; $0.01 < P < 0.10$, yellow; $0.10 < P < 0.50$, green; $0.50 < P$, blue. The β coefficient for GDM was derived from stage 1 genome-scan by Kwak et al. [42], and that for type 2 diabetes was derived from a GWAS by Asian Genetic Epidemiology Network [90]. The two *CDC123/CAMK1D* variants are distinguished by *CDC123/CAMK1D* for rs10906115 and *CDC123/CAMK1D** for rs12779790. The two *KCNQ1* variants are distinguished by *KCNQ1* for rs231362 and *KCNQ1** for rs2237892 (Adopted from Kwak et al., Diabetes. 2012;61(2):531–41)

Table 1

Variants significantly associated with GDM in meta-analysis of 23 studies after the Bonferroni correction ($P < 5 \times 10^{-4}$)

SNP	CHR	POS	Nearest gene	Risk allele	Other allele	OR (95% CI)	P	Het I ²	Het P	Effective sample size	Number of studies
rs4402960	3	185,511,687	<i>IGF2BP2</i>	T	G	1.09 (1.04–1.13)	5.1×10^{-5}	52.1	0.022	20,388	11
rs1470579	3	185,529,080	<i>IGF2BP2</i>	C	A	1.14 (1.08–1.21)	5.4×10^{-6}	81.5	4.5×10^{-3}	11,413	3
rs7754840	6	20,661,250	<i>CDKAL1</i>	C	G	1.15 (1.10–1.20)	2.0×10^{-10}	83.2	1.1×10^{-7}	19,779	9
rs7756992	6	20,679,709	<i>CDKAL1</i>	G	A	1.15 (1.10–1.21)	1.3×10^{-8}	72.8	5.5×10^{-4}	17,283	8
rs7041847	9	4,287,466	<i>GLIS3</i>	A	G	1.13 (1.06–1.20)	6.6×10^{-5}	0	0.959	7650	2
rs7034200	9	4,289,050	<i>GLIS3</i>	A	C	1.12 (1.06–1.17)	1.3×10^{-5}	30	0.232	13,549	4
rs2383208	9	22,132,076	<i>CDKN2A/2B</i>	A	G	1.15 (1.07–1.24)	1.9×10^{-4}	32.8	0.222	9065	2
rs10811661	9	22,134,094	<i>CDKN2A/2B</i>	T	C	1.16 (1.09–1.23)	1.0×10^{-6}	69.2	1.1×10^{-3}	17,500	9
rs1111875	10	94,462,882	<i>HHEX/ID E</i>	C	T	1.09 (1.04–1.14)	4.2×10^{-4}	58	0.036	15,395	6
rs5015480	10	94,465,559	<i>HHEX/ID E</i>	C	T	1.15 (1.09–1.22)	1.2×10^{-6}	40.3	0.137	12,134	6
rs4506565	10	114,756,041	<i>TCF7L2</i>	T	A	1.20 (1.13–1.28)	2.7×10^{-9}	82.9	2.9×10^{-3}	9513	3
rs7903146	10	114,758,349	<i>TCF7L2</i>	T	C	1.16 (1.10–1.22)	6.1×10^{-8}	75.5	4.3×10^{-4}	15,782	7
rs12255372	10	114,808,902	<i>TCF7L2</i>	T	G	1.14 (1.06–1.22)	2.1×10^{-4}	79	7.6×10^{-4}	11,631	5
rs1387153	11	92,673,828	<i>MTNR1B</i>	T	C	1.22 (1.15–1.29)	2.8×10^{-11}	20.9	0.276	11,705	6
rs10830963	11	92,708,710	<i>MTNR1B</i>	G	C	1.24 (1.19–1.29)	4.1×10^{-26}	74.8	3.6×10^{-6}	24,237	14
rs7957197	12	121,460,686	<i>HNF1A</i>	T	A	1.15 (1.07–1.24)	1.3×10^{-4}	61.7	0.05	12,939	4

CHR, chromosome; CI, confidence interval; Het, heterogeneity; OR, odds ratio; POS, position in GRCh37/hg19; SNP, single nucleotide polymorphism. Meta-analysis was performed with fixed-effect inverse-variance weighting using METAL [89]. Variants with genome-wide significance ($P < 5 \times 10^{-8}$) are shown in bold. Detailed results of individual contributing studies are in the Supplementary Table

Table 2

Studies investigating PRS to predict GDM/T2D, or glycemic traits during pregnancy

First author	Year	Ancestry	Outcome	Sample size (case/control)	Number of variants	Variant selection for PS	Method of PS	Risk of outcome by PS	Other findings
Moen GH	2018	European	Fasting Glucose	529	33	FG variants	Weighted PS	NA	GRS explained 4.95% of variance of FG GW 14–16
Powe CE	2018	European	Fasting Glucose (Gen3G)	551	38	FG variants	Weighted PS	0.39 (0.27–0.51) per unit increase	GRS explained 7% of variance of FG
Powe CE	2018	European	Fasting Glucose (HAPO)	1380	38	FG variants	Weighted PS	0.42 (0.06–0.18) per unit increase	GRS explained 7% of variance of FG
Lauenborg J	2008	European	GDM	2127 (244/1883)	11	T2D variants	Weighted PS	1.18 (1.10–1.27) per unit increase	AUC ROC clinical 0.62; AUC ROC clinical + PS 0.68
Sullivan SD	2014	Multi-ethnic	GDM	1383 (281/1102)	34	T2D variants	Weighted PS	1.05 (1.00–1.08) per unit increase	
Comrier H	2015	European	GDM	296 (214/82)	36	T2D variants	Explained-variance PS	NA	Significantly higher PS in cases vs controls (1.21 ± 0.18 vs 1.17 ± 0.15, P < 0.0001)
Kawai VK	2017	European	GDM	1996 (458/1538)	34	T2D or FG variants	Weighted PS	1.11 (1.08–1.14) per unit increase	AUC ROC clinical 0.67; AUC ROC clinical + PS 0.70
Ding M	2018	European	GDM	8722 (2636/6086)	11	T2D variants	Weighted PS	1.04 (1.03–1.05) per unit increase	
Powe CE	2018	European	GDM (Gen3G)	551 (43/508)	85	T2D variants	Weighted PS	1.06 (1.01–1.10) per unit increase	
Powe CE	2018	European	GDM (HAPO)	1380 (207/1173)	85	T2D variants	Weighted PS	1.03 (1.01–1.06) per unit increase	
Ekelund M	2012	Multi-ethnic	T2D	637 (134/503)	13	T2D variants	Weighted PS	1.11 (1.05–1.18) per unit increase	
KwakSH	2013	East Asian	T2D	395 (116/279)	48	T2D variants	Weighted PS	1.66 (1.30–2.13) per unit increase	AUC ROC clinical 0.74; AUC ROC clinical + PS 0.78
Comrier H	2015	European	T2D/Prediabetes	214 (135/79)	36	T2D variants	Explained-variance	NA	AUC ROC clinical 0.63; AUC ROC clinical + PS 0.67
LiM	2020	European	T2D	2434 (601/1833)	59	T2D or FG variants	Unweighted PS	1.07(1.01–1.14) per 5 risk alleles	

AUC, area under the curve; *FG*, fasting glucose; *GW*, gestational week; *NA*, not available; *PS*, polygenic score; *ROC*, receiver operating characteristics; *T2D*, type 2 diabetes

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