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A Polygenic Risk Score Associated with Gestational Diabetes Mellitus in an American Indian Population

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is a state of hyperglycemia during pregnancy, increasing the risk of birth complications, and subsequent type 2 diabetes mellitus in the mother and offspring. Risk factors such as diet, obesity, and family history have demonstrated strong association with GDM, but no clear pathophysiology has been ascertained. Methods: Analysis was conducted on 38 women with and 296 without GDM, within a case/control study of pre-eclampsia. The genetic variants examined were selected from among a published polygenic risk score of 10 variants (PRS-10). [1] Genetic models were evaluated for each variant by multivariate logistic regression methods adjusted for age, body mass index, nulliparity and pre-eclampsia. A risk score comprised of the total risk alleles among the 7 variants (PRS-7) was evaluated. Results: Multivariate logistic regression showed significant, independent, positive associations between body-mass index (BMI), age, the posited PRS-7 (OR 1.87, 95% CI 1.43-2.45, $p=5.3x10^{-6}$) and GDM. In univariate analysis, rs1421085 was associated with GDM (OR 0.50, 95% CI 0.26-0.95, p=0.034), but not after adjustment for covariates and paradoxically not for the expected risk allele. None of the other 6 variants showed individual association with GDM. An independent association of PRS-7, rs1421085 and established risk factors (age and BMI) with GDM is demonstrated. The previously published meta-analysis of PRS-10 showed a degree of heterogeneity ($p_Q=0.03$) among the 3 cohorts analyzed, suggesting that variant effects may differ according to genetic background. Conclusion: We replicate and further refine results of a previously published polygenic risk score for GDM in an ethically unrelated population.

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Research in Context:

What is already known about this subject?

- Within primarily European cohorts, a polygenic risk score (PRS) comprised of 10 variants is associated with gestational diabetes.

What is the key question?

- Can this PRS be replicated, especially in a distantly related population?

What are the new findings?

- The current analysis confirms this association using a subset of 7 variants (derived from the previous publication) among an American Indian cohort

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- Further, sensitivity analysis indicates only 3 of these variants may be sufficient to detect this association.

  How might this impact on clinical practice in the foreseeable future?
- With sufficient sensitivity, a PRS could reduce the need for complex and onerous gestational diabetes screening methods

Introduction

Gestational diabetes mellitus (GDM) is a state of hyperglycemia in pregnant women that can be diagnosed as early as 24 weeks of gestation. [2] Recommended diagnostic criteria for GDM require 2 or more values exceeding limits after a definitive 3-hour oral glucose tolerance test. [2] Consequences of GDM can lead to birth complications such as macrosomia, Cesarean section, increased risk of subsequent type 2 diabetes mellitus (DM-II) in the mother and increased prevalence of DM-II prevalence among offspring. [3] GDM affects approximately 15% of pregnant women worldwide. [3] Risk factors such as maternal age at delivery, diet, increased body mass index (BMI), and family history have demonstrated their strong association with GDM but no clear pathophysiology has been ascertained. [4] Nearby Canadian aboriginal populations have been shown to experience a greater prevalence of GDM than other ethnic groups in the United States. [5]

Since 2004, the Genetics and Pre-eclampsia Study (GPS) of Turtle Mountain Community College has enrolled over 450 pre-eclampsia cases and controls. [6,7] Sufficient genetic and medical record information on associated risk factors, including GDM, was obtained from a subset (N=334) of participants with identified GDM and a random selection of controls without GDM, to allow the current analysis.

Insight into the pathophysiology of GDM has been derived from associations with genetic variants that confer higher risk of GDM. For example, Powe et al [1] described a "Pregnancy Cluster 1" (referred to here as "PRS-10") including variants of the following genes: *MRPS30, FTO, GLP2R, SLC2A2, MTNR1B, SHQ1, CRHR2, PIK3R1, MC4R, PURG*. This PRS-10 was associated with increased risk of GDM, demonstrating an odds ratio of 1.24 (p-value=6.20×10^{-7}). The present study sought replication of the above published association of PRS-10 variants with GDM. Table 1 summarizes PRS-10 variants, possible mechanistic relationship with GDM and the subset analyzed in the current report.

Table 1. PRS-10 genetic variants and those in the current analysis.

Gene	SNP*	risk / alternate allele	Included in current analysis	Theorized mechanism:
MC4R	rs523288	T/A	+	Obesity [1,8,9]
PURG	rs10954772	T/C	+	Adiposity [1,10]
CRHR2	rs917195	C/T	+	Pancreatic beta-cell dysfunction [1]
FTO	rs1421085	C/T	+	Obesity [1,8]
MTNR1B	rs10830963	G/C	+	Insulin resistance Pancreatic beta-cell dysfunction [1,11]

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PIK3R1	rs4976033	G/A	+	Insulin resistance [12]
SHQ1	rs13085136	C/T	+	Adiposity [1,13]
MRPS30	rs6884702	G/A		Unknown [1]
GLP2R	rs7222481	C/G		Pancreatic beta-cell dysfunction [1,14]
SLC2A2	rs9873618	G/A		Hepatic glucose uptake [1]

* Single Nucleotide Polymorphism.

In addition to genetic risks, contributing factors such as maternal age at delivery, and BMI were analyzed. Advanced maternal age has been associated with oxidative stress, endothelial dysfunction, and increased inflammation, all of which has been linked to GDM. [15] Low or normal BMI (<30) and nulliparity were "protective factors" against the development of GDM. [16–18] Although GDM is a recognized risk factor for pre-eclampsia (PE), [19] whether the reverse is true and whether both are independent of each other is an open question.

Methods

Written, informed consent was obtained from all participants permitting the analysis of potential genetic and other PE risk factors, including GDM. Approval was also obtained from the participants' Tribal governments.

The above referenced GPS dataset and samples were accessed to conduct the present analysis. The study size was determined by the genotype availability of the identified variants of interest. In the prior GPS analyses, investigating genetic associations with pre-eclampsia, gestational diabetes mellitus (GDM) and pre-existing diabetes were included as covariates, though the primary focus was on PE. Data on these conditions were abstracted from medical records or birth certificates by one of the authors or a supervised laboratory assistant. GDM was defined as the presence of a clinical diagnosis of "gestational diabetes" or "glucose intolerance" during pregnancy, without prior history of diabetes. Some cases of GDM may have been missed due to incomplete records, as the GPS did not specifically focus on diabetes. Participants with a history of diabetes prior to pregnancy were excluded.

In assessing each variant's potential association with GDM, for both cases and controls, adjustment was conducted for age at delivery, nulliparity, BMI calculated from weight at first prenatal visit and a history of PE during the pregnancy. The diagnosis of PE was consistent with previously published GPS methods [6] and required at least 2 of 3 criteria reflecting hypertension, proteinuria and a clinical diagnosis of PE.

Salivary samples were collected and processed according to manufacturer's protocol (Oragene). Genotypic data from a Illumina Infinium microarray (ITMAT-Broad-CARe, IBC) [20] was available for 2 SNPs, 4 variants were genotyped by TaqMan assay (ThermoFisher Scientific), and one was assessed by Sanger sequencing (Big Dye Terminator 3.1, ThermoFisher Scientific) after a custom TaqMan assay failed. TaqMan assays were unavailable for the remaining SNPs shown in Table 1. A TaqMan assay was also used to replicate microarray genotyping results and allele designation for rs1421085 with confirmation on 43 of 44 samples. Imputation of missing genotypic data was not utilized and covariate information was complete.

SPSS v.29.0.2.0 was utilized to run all statistical analysis. Descriptive statistics show means (SD) for quantitative traits and N (%) for discrete variables. Tests of statistical significance utilized chi-square and the T test of independent means for discrete and continuous variables respectively. The

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independent variables included the genetic variants (Table 1), with GDM as the dependent variable. Multivariate logistic regression models included age at delivery, BMI, nulliparity and PE. Since all of these four covariates are known to be associated with risk of GDM and some are correlated with each other, it was felt necessary to adjust for all. To avoid confounding from potential population stratification, a principal components analysis (PCA) of the microarray genotypes was conducted. [21] The 45,554 IBC SNPs with rsID designation were filtered to exclude the 7 variants included in the risk score, any failing to genotype in any sample, those with a minor allele frequency less than 0.01, and those exhibiting linkage disequilibrium of $r^2>0.10$. There were 8,655 SNPs remaining in the PCA analysis and the top 10 principal components (PCs) were entered into the multivariate model. The odds ratio and 95% confidence intervals are reported, and statistical significance was evaluated at the p=0.05 level.

In partial replication of Powe et al, [1] the 7 available genotypes were used to create the present PRS-7. This score was a summation of risk alleles available (Table 1) for each participant. The distribution of PRS-7 was from 0 to 10 from a possible total of 14.

Results

The primary findings are independent associations between GDM, greater age at delivery, increased BMI, and the proposed PRS-7, in a multivariate logistic regression model.

Case, control and covariate distribution is shown in Table 2. Risk allele frequency in the complete cohort is found in Table 3.

Univariate logistic regression results, as well as those of a model incorporating all covariates, and single variant association models adjusted for all covariates are listed in Table 4 below. Only the results of those genetic models (eg additive, dominant etc) with the smallest p values were displayed, and that model continued to be used in subsequent analyses.

The distribution of PRS-7 was from 0 to 10 from a possible total of 14 as seen in Table 5.

Table 2. Case-Control Characteristics.

	GDM	Control	p value
Number (N)	38	296	
Age at delivery mean (SD)	28.0 (6.48)	23.8 (5.73)	$3x10^{-5}$
Parity, N (% nulliparous)	16 (42.1%)	151 (51.0%)	0.301
Body-Mass index (SD)	34.8 (8.10)	28.7 (7.15)	$1.4x10^{-6}$
Pre-eclampsia, N (% yes)	22 (57.9%)	117 (39.5%)	0.031

Table 3. Frequency of Risk Alleles and assessment of Hardy-Weinberg Equilibrium.

	Risk Allele*	Allele frequency (%)	p value
rs523288	T	13.5	0.621

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rs10954772	T	30.1	0.812
rs917195	C	71.3	0.920
rs1421085	C	27.1	0.361
rs10830963	G	28.4	0.679
rs4976033	G	38.3	0.871
rs13085136	C	88.3	0.091

* as per Powe et al[1].

Table 4. Logistic Regression, genetic model for each variant with lowest p value shown.

Univariate Analysis				
	Risk/Alt Allele*	Odds ratio	95% Confidence Interval	p value
Age at delivery		1.114	1.06 - 1.17	<0.001
nulliparity		0.698	0.35 - 1.38	0.303
Body-Mass index		1.093	1.05 - 1.14	<0.001
Pre-eclampsia		2.104	1.06 - 4.18	0.033
rs523288, T-ADD	T/A	1.408	0.65 - 3.06	0.388
rs10954772, T-Rec	T/C	0.240	0.03 - 1.87	0.173
rs917195, C-Dom	C/T	0.606	0.15 - 2.42	0.478
rs1421085, C-ADD	C/T	0.499	0.26 - 0.95	0.034
rs10830963, G-Rec	G/C	1.403	0.45 - 4.33	0.556
rs4976033, G-Dom	G/A	1.131	0.46 - 2.79	0.789
rs13085136, C-ADD	C/T	0.923	0.34 - 2.52	0.876
PRS-7		1.214	1.05 - 1.40	0.007
PRS-3**		1.626	1.17 - 2.25	0.003
Covariate-only model				
Age at delivery		1.130	1.04 - 1.23	0.005
nulliparity		1.885	0.57 - 6.20	0.297

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Body-Mass index		1.079	1.02 - 1.14	0.005
Pre-eclampsia		1.789	0.70 - 4.56	0.223
PC-1***		0.050	0.00 - 267.8	0.494
PC-2		0.021	0.00 - 4,033	0.534
PC-3		0.013	0.00 - 96.8	0.341
PC-4		0.149	0.00 - 2,668	0.703
PC-5		0.446	0.00 - 6,918	0.870
PC-6		0.001	0.00 - 173.5	0.251
PC-7		0.566	0.00 - 58,846	0.923
PC-8		0.388	0.00 - 15,288	0.861
PC-9		1.783	0.002 - 1,756	.869
PC-10****		21,341	1.358 - 33,545,827	.043
Single-variant association adjusting for other covariates				
rs523288, T-ADD	T/A	1.605	0.53 - 4.86	0.402
rs10954772, T-Rec	T/C	0.971	0.74 - 12.68	0.982
rs917195, C-Dom	C/T	0.412	0.06 - 2.72	0.357
rs1421085, C-ADD	C/T	0.560	0.25 - 1.26	0.162
rs10830963, G-Rec	G/C	2.023	0.49 - 8.31	0.328
rs4976033, G-Dom	G/A	1.623	0.42 - 6.24	0.481
rs13085136, C-ADD	C/T	0.664	0.19 - 2.30	0.519
PRS-7		1.871	1.43 - 2.45	$5.3x10^{-6}$
PRS-3		3.364	1.95 - 5.80	$1.2x10^{-5}$

* as per Powe et al[1]. ** a subset of PRS-7 comprised of the three genotypes with odds ratios >1 in univariate analysis. *** principal component 1, etc. **** results considered unreliable, likely due to low frequency of component SNPs.

Table 5. Distribution of Polygenic Risk Scores (PRS-7).

	N (%)	Cumulative %
0	35 (10.5)	10.5
1	65 (19.5)	29.9
2	51 (15.3)	45.2

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3	42 (12.6)	57.8
4	37 (10.5)	68.9
5	32 (9.6)	10.5
6	34 (10.2)	88.6
7	26 (7.8)	96.4
8	9 (2.7)	99.1
9	2 (0.6)	99.7
10	1 (0.3)	100.0

Discussion

A multivariate analysis adjusted for age and BMI, utilizing a subset of a previously reported polygenic risk score found a significant association with GDM (OR 1.87, 95% CI 1.43-2.45, $p=5.3x10^{-6}$). Age at delivery and BMI were also independently linked to increased risk of GDM. Despite the association of the *FTO*, rs1421085 C allele with increased BMI and GDM risk in the literature, in the present analysis the C allele was found to confer lower univariate risk (but not after adjustment in the multivariate model).

We examined a selection of 7 SNPs among the 10 genes associated with GDM in the literature. [1] These SNPs were variants of—*MC4R, PURG, CRHR2, FTO, MTNR1B, PIK3R1*, and *SHQ1*—and were chosen from Powe et al's "Pregnancy Cluster 1", [1] after consideration of TaqMan assay and previous microarray result availability., These SNPs have been related to risk of GDM, type 2 diabetes mellitus, and/or reduced insulin sensitivity. [13,22,23]

The *MTNR1B* gene SNP, rs10830963, has been among the most intensely studied genes related to glucose homeostasis in pregnancy. [11] *MTNR1B* encodes for melatonin receptor 1B binding melatonin, which reduces insulin secretion from pancreatic beta cells. The presence of the G allele of this variant increases the expression of melatonin receptor 1B and increased melatonin binding, resulting in low insulin secretion. [24] A meta-analysis of 8 cohorts (3,296 cases and 3,709 controls) found an odds ratio of 2.228 (95% CI 1.224-4.055, p=0.009) modeling an rs10830963 G recessive genotype on GDM risk [22]. The present analysis showed the same direction of effect but was not statistically significant.

The *PIK3R1* gene plays a crucial role in regulating insulin signaling by encoding a key regulatory subunit interacting with insulin receptor substrates (IRS1/2). Binding of p85alpha (produced by *PIK3R1*) to IRS1/2 triggers downstream effects including increasing GLUT4 at the cell membrane, stimulating glycogen synthesis, and suppressing gluconeogenesis. [12] A study examining insulin sensitivity indices and gene variants affecting these indices found that *PIK3R1* gene rs4976033 variant, was associated with changes in glucose levels during an oral glucose tolerance test (OGTT) at 0, 30, and 120 minutes suggesting a potential role in reducing insulin sensitivity. [23]

MC4R encodes the melanocortin 4 receptor, helping regulate satiety and hunger either by its gain or loss of function. [25] Gain of function increases satiety while loss leads to overeating and then eventually obesity. The current study concludes that the MC4R gene variant rs523288 is associated with increased risk of GDM by possibly predisposing patients to a higher BMI.

The FTO gene SNP, rs1421085, may indirectly influence GDM development by increased maternal adiposity. The CRISPR–Cas9 editing of the T to C allele of this variant in adipocytes causes increased expression of IRX3 and IRX5 genes and shifts the function of the cell towards that of fat storage and reduced mitochondrial thermogenesis. [26] Saucedo et al also found the risk (C allele) is associated with increased weight gain in pregnancy as well as increased adiponectin and TNF-alpha levels. [27]

Among the 7 SNPs reported here, only rs1421085 was individually associated with GDM in univariate analysis (Table 4). Finding the C allele associated with reduced risk in this cohort, in contrast to the literature, is difficult to explain. We have checked the direction of effect repeatedly

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and conducted replicate genotyping of multiple samples with a TaqMan assay to confirm the microarray designation of alleles.

Further analysis of our cohort failed to provide evidence for any association between the other 6 SNPs evaluated, either through univariate or multivariate logistic regression models adjusting maternal age at delivery and BMI.

The fact that our PRS-7, comprised of the total number of alleles reportedly contributing to risk from these, showed strong evidence of association with GDM was unexpected, especially since 4 of this group exhibited trends in conflict with the anticipated risk allele (albeit only rs1421085 was statistically significant). Since only 3 of the SNPs in PRS-7 showed association with GMD in the expected direction of effect, we conducted a sensitivity analysis of this group of variants alone, demonstrating an increased odds ratio with similar significance (OR 3.36, 1.95-5.80, $p=1.2x10^{-5}$).

The current study aimed to analyze gene variants associated with the development of GDM and applied it to our smaller diverse Native American cohort. With a total of 334 participants, our cohort provided a limited but reasonable dataset for statistical analysis in this community. We were able demonstrate results consistent with that of different populations as referenced by Powe et al. [1] The strength of association between GDM and PRS-7 and an even more limited PRS-3 was unanticipated, especially given the lack of significant results when evaluating each SNP individually. Confirmation of the relationship of BMI and age at delivery in this population was reassuring. Interestingly, the *FTO* risk allele analyzed was protective against GDM in the present analysis.

GDM plays a significant role in maternal and neonatal health outcomes. The ability to better detect the propensity for developing GDM is a useful diagnostic tool that could enhance management or aid in prevention of GDM in the future.

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References

1. Powe CE, Udler MS, Hsu S, Allard C, Kuang A, Manning AK, Perron P, et al. Genetic Loci and Physiologic Pathways Involved in Gestational Diabetes Mellitus Implicated Through Clustering. Diabetes. 2021 Jan;70(1):268-281. doi: 10.2337/db20-0772. Epub 2020 Oct 13. PMID: 33051273.
2. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018 Feb;131(2):e49-e64. doi: 10.1097/AOG.0000000000002501. PMID: 29370047.
3. Modzelewski R, Stefanowicz-Rutkowska MM, Matuszewski W, Bandurska-Stankiewicz EM. Gestational Diabetes Mellitus-Recent Literature Review. J Clin Med. 2022 Sep 28;11(19):5736. doi: 10.3390/jcm11195736. PMID: 36233604; PMCID: PMC9572242.
4. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci. 2018 Oct 26;19(11):3342. doi: 10.3390/ijms19113342. PMID: 30373146.

 doi:10.20944/preprints202506.2195.v1

5. Dyck R, Klomp H, Tan LK, Turnell RW, Boctor MA. A comparison of rates, risk factors, and outcomes of gestational diabetes between aboriginal and non-aboriginal women in the Saskatoon health district. Diabetes Care. 2002 Mar;25(3):487-93. doi: 10.2337/diacare.25.3.487. PMID: 11874935.
6. Best LG, Nadeau M, Davis K, Lamb F, Bercier S, Anderson CM. Genetic variants, immune function, and risk of pre-eclampsia among American Indians. Am J Reprod Immunol. 2012 Feb;67(2):152-9. doi: 10.1111/j.1600-0897.2011.01076.x. Epub 2011 Oct 17. PMID: 22004660.
7. Best LG, Saxena R, Anderson CM, Barnes MR, Hakonarson H, Falcon G, et al. Two variants of the C-reactive protein gene are associated with risk of pre-eclampsia in an American Indian population. PLoS One. 2013 Aug 5;8(8):e71231. doi: 10.1371/journal.pone.0071231. Erratum in: PLoS One. 2013 Sep 23;8(9). doi: 10.1371/annotation/7f3e30b8-8dfa-4bb7-b34e-884248628454. PMID: 23940726.
8. Bjørnland T, Langaas M, Grill V, Mostad IL. Assessing gene-environment interaction effects of FTO, MC4R and lifestyle factors on obesity using an extreme phenotype sampling design: Results from the HUNT study. PLoS One. 2017 Apr 6;12(4):e0175071. doi: 10.1371/journal.pone.0175071. PMID: 28384342.
9. Namjou B, Stanaway IB, Lingren T, Mentch FD, eMERGE Network; Harley JB et al. Evaluation of the MC4R gene across eMERGE network identifies many unreported obesity-associated variants. Int J Obes (Lond). 2021 Jan;45(1):155-169. doi: 10.1038/s41366-020-00675-4. Epub 2020 Sep 20. PMID: 32952152.
10. Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet. 2019 Jan 1;28(1):166-174. doi: 10.1093/hmg/ddy327. PMID: 30239722.
11. Lowe WL Jr, Kuang A, Hayes MG, Hivert MF, Scholtens DM. Genetics of glucose homeostasis in pregnancy and postpartum. Diabetologia. 2024 Dec;67(12):2726-2739. doi: 10.1007/s00125-024-06256-8. Epub 2024 Aug 24. PMID: 39180581.
12. Tsay A, Wang JC. The Role of PIK3R1 in Metabolic Function and Insulin Sensitivity. Int J Mol Sci. 2023 Aug 11;24(16):12665. doi: 10.3390/ijms241612665. PMID: 37628845.
13. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet. 2018 Nov;50(11):1505-1513. doi: 10.1038/s41588-018-0241-6. Epub 2018 Oct 8. PMID: 30297969.
14. Ramos-Levi A, Barabash A, Valerio J, García de la Torre N, Mendizabal L, Zulueta M, et al. Genetic variants for prediction of gestational diabetes mellitus and modulation of susceptibility by a nutritional intervention based on a Mediterranean diet. Front Endocrinol (Lausanne). 2022 Oct 13;13:1036088. doi: 10.3389/fendo.2022.1036088. PMID: 36313769.
15. Sun M, Luo M, Wang T, Wei J, Zhang S, Shu J, et al. Effect of the interaction between advanced maternal age and pre-pregnancy BMI on pre-eclampsia and GDM in Central China. BMJ Open Diabetes Res Care. 2023 Apr;11(2):e003324. doi: 10.1136/bmjdrc-2023-003324. PMID: 37085280.
16. Giannakou K, Evangelou E, Yiallouros P, Christophi CA, Middleton N, Papatheodorou E, et al. Risk factors for gestational diabetes: An umbrella review of meta-analyses of observational studies. PLoS One. 2019 Apr 19;14(4):e0215372. doi: 10.1371/journal.pone.0215372. PMID: 31002708.
17. Zhang Y, Xiao CM, Zhang Y, Chen Q, Zhang XQ, Li XF, et al. Factors Associated with Gestational Diabetes Mellitus: A Meta-Analysis. J Diabetes Res. 2021 May 10;2021:6692695. doi: 10.1155/2021/6692695. PMID: 34046504.
18. Dos Santos PA, Madi JM, da Silva ER, Vergani DOP, de Araújo BF, Garcia RMR. Gestational Diabetes in the Population Served by Brazilian Public Health Care. Prevalence and Risk Factors. Rev Bras Ginecol Obstet. 2020 Jan;42(1):12-18. doi: 10.1055/s-0039-1700797. Epub 2020 Feb 27. PMID: 32107761.
19. Roberts J. Current perspectives on preeclampsia. J Nurse Midwifery. 1994 Mar-Apr;39(2):70-90. doi: 10.1016/0091-2182(94)90015-9. PMID: 8027850.
20. Keating BJ, Tischfield S, Murray SS, Bhangale T, Price TS, Glessner JT, et al. Concept, design and implementation of a cardiovascular gene-centric 50 k SNP array for large-scale genomic association studies. PLoS One. 2008;3(10):e3583. doi: 10.1371/journal.pone.0003583. Epub 2008 Oct 31. PMID: 18974833.
21. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007 Sep;81(3):559-75. doi: 10.1086/519795. Epub 2007 Jul 25. PMID: 17701901.

 doi:10.20944/preprints202506.2195.v1

22. Bai Y, Tang L, Li L, Li L. The roles of ADIPOQ rs266729 and MTNR1B rs10830963 polymorphisms in patients with gestational diabetes mellitus: A meta-analysis. Gene. 2020 Mar 10;730:144302. doi: 10.1016/j.gene.2019.144302. Epub 2019 Dec 26. PMID: 31884106.
23. Suleman S, Madsen AL, Ängquist LH, Schubert M, Linneberg A, Loos RJF et al. Genetic Underpinnings of Fasting and Oral Glucose-stimulated Based Insulin Sensitivity Indices. J Clin Endocrinol Metab. 2024 Oct 15;109(11):2754-2763. doi: 10.1210/clinem/dgae275. PMID: 38635292.
24. Vejrazkova D, Vankova M, Vcelak J, Krejci H, Anderlova K, Tura A, et al. The rs10830963 Polymorphism of the MTNR1B Gene: Association With Abnormal Glucose, Insulin and C-peptide Kinetics. Front Endocrinol (Lausanne). 2022 Jun 6;13:868364. doi: 10.3389/fendo.2022.868364. PMID: 35733780.
25. Liu Z, Hruby VJ. MC4R biased signalling and the conformational basis of biological function selections. J Cell Mol Med. 2022 Aug;26(15):4125-4136. doi: 10.1111/jcmm.17441. Epub 2022 Jul 11. PMID: 35818295.
26. Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, et al. FTO Obesity Variant Circuitry and Adipocyte Browning in Humans. N Engl J Med. 2015 Sep 3;373(10):895-907. doi: 10.1056/NEJMoa1502214. Epub 2015 Aug 19. PMID: 26287746.
27. Saucedo R, Valencia J, Gutierrez C, Basurto L, Hernandez M, Puello E, Rico G, Vega G, Zarate et al. Gene variants in the FTO gene are associated with adiponectin and TNF-alpha levels in gestational diabetes mellitus. Diabetol Metab Syndr. 2017 May 12;9:32. doi: 10.1186/s13098-017-0234-0. PMID: 28507607.