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Maternal Genotype and Gestational Diabetes

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Abstract

OBJECTIVE—To determine whether genetic variants associated with glucose homeostasis are associated with gestational diabetes (GDM).

STUDY DESIGN—We genotyped 899 self-identified Caucasian women and 386 self-identified African-American women in the Pregnancy, Infection and Nutrition (PIN) Studies cohorts for 36 single-nucleotide polymorphisms (SNPs) associated with type 2 diabetes (T2DM) and/or glucose homeostasis in European populations.

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RESULTS—GDM was diagnosed in 56 of 899 (6.2%) Caucasian and 24 of 386 (6.2%) African-American women. Among Caucasian women, GDM was associated with carriage of *TCF7L2* rs7901695, *MTNR1B* rs10830963 and *GCKR* rs780094 alleles associated with T2DM and fasting glucose in non-pregnant populations. Among African-American participants, we found an increased risk among *TSPAN8* rs7961581 C allele homozygotes and reduced risk among carriers of the *JAZF1* rs864745 T allele.

CONCLUSION—We found several SNPs that are associated with GDM risk in the PIN cohorts. Maternal genotyping may identify women at risk for impaired gestational glucose tolerance.

Keywords

diabetes; gestational diabetes; genetics; single nucleotide polymorphisms

Introduction

Gestational diabetes (GDM) affects from 2.2 to 8.8 percent of pregnant women[1]. This condition is associated with adverse perinatal outcomes for both mother and infant, and the risks to the mother-infant dyad persist after birth[2–5]. Infants born to women diagnosed with GDM have an increased likelihood of developing type 2 diabetes mellitus[2,3], as well as a 2-fold risk of obesity, metabolic syndrome or both when compared with children born to normoglycemic women[4]. Mothers diagnosed with GDM have an increased risk of developing GDM in subsequent pregnancies, as well as metabolic syndrome and type 2 diabetes later in life[5].

Risk factors for GDM include increased maternal pregravid BMI, advanced maternal age, and family history of type 2 diabetes[6]. Recent work in non-pregnant populations has identified common genetic variants associated with diabetes, some of which are associated with GDM risk in studies in Asian and European populations[7–14]. Identifying genetic variants associated with gestational diabetes may allow early identification of women at risk, facilitating intervention prior to usual GDM diagnosis late in the second trimester of pregnancy. Moreover, elucidating molecular mechanisms underlying GDM risk may identify novel treatment targets and allow selection of therapy tailored to the vulnerabilities of individual patients. However, no studies to our knowledge have measured associations between common type 2 diabetes risk variants and GDM in Caucasian or African American US populations.

To address this gap, we quantified associations between type 2 diabetes risk variants and GDM in a secondary analysis of a prospective cohort study among Caucasian and African American women in central North Carolina. We hypothesized that maternal carriage of risk alleles associated with type 2 diabetes and glucose homeostasis would be associated with increased GDM risk.

Materials and Methods

The Pregnancy, Infection and Nutrition (PIN) Cohort study comprises three prospective cohorts of more than 5000 women enrolled in early to mid-pregnancy. Participants enrolled in PIN1 and PIN2 were 24–29 weeks gestation at study entry, and were recruited from University of North Carolina Resident and Private Physician Obstetrics Clinic and the Wake County Department of Human Services and Wake Area Health Education Center prenatal care clinics from August 1995 through June 2000. Subjects enrolled in PIN3 were less than 20 weeks gestation at study entry and were recruited from the prenatal clinics at UNC hospitals from January 2001 to June 2005. The Institutional Review Board of the University

of North Carolina at Chapel Hill approved the study. Women who consented for genetic studies and had extracted DNA available were eligible for inclusion in this analysis.

Our specimens included 1363 PIN participants for whom DNA had previously been extracted for other studies, as well as 385 women with previously un-extracted DNA who had participated in the PIN Postpartum study and had given consent for genetic analysis, for a total of 1748 pregnancies. Sufficient DNA for genotyping was available for 1586 pregnancies. We allowed for only one pregnancy during the study period. If data were available for multiple pregnancies (N=21), we included the pregnancy with the most complete SNP data (n = 1565). We further excluded a non-concordant duplicate sample, participants whose race was neither Caucasian nor African American (N=104), participants with discordant self-reported race and ancestry estimates calculated from genotyped ancestry informative markers (n=5) or failed genotyping in >20% of the ancestry markers (N=64), consistent with other published studies in this cohort, leaving 1391 eligible participants. Finally, we excluded women who were missing data on pre-gravid BMI (n=38) or gestational diabetes (n= 68), leaving 1285 women available (899 Caucasian and 386 African American) for analysis.

Determination of pre-gravid BMI

Pre-gravid BMI was calculated based on self-reported pre-gravid weight and height at the first prenatal visit. Self-reported pre-gravid weights were examined for biological plausibility and imputed if deemed appropriate (<5% of weights were imputed) according to a previously-described algorithm[15]. This imputed weight was calculated using the measured weight at the first prenatal visit (if taken prior to 15 weeks) minus the recommended amount of weight to be gained in the first and second trimesters as defined by the Institute of Medicine[16].

Study covariates

The PIN datasets include information from telephone interviews, self-administered questionnaires, medical chart abstraction, and biological specimen collection. Information on race/ethnicity (non-Hispanic white, non-Hispanic black, and other) and maternal age was self-reported by the mother.

Outcome assessment

Gestational diabetes was ascertained through prospective review of prenatal records by trained abstractors. As part of routine clinical care, study participants underwent glucose loading test (GLT) screening at 24–29 weeks. Participants with GLT values ≥140 mg/dL at UNC sites or ≥130 mg/dL at Wake County sites underwent a diagnostic 100g oral glucose tolerance test (OGTT). Individuals with 2 or more values above established cut points (fasting >95 mg/dL, 1 hour >180mg/dL, 2 hour > 155 mg/dL, 3 hour >140mg/dL) were diagnosed with gestational diabetes[17].

Genotyping

Genotyping for 36 SNPs was performed Children's Hospital of Boston using the Sequenom iPLEX platform[18]. We genotyped SNPs previously reported to be associated with type 2 diabetes and/or glucose homeostasis in GWAS studies of non-pregnant European and Asian populations[19–28]. All SNPs were tested for Hardy-Weinberg equilibrium among self-identified white participants using a threshold of $p < 0.001$. In genetic association studies, differences in allele frequency among ethnic groups can confound relationships between genotype and disease outcome. To address population stratification in this cohort, we

genotyped all participants for 37 ancestry-informative markers that have been used successfully in other genetic association studies[29].

Population Stratification

STRUCTURE was used to infer population substructure and assign individuals to populations using probabilistic clustering methods[30]. We analyzed self-identified white and black participants separately, and we included probability of Yoruban ancestry as a covariate among self-identified black women.

Statistical analysis

We used logistic regression to model the association between risk allele carriage and gestational diabetes in our study population. In this pilot study, p values of <.05 were considered statistically significant. Because the prevalence of gestational diabetes in our cohort was about 6%, we ascertained <5 cases for some genotypes. The asymptotic theory underlying maximum likelihood regression does not hold with such small numbers of cases. We therefore used exact logistic regression to quantify associations in the setting of <5 cases per genotype, adjusting for age and BMI group. For SNPs with ≥ 5 cases for each genotype, we used maximum likelihood logistic regression. To determine whether to quantify genotype using a categorical model or an additive model, which assumes a monotonic relationship between number of risk alleles and outcome, we used the likelihood ratio test to compare the categorical model with the additive model. If the categorical model fit was superior at a significance level of .05, we modeled genotype categorically. If not, we used an additive model. This approach allowed us to identify additive, autosomal dominant and autosomal recessive patterns of association. We then used logistic regression to model the association between risk genotype and GDM, adjusting for maternal age, pregravid BMI, and probability of Yoruban ancestry. Because the purpose of our study was to estimate the strength of associations between SNPs and GDM risk, rather than test whether a specific hypothesis was true or false, adjustment for multiple comparisons was not performed.

Results

Of the 48 SNPs attempted, 38 were successfully genotyped for more than 90% of samples and were consistent with Hardy-Weinberg equilibrium in the self-described White/ Caucasian population. Compared with white participants in our cohort, African American women were younger, had slightly higher pre-gravid BMIs, lower glucose loading test results, and earlier gestational ages at birth (Table 1). GDM was diagnosed in 56 of 899 (6.2%) Caucasian and 24 of 386 (6.2%) African-American women.

Among Caucasian women, we found linear association between GDM and carriage of the *MTNR1B* rs10830963 effect allele (OR 1.65, 95% CI 1.10–2.48 per G allele), *GCKR* rs780094 (OR 1.58, 95% CI 1.03–2.42 per C allele) and *TCF7L2* rs7901695 (OR per T allele 1.98, 95% CI 1.31–2.99).

Among African-American participants, the number of GDM cases was low, requiring exact logistic regression for all but two variants (Table 2). We found an increased risk of GDM among homozygotes for the *TSPAN8* rs7961581 C allele (OR 6.83, 95% CI 1.28–31.13), compared with homozygotes for the low-risk T allele. Among participants homozygous for the C allele, 4/13 (30.8%) developed GDM. We found a reduced risk of GDM among participants with the *JAZF1* rs864745 T risk allele (OR per T allele 0.46, 95% CI 0.06–0.88).

Comment

In a secondary analysis of a prospective cohort study, we found evidence of associations between gestational diabetes and common genetic variants near *MTNR1B, GCKR* and *TCF7L2* among Caucasian women. These results support our hypothesis that genetic variants associated with type 2 diabetes and glucose homeostasis in non-pregnant populations are associated with GDM risk. Among African-American women, we found an increased risk of GDM among women heterozygous for a genetic variant near *TSPAN8*, and we found a decreased risk with carriage of a variant near *JAZF1*. Given the small number of cases among African-American women, these results should be interpreted with caution.

These results confirm and extend earlier work on associations between genetic variants and GDM risk. Our study is the first to our knowledge to quantify associations between diabetes risk allele carriage and GDM in a US population, as well as the first to report associations among African-American women. In case:control studies in Korea[7,10,11,14] and China[8], authors have reported associations between GDM risk and genetic variants associated with T2DM, insulin secretion and fasting glucose. Similarly, studies in European[9,13,31–33] and Australian[12] populations have reported associations between T2DM and fasting glucose-associated SNPs and both GDM and pregnancy glucose homeostasis.

In our analysis of Caucasian women in our cohort, we found an association between the *MTNR1B* rs10830963 risk allele and GDM, consistent with a recent Korean GDM case:control study[10]. Melatonin receptor 1B is expressed in pancreatic islet cells, and melatonin suppresses insulin secretion in vitro. Expression of *MTNR1B* is reduced in beta cells of individuals with type 2 diabetes, compared with euglycemic individuals[34]. Recently, exon resequencing of *MTNR1B* among 7632 European individuals identified rare partial-and total-loss-of-function variants that were associated with a >5-fold odds of type 2 diabetes, establishing a functional link between this gene and type 2 diabetes[35].

We also found an association between carriage of the *GCKR rs780094* risk allele and GDM. *GCKR* modulates glucokinase, which catalyzes hepatic phosphorylation of glucose, leading to synthesis of glycogen and triglycerides in the fed state. Variants in *GCKR* are associated with reciprocal effects on fasting glucose vs. triglycerides and C-reactive protein[36–38], and with differential response to metformin and lifestyle therapy in the Diabetes Prevention Program clinical trial[39].

In addition, we found an association between the *TCF7L2 rs7901695* and GDM. This variant is in LD with rs7903146 (r^2=.84) in Caucasian populations, and authors have reported associations between rs7903146 and GDM among Greek[40], British, Australian[12], Swedish[931], and Danish women[13]. Variants near *TCF7L2* modulate both glucose and incretin-stimulated insulin secretion, as well as conversion of pro-insulin to insulin[41].

Among African-American participants, our small sample size and low risk allele frequencies limited our power to detect associations. Our findings were driven by small numbers of cases (4/13 among TSPAN8 C homozygotes and 5/23 among JAZF1 C homozygotes), and should therefore be interpreted with caution.

Our results must be interpreted within the context of the study design. Strengths of our study include our prospective ascertainment of gestational diabetes and our selection of cases and controls from within a pregnancy cohort study. This approach reduces the risk of misclassification, which may occur in other studies that have used non-diabetic middle-aged women or men as controls. Moreover, our use of ancestry informative markers reduces errors due to population stratification. However, our sample size was small, reducing our ability to detect effects associated with risk allele carriage. For the majority of SNPs we

genotyped, odds ratios for type 2 diabetes in GWAS studies were less than 1.2. Such effect sizes are considerably smaller than we were powered to detect in our population. Our power for detecting risk among African American participants was further limited by our small sample size (N=386) and differences in linkage disequilibrium patterns in Caucasian and African American populations. Multiple testing is also a concern. To address this issue, we limited our analysis to candidate SNPs that have been validated in multiple large studies. Nevertheless, it is possible that our findings are due to chance, and further studies in other cohorts will be needed to validate our results.

In conclusion, we found evidence that maternal diabetes-risk allele genotype is associated with gestational diabetes in a prospective cohort study. Further studies are needed to validate these results in other cohorts and to determine whether maternal genotype can be used to identify women at risk and inform treatment strategies for impaired gestational glucose tolerance.

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Table 1

Study Population

	Caucasian	**African American**
N	900	386
GDM cases	56	24
	Mean (SD)	Mean (SD)
Maternal age	28.3 (6.1)	24.1 (5.5)
Pregravid BMI	25.2 (6.5)	27.8 (8.2)
GA at delivery wks	38.3 (2.4)	37.6 (3.0)
Infant birth weight g	3281 (647)	2973 (734)
Gestational weight gain kg	15.4 (6.2)	13.5 (7.8)
Glucose loading test	108.5 (26.4)	106.0 (31.7)

Table 2

Maternal genotype and probability of gestational diabetes.

%				Caucasian				African–American			
Gene **rs number**	**Risk allele**	**Other allele**	**Risk alleles**	**RAF**	**GDM / Total**	**GDM %**	**OR (95 CI)**	**RAF**	**GDM / Total**	**GDM %**	**OR (95% CI)**
ADAMTS9 rs4607103	C	T	0	0.74	4/62	6.5	1.00 (ref)[3]	0.72	1/29	3.4	1.00 (ref)[3]
			1		15/351	4.3	0.74 (0.22–3.22)		12/160	7.5	2.01 (0.26–91.33)
			2		37/486	7.6	1.40 (0.46–5.72)		11/197	5.6	1.33 (0.17–60.89)
ADCY5 rs11708067	A	G	0	0.76	3/45	6.7	1.00 (ref)[3]	0.86	0/11	0	1.00 (ref)[3]
			1		20/325	6.2	0.84 (0.23–4.70)		6/87	6.9	0.69 (0.11– >999.99)
		2		32/508	6.3	0.82 (0.23–4.45)		17/282	6	0.69 (0.13– >999.99)	
ADCY5 rs2877716	C	T	0	0.74	5/53	9.4	1.00 (ref)[1]	0.77	1/24	4.2	1.00 (ref)[3]
			1		19/351	5.4	0.94 (0.59–1.49)		6/129	4.7	0.96 (0.10–47.41)
			2		30/477	6.3	0.88 (0.35–2.21)		16/226	7.1	1.52 (0.21–68.13)
ADRA2A rs10885122	G	T	0	0.88	2/17	11.8	1.00 (ref)[3]	0.32	10/172	5.8	1.00 (ref)[3]
			1		8/174	4.6	0.41 (0.07–4.47)		10/169	5.9	1.02 (0.37–2.86)
			2		46/691	6.7	0.58 (0.12–5.52)		3/35	8.6	1.49 (0.24–6.43)
BCL11A rs243021	T	C	0	0.48	11/255	4.3	1.00 (ref)[1]	0.39	9/135	6.7	1.00 (ref)[3]
			1		29/415	7	1.37 (0.93–2.01)		12/202	5.9	0.77 (0.28–2.19)
			2		16/226	7.1	1.86 (0.86–4.03)		3/48	6.3	0.88 (0.14–3.83)
CDC123 rs12779790	G	A	0	0.18	37/605	6.1	1.00 (ref)	0.14	20/282	7.1	1.00 (ref)[3]
			1		14/244	5.7	1.26 (0.79–2.01)		3/95	3.2	0.47 (0.09–1.66)
			2		5/33	15.2	1.58 (0.62–4.05)		1/5	20	3.03 (0.05–39.12)
CDKAL1 rs10946398	C	A	0	0.31	31/413	7.5	1.00 (ref)[3]	0.62	4/54	7.4	1.00 (ref)[3]
			1		23/405	5.7	0.75 (0.41–1.37)		11/186	5.9	0.83 (0.23–3.81)
			2		2/79	2.5	0.35 (0.04–1.44)		8/142	5.6	0.81 (0.20–3.97)
CDKN2A2B rs10811661	T	C	0	0.82	2/33	6.1	1.00 (ref)[3]	0.94	0/1	0	1.00 (ref)[3]

%				Caucasian				African–American			
Gene **rs number**	**Risk allele**	**Other allele**	**Risk alleles**	**RAF**	**GDM / Total**	**GDM %**	**OR (95 CI)**	**RAF**	**GDM / Total**	**GDM %**	**OR (95% CI)**
			1		15/256	5.9	0.99 (0.21–9.57)		4/47	8.5	0.17 (0.01– >999.99)
			2		39/599	6.5	1.08 (0.25–9.84)		20/336	6	0.12 (0.01– >999.99)
CRY2 rs11605924	A	C	0	0.48	12/236	5.1	1.00 (ref)[1]	0.85	0/6	0	1.00 (ref)[3]
			1		28/449	6.2	1.24 (0.84–1.84)		8/104	7.7	0.49 (0.08– >999.99)
			2		15/209	7.2	1.54 (0.70–3.39)		16/275	5.8	0.34 (0.06– >999.99)
DGKB TMEM195 rs2191349	T	G	0	0.54	15/171	8.8	1.00 (ref)[1]	0.6	3/52	5.8	1.00 (ref)[3]
			1		24/437	5.5	0.79 (0.53–1.19)		13/200	6.5	1.27 (0.32–7.43)
			2		13/242	5.4	0.63 (0.28–1.43)		8/125	6.4	1.22 (0.27–7.57)
DUSP9 rs5945326	A	G	0	0.78	4/55	7.3	1.00 (ref)[3]	0.79	1/16	6.3	1.00 (ref)[3]
			1		16/290	5.5	0.84 (0.25–3.69)		4/125	3.2	0.46 (0.04–25.00)
			2		34/544	6.3	0.94 (0.31–3.89)		18/237	7.6	1.26 (0.16–59.69)
FADS1 rs174550	T	C	0	0.68	4/92	4.3	1.00 (ref)[3]	0.93	0/2	0	1.00 (ref) [3]
			1		20/395	5.1	1.12 (0.36–4.68)		3/50	6	0.06 (0.01– >999.99)
			2		32/407	7.9	1.90 (0.64–7.69)		21/328	6.4	0.07 (0.01– >999.99)
G6PC2 rs560887	C	T	0	0.71	6/70	8.6	1.00 (ref)[1]	0.93	0/1	0	1.00 (ref)[3]
			1		26/385	6.8	0.82 (0.54–1.26)		5/49	10.2	0.22 (0.01– >999.99)
			2		24/437	5.5	0.67 (0.29–1.58)		18/332	5.4	0.12 (0.01– >999.99)
GCK rs4607517	A	G	0	0.04	49/780	6.3	1.00 (ref)[3]	0.01	23/364	6.3	1.00 (ref)[3]
			1		3/56	5.4	1.00 (0.19–3.35)		1/8	12.5	2.00 (0.04–19.14)
			2		0/2	0	9.44 (0.00–80.42)		0/1	0	20.31 (0.00–385.91)
GCKR rs1260326	C	T	0	0.59	5/159	3.1	1.00 (ref)	0.83	1/8	12.5	1.00 (ref)[3]
			1		26/421	6.2	1.49 (1.00–2.24)		7/114	6.1	0.68 (0.06–38.86)
			2		25/316	7.9	2.23 (0.99–5.02)		16/264	6.1	0.68 (0.07–35.97)
GCKR rs780094	C	T	0	0.58	5/155	3.2	1.00 (ref)	0.86	0/4	0	1.00 (ref)[3]

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%				Caucasian				African–American			
Gene **rs number**	**Risk allele**	**Other allele**	**Risk alleles**	**RAF**	**GDM / Total**	**GDM %**	**OR (95 CI)**	**RAF**	**GDM / Total**	**GDM %**	**OR (95% CI)**
			1		23/399	5.8	**1.58 (1.03–2.42)**		6/93	6.5	0.20 (0.03– >999.99)
			2		24/290	8.3	**2.50 (1.07–5.84)**		16/271	5.9	0.19 (0.03– >999.99)
GIPR rs10423928	A	T	0	0.21	36/554	6.5	1.00 (ref)[3]	0.14	18/275	6.5	1.00 (ref)[3]
			1		16/272	5.9	0.87 (0.44–1.66)		4/87	4.6	0.75 (0.18–2.42)
			2		2/52	3.8	0.56 (0.06–2.34)		0/7	0	1.56 (0.00–8.85)
GLIS3 rs7034200	A	C	0	0.48	18/246	7.3	1.00 (ref)	0.61	3/56	5.4	1.00 (ref)[3]
			1		28/439	6.4	0.84 (0.57–1.24)		10/187	5.3	0.84 (0.20–5.00)
			2		10/209	4.8	0.71 (0.33–1.55)		11/140	7.9	1.23 (0.30–7.31)
HHEX IDE rs1111875	C	T	0	0.59	10/166	6	1.00 (ref)	0.76	1/20	5	1.00 (ref)[3]
			1		25/412	6.1	1.05 (0.71–1.55)		8/144	5.6	1.35 (0.16–64.99)
			2		21/319	6.6	1.10 (0.50–2.40)		15/222	6.8	1.45 (0.19–66.21)
IGF2BP2 rs4402960	T	G	0	0.33	27/415	6.5	1.00 (ref)	0.52	2/80	2.5	1.00 (ref)[3]
			1		22/371	5.9	0.91 (0.61–1.36)		16/200	8	3.80 (0.84–35.53)
			2		7/108	6.5	0.82 (0.37–1.84)		6/98	6.1	2.92 (0.49–31.15)
IRS1 rs2943641	C	T	0	0.66	8/107	7.5	1.00 (ref)	0.71	3/31	9.7	1.00 (ref)[3]
			1		23/385	6	0.96 (0.64–1.45)		9/165	5.5	0.55 (0.12–3.47)
			2		24/398	6	0.92 (0.41–2.09)		12/189	6.3	0.61 (0.14–3.66)
JAZF1 rs864745	T	C	0	0.51	13/219	5.9	1.00 (ref)	0.75	5/23	21.7	1.00 (ref)[1]
			1		22/373	5.9	1.19 (0.81–1.74)		8/141	5.7	**0.46 (0.24–0.88)**
			2		19/242	7.9	1.41 (0.66–3.03)		9/212	4.2	**0.21 (0.06–0.78)**
KCNJ11 rs5215	C	T	0	0.38	20/346	5.8	1.00 (ref)	0.06	21/344	6.1	1.00 (ref)[3]
			1		24/419	5.7	1.21 (0.81–1.80)		3/39	7.7	1.35 (0.24–5.06)
			2		12/134	9	1.46 (0.66–3.23)		0/3	0	9.17 (0.00–64.73)
KCNQ1 rs2237892	C	T	0	0.95	0/5	0	1.00 (ref)[3]	0.91	0/5	0	1.00 (ref)[3]

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%				Caucasian				African–American			
Gene **rs number**	**Risk allele**	**Other allele**	**Risk alleles**	**RAF**	**GDM / Total**	**GDM %**	**OR (95 CI)**	**RAF**	**GDM / Total**	**GDM %**	**OR (95% CI)**
			1		5/69	7.2	0.28 (0.04– >999.99)		4/56	7.1	0.53 (0.07– >999.99)
			2		50/777	6.4	0.32 (0.06– >999.99)		19/313	6.1	0.56 (0.09– >999.99)
MADD rs7944584	A	T	0	0.72	4/69	5.8	1.00 (ref)[3]	0.96	0/1	0	1.00 (ref)[3]
			1		27/360	7.5	1.33 (0.43–5.50)		3/31	9.7	0.04 (0.00– >999.99)
			2		25/467	5.4	0.95 (0.31–3.93)		21/354	5.9	0.03 (0.00– >999.99)
MTNR1B rs10830963	G	C	0	0.28	21/472	4.4	1.00 (ref)[1]	0.06	22/334	6.6	1.00 (ref)[3]
			1		27/335	8.1	**1.65 (1.10–2.48)**		2/43	4.7	0.53 (0.06–2.38)
			2		7/82	8.5	**2.73 (1.21–6.16)**		0/3	0	6.85 (0.00–48.15)
NOTCH2 rs10923931	T	G	0	0.1	42/722	5.8	1.00 (ref)[3]	0.33	10/177	5.6	1.00 (ref)[3]
			1		13/168	7.7	1.39 (0.66–2.77)		10/162	6.2	1.14 (0.41–3.19)
			2		0/4	0	2.47 (0.00–16.36)		4/47	8.5	1.64 (0.35–6.25)
PPARG rs1801282	C	G	0	0.89	1/12	8.3	1.00 (ref)	0.97	0/0	-	
			1		9/174	5.2	0.51 (0.06–25.16)		2/20	10	1.00 (ref)[3]
			2		46/709	6.5	0.68 (0.09–31.23)		21/362	5.8	0.56 (0.11–5.55)
PRC1 rs8042680	A	C	0	0.34	24/390	6.2	1.00 (ref)[1]	0.88	1/6	16.7	1.00 (ref)[3]
			1		22/402	5.5	1.20 (0.80–1.81)		4/83	4.8	0.33 (0.02–20.49)
			2		10/105	9.5	1.45 (0.64–3.27)		19/296	6.4	0.44 (0.04–23.24)
SLC30A8 rs11558471	A	G	0	0.69	3/77	3.9	1.00 (ref)[3]	0.89	0/4	0	1.00 (ref)[3]
			1		26/397	6.5	1.79 (0.52–9.61)		3/74	4.1	0.15 (0.02– >999.99)
			2		27/425	6.4	1.68 (0.49–9.02)		21/308	6.8	0.29 (0.04– >999.99)
SLC30A8 rs13266634	C	T	0	0.68	4/88	4.5	1.00 (ref)[3]	0.89	0/4	0	1.00 (ref)[3]
			1		25/396	6.3	1.46 (0.48–5.99)		3/73	4.1	0.14 (0.02– >999.99)
			2		27/409	6.6	1.48 (0.49–6.08)		21/302	7	0.30 (0.04– >999.99)
TCF2 rs4430796	A	G	0	0.52	10/221	4.5	1.00 (ref)[2]	0.34	12/170	7.1	1.00 (ref)[3]

%				Caucasian				African–American			
Gene **rs number**	**Risk allele**	**Other allele**	**Risk alleles**	**RAF**	**GDM / Total**	**GDM %**	**OR (95 CI)**	**RAF**	**GDM / Total**	**GDM %**	**OR (95% CI)**
			1		33/415	8	2.08 (0.99–4.37)		10/173	5.8	0.74 (0.27–1.97)
			2		13/261	5	1.17 (0.49–2.77)		2/43	4.7	0.68 (0.07–3.33)
TCF7L2 rs7901695	C	T	0	0.3	17/432	3.9	1.00 (ref)[1]	0.44	5/126	4	1.00 (ref)[3]
			1		30/387	7.8	**1.98 (1.31–2.99)**		15/177	8.5	2.30 (0.75–8.45)
			2		9/79	11.4	**3.93 (1.73–8.94)**		4/83	4.8	1.30 (0.25–6.34)
THADA rs7578597	T	C	0	0.9	0/8	0	1.00 (ref)[3]	0.76	4/28	14.3	1.00 (ref)[3]
			1		10/169	5.9	0.69 (0.12– >999.99)		9/126	7.1	0.39 (0.09–1.98)
			2		46/713	6.5	0.84 (0.16– >999.99)		11/225	4.9	0.29 (0.07–1.39)
TSPAN8 rs7961581	C	T	0	0.28	25/461	5.4	1.00 (ref)[1]	0.18	14/256	5.5	1.00 (ref)[3]
			1		24/351	6.8	1.32 (0.88–2.00)		6/114	5.3	1.02 (0.31–2.96)
			2		6/76	7.9	1.75 (0.77–4.01)		4/13	30.8	**6.83 (1.28–31.13)**
VPS13C rs17271305	G	A	0	0.41	22/305	7.2	1.00 (ref)[3]	0.11	18/300	6	1.00 (ref)[3]
			1		29/444	6.5	0.86 (0.46–1.62)		5/80	6.3	1.05 (0.29–3.11)
			2		4/142	2.8	0.40 (0.10–1.23)		1/4	25	3.55 (0.06–52.14)
WFS1 rs10010131	G	A	0	0.59	9/149	6	1.00 (ref)[1]	0.64	4/46	8.7	1.00 (ref)[3]
			1		25/433	5.8	1.18 (0.79–1.77)		11/188	5.9	0.62 (0.17–2.90)
			2		22/316	7	1.40 (0.62–3.14)		9/151	6	0.64 (0.16–3.05)
ZFAND6 rs11634397	G	A	0	0.67	6/102	5.9	1.00 (ref)[1]	0.44	6/113	5.3	1.00 (ref)[1]
			1		28/378	7.4	0.89 (0.59–1.33)		11/196	5.6	1.34 (0.71–2.53)
			2		22/413	5.3	0.79 (0.35–1.77)		6/70	8.6	1.79 (0.50–6.38)

[1] Maximum likelihood logistic regression, linear model, adjusting for age, pregravid BMI, and probability of Yoruban ancestry

[2] Maximum likelihood logistic regression, genotype model, adjusting for age, pregravid BMI, and probability of Yoruban ancestry, with inverse probability of sampling weights.

[3] Exact logistic regression, adjusting for age and BMI category