NOTE

Association of common polymorphisms with gestational diabetes mellitus in Japanese women: A case-control study

Yoshifumi Kasuga^{1), 2)}, Kenichiro Hata²⁾, Atsushi Tajima³⁾, Daigo Ochiai¹⁾, Yoshifumi Saisho⁴⁾, Tadashi Matsumoto¹⁾, Naoko Arata⁵⁾, Kei Miyakoshi¹⁾ and Mamoru Tanaka¹⁾

¹⁾ Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo 160-8582, Japan

²⁾ Department of Maternal-Fetal Biology, National Research Institute for Child Health and Development, Tokyo 157-8583, Japan

³⁾ Department of Bioinformatics and Genomics, Graduate School of Advanced Preventive Medical Sciences, Kanazawa University, Kanazawa 920-8640, Japan

⁴⁾ Department of Internal Medicine, Keio University School of Medicine, Tokyo 160-8582, Japan

⁵⁾ Department of Women's Health, National Center for Child Health and Development, Tokyo 157-8583, Japan

Abstract. Gestational diabetes (GDM) and type 2 diabetes (T2DM) share part of pathomechanism and several T2DM susceptibility genes are demonstrated to be associated with GDM. No information on the genetics of GDM, however, was available in Japanese women. In this study, T2DM risk variants (45 single nucleotide polymorphisms [SNPs] from 36 genes) identified in previous studies were genotyped using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry in a cohort of 171 Japanese women with GDM and 128 normal glucose tolerance (NGT) diagnosed by the new International Association of Diabetes in Pregnancy Study Group criteria. Of 45 SNPs, three genetic variants were nominally associated with the development of GDM: rs266729 ($p = 0.013$, odds ratio [OR]: 1.56, 95% confidence interval [CI]: 1.10–2.23) in *ADIPOQ*, rs10811661 ($p = 0.035$, OR: 1.46, 95% CI: 1.03–2.08) in *CDKN2A/2B*, and rs9505118 ($p = 0.046$, OR: 1.41, 95% CI: 1.01–1.97) in *SSRI-RREB1*. There was a significant difference in the number of risk alleles of three variants between women with GDM and NGT (3.79 ± 1.33 vs. 3.05 ± 1.41 , $p = 6.0 \times 10^{-6}$). In combined analysis of three genetic variants, women with five or more risk alleles had a 7.32-fold increased risk of GDM ($p = 5.6 \times 10^{-5}$, 95% CI: 4.54–11.96), compared with those having no more than one risk allele. Our results suggest several risk variants of T2DM had cumulative effects on the development of GDM in Japanese women.

Key words: Gestational diabetes mellitus, Single nucleotide polymorphism, Japanese women

GESTATIONAL DIABETES MELLITUS (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, is a multifactorial disease that is similar to type 2 diabetes mellitus (T2DM): glucose intolerance is likely to be caused by the combination of environmental and genetic effects [1, 2]. With the recent advances in high-throughput genotyping technologies, the genetics of GDM as well as T2DM has been investigated over the past decade. For instance, genetic variants associated with insulin sensitivity and

beta cell function have been related to T2DM in various racial or ethnic groups including Japanese population by the linkage analysis, the candidate gene approach, and the genome-wide association studies (GWAS) [3–6]. In particular, several T2DM susceptibility genes were related to the development of GDM in Caucasians [7–11]. Since the susceptibility to glucose intolerance depends on racial or ethnic groups, the effect of T2DM risk genetic variants on GDM might be different between Caucasian and Japanese women. To date, however, no information on risk variants of GDM was available in Japanese women.

Women with GDM are at a high risk of developing future T2DM as well as perinatal complications (*i.e.* pregnancy-induced hypertension and macrosomia) [2, 12]. Offspring born to mother with GDM carries a risk of early onset obesity and glucose intolerance [12, 13]. Therefore, the optimal management of GDM is important not only to perinatal care, but also to maternal and

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Correspondence to: Kenichiro Hata, M.D., Ph.D., Department of Maternal-Fetal Biology, National Research Institute for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8583, Japan. E-mail: hata-k@ncchd.go.jp

Co-correspondence to: Kei Miyakoshi, M.D., Department of Obstetrics and Gynecology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.

E-mail: kei.z7@keio.jp

children's healthcare. In general, Asians are classified as a highly susceptible to glucose intolerance [14-16]. This means that genetic information would contribute to the identification of women at highest risk of T2DM as well as the understanding of the pathophysiology of GDM in Japanese women.

With this background, the current study was designed to examine the association between T2DM or GDM susceptibility genes previously reported and the development of GDM in Japanese women. Especially, in the present study, glucose tolerance status was evaluated by a single criterion (*i.e.* the new criteria proposed by International Association of Diabetes in Pregnancy Study Group [IADPSG]) and pregnant women with normal glucose tolerance (NGT) were considered as control to account for the environmental influence (*i.e.* pregnancy).

Materials and Methods

Subjects

We recruited a total of 299 Japanese women with singleton pregnancies who underwent the diagnostic 75g oral glucose tolerance test (75g-OGTT) at 24–32 gestational weeks at Keio University Hospital or at the National Center for Child Health and Development from April 2011 until December 2014. Gestational age was confirmed by crown-rump length measurements in the first trimester. Women with multi-fetal pregnancies, fetal congenital anomalies, overt diabetes in pregnancy, pre-gestational diabetes mellitus (*i.e.* type 1 diabetes and T2DM), and hypertensive disorders in pregnancy, chronic hypertension, and the use of medications known to affect glucose metabolism were excluded. This research was performed in accordance with the Declaration of Helsinki and informed consent was obtained from patients, where appropriate. The study was approved by Keio University School of Medicine Ethics Committee (No. 20100154) and the institutional review board of National Research Institute for Child Health and Development (No. 406).

According to IADPSG criteria, GDM was diagnosed if one or more values reached or exceeded the following thresholds: fasting plasma glucose level (FPG), 92 mg/dL (5.1 mmol/L); 1h-plasma glucose level during 75g-OGTT (1h-PG), 180 mg/dL (10.0 mmol/L); and 2h-plasma glucose level during 75g-OGTT (2h-PG), 153 mg/dL (8.5 mmol/L). Overt diabetes in pregnancy was defined as HbA1c > 6.5%,

FPG $\geq$ 126 mg/dL (7.0 mmol/L), or random plasma glucose level $\geq$ 200 mg/dL (11.1 mmol/L): the latter needing to be confirmed by one of the former [17]. Women with normal OGTT results were considered as NGT (*i.e.* control) in this study. As a result, there were 171 women with GDM and 128 with NGT in this study cohort. Statistical power of the current analysis using 171 GDM and 128 NGT was calculated using Genetic Power Calculator in the GDM prevalence rate of 10% [18]. The current study had 57% or 85% power to detect a GDM-susceptible allele with a genotype relative risk (GRR) of 1.4 or 1.6 (under an additive model in log-odds scale), respectively, assuming that the type I error rate was 0.05 and the susceptible allele frequency was 0.3.

Assessment of insulin sensitivity, insulin secretion, and beta cell function

Insulin sensitivity and insulin secretion were evaluated by parameters calculated using the diagnostic 75g-OGTT. The insulin sensitivity was estimated by the whole-body insulin sensitivity index derived from the OGTT (IS_{OGTT}) and the homeostasis model assessment of insulin resistance (HOMA-IR), and Quantitative insulin sensitivity check index (QUICKI). The IS_{OGTT} was calculated by the following formula: $10,000 / \text{square root} \{PG_0 \times Ins_0 \times (PG_0 + PG_{60} \times 2 + PG_{120}) / 2 \times (Ins_0 + Ins_{60} \times 2 + Ins_{120}) / 2\}$, where PG_y and Ins_y represent plasma glucose (mg/dL) and insulin values (mU/L), respectively, at time y min during the OGTT [19]. The HOMA-IR was calculated as $(PG_0 \times Ins_0) / 405$ [20]. The QUICKI was estimated as follows: $1 / [\log(Ins_0) + \log(PG_0)]$ [21]. Insulin secretion was assessed by the Insulinogenic Index (IGI: $\{Ins_{30} - Ins_0\} / \{PG_{30} - PG_0\}$) during the OGTT [22]. To evaluate beta cell function, we calculated the OGTT-derived disposition index using the following measures: Insulin Secretion-Sensitivity Index-2 (ISSI-2: $IS_{OGTT} \times \text{the ratio of the total area under the insulin curve to the total area under the glucose curve during the OGTT}$) [23].

SNP selection and genotyping

A PubMed search was performed in October 2014 and we retrieved 151 SNPs from 88 genes, previously reported to be associated with T2DM or GDM (Supplementary Table 1). It is well known that an impaired insulin secretion plays a critical role in the development of T2DM or GDM in east Asian

including Japanese [24, 25]. Therefore, most of SNPs analyzed were insulin secretion candidate SNPs. Several T2DM susceptibility genes were identified in Japanese as well as Caucasian. All GDM risk gene variants examined were found in subjects other than Japanese. We selected the SNPs based on the criterion of the minor allele frequency (MAF) > 30% in Japanese population because this selection could provide adequate statistical power to detect SNPs with $GRR \geq 1.4$ in our study cohort, as was described above. Additionally, gene-based tag SNPs (pairwise $r^2 < 0.8$) using HapMap-JPT in this study and several SNPs were excluded because of technical reasons (e.g. polymerase chain reaction failures). Finally, we investigated the association between 45 SNPs from 36 genes and the development of GDM. All polymorphisms analyzed in this study were in Hardy-Weinberg equilibrium.

Maternal peripheral blood samples were collected after delivery and genomic DNA was extracted using QIAasympy DNA Midi Kit (96) (Qiagen, Valencia, CA, USA). Genotyping was performed using high-throughput genotyping MassARRAY® platform (Sequenom, Inc, San Diego, CA, USA). The primers including amplification and extension were designed using Assay Design Suite® (Sequenom, <https://seqpws1.sequenom.com/AssayDesignerSuite.html>) (Supplementary Table 2). Negative controls, at least quadruplicate, were placed at all 384 plates as quality controls. SNP genotyping success rate was > 94% and the concordance rate for genotyping was > 99.8% in this study.

Statistical analysis

Per-allele odd ratios (ORs) and their 95% confidence intervals (CIs) for the association between SNPs and GDM were estimated by logistic regression analysis. The possibility of multiple testing was avoided by Bonferroni correction. Therefore, we examined the combined effects of genetic variants on Japanese GDM and the cumulative effects of risk alleles at GDM-associated SNPs having lower p -value (pre-Bonferroni correction) [26]. Data are presented as mean $\pm$ SD or the number of cases (percent). Continuous data were compared between the GDM and NGT groups by Student's t -test. The frequencies of SNPs between the two groups were evaluated by logistic regression analysis. Categorical variables were analyzed by the Fisher's exact test.

Statistical analyses were performed using SPSS v.22 (IBM, Chicago, IL, USA). A p -value < 0.05 was considered statistically significant. The calculation of linkage disequilibrium (LD) among SNPs and construction of a forest plot of per-allele ORs were done with R (version 3.3.1).

Results

Maternal characteristics

Maternal characteristics and metabolic measurements of the GDM and NGT (*i.e.* control) groups are shown in Table 1. There were no notable differences in maternal age at delivery, pregravid BMI, and the rate of overweight or nulliparous between the GDM and NGT groups. A first-degree family history of T2DM was more prevalent women with GDM, compared with NGT. With regard to metabolic measurements, FPG, 1h-PG, 2h-PG, and HOMA-IR were significantly higher in the GDM group compared with those in the NGT group. Women with GDM showed significantly lower levels of IS_{OGTT} , QUICKI, IGI, and ISSI-2, compared with NGT ($p < 0.05$).

Table 1 Comparison of maternal characteristics between the gestational diabetes mellitus and normal glucose tolerance groups

	GDM (n = 171)	NGT (n = 128)	<i>p</i> -value
Maternal age at delivery (years)	36.1 $\pm$ 4.6	36.6 $\pm$ 4.3	0.36
Pre-pregnancy BMI (kg/m ²)	21.4 $\pm$ 3.3	20.7 $\pm$ 2.5	0.05
Pre-pregnancy overweight	24 (14.0)	10 (7.8)	0.18
Nulliparous	111 (64.9)	79 (61.7)	0.63
A first-degree family history of diabetes	33 (19.3)	9 (7.0)	0.002
Prior miscarriage	57 (33.3)	58 (45.3)	0.04
Gestational week at OGTT (weeks)	27.5 $\pm$ 3.1	27.8 $\pm$ 2.8	0.36
Plasma glucose of OGTT			
0 min (mg/dL)	85.9 $\pm$ 7.5	82.3 $\pm$ 4.8	2.0×10^{-6}
60 min (mg/dL)	174.1 $\pm$ 25.0	141.4 $\pm$ 21.0	4.1×10^{-28}
120 min (mg/dL)	154.7 $\pm$ 25.6	121.0 $\pm$ 17.1	2.2×10^{-30}
IS_{OGTT}	5.09 $\pm$ 2.46	7.79 $\pm$ 3.51	6.5×10^{-12}
HOMA-IR	1.88 $\pm$ 1.68	1.14 $\pm$ 0.62	6.0×10^{-6}
QUICKI	0.36 $\pm$ 0.03	0.38 $\pm$ 0.04	9.1×10^{-9}
Insulinogenic index	0.78 $\pm$ 0.49	1.03 $\pm$ 0.99	0.01
ISSI-2	1.75 $\pm$ 0.54	2.46 $\pm$ 0.70	1.3×10^{-13}

BMI, body mass index; overweight, BMI ≥ 25 kg/m²; OGTT, oral glucose tolerance test; IS_{OGTT} , Insulin sensitivity index from OGTT; HOMA-IR, homeostasis model assessment for insulin resistance; QUICKI, quantitative insulin sensitivity check index; ISSI-2, Insulin Secretion-Sensitivity Index-2; Data, mean $\pm$ SD or N (%).

Case-control study

In this study, we evaluated the frequencies of 45 SNPs in the GDM and NGT groups using logistic regression analysis. The individual allele odds ratio (OR) is shown in Fig. 1 and Supplementary Table 3. Three genetic variants had nominal associations with GDM (rs266729 [$p = 0.013$, OR: 1.56, 95% CI: 1.10–

2.23], rs10811661 [$p = 0.035$, OR: 1.46, 95% CI: 1.03–2.08], and rs9505118 [$p = 0.046$, OR: 1.41, 95% CI: 1.01–1.97]). Therefore, we examined the combined effects of the risk alleles from these three genetic variants (rs266729, rs10811661, and rs9505118). Taking into account these three variants, each individual could harbor between 0 and 6 possible risk alleles.

Fig. 1 A forest plot of per-allele odds ratio of 45 single nucleotide polymorphisms examined in this study
SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval.

The distribution of risk alleles of the three genetic variants in the GDM and NGT groups are shown in Fig. 2A. The percentages of subjects with GDM increased in the subgroups with more risk alleles. Furthermore, there was a significant difference in the number of T2DM risk alleles between women with GDM and NGT (3.79 ± 1.33 vs. 3.05 ± 1.41 , $p = 6.0 \times 10^{-6}$). Especially, women with five or more risk alleles showed a 7.32-fold increased risk of GDM ($p = 5.6 \times 10^{-5}$, 95% CI: 4.54–11.97), compared with those having no more than one risk allele (Fig. 2B). The LD values among three SNPs calculated using r^2 were under 0.02 in both GDM and NGT groups.

Discussion

With the development of genetic association studies, information on T2DM susceptibility genes has been accumulated in Japanese population. To date, however, no studies on GDM risk variants in Japanese women have been reported, although GDM may share genetic backgrounds with T2DM to some extent. In addition, there is a paucity of information on genetics of GDM by the new IADPSG criteria because the number of healthcare associations adopting the criteria is still limited [27]. Therefore, we designed the current study to examine the association of previously reported T2DM or GDM susceptibility genes with having GDM by the new IADPSG criteria in Japanese women.

It is demonstrated that the prevalence of GDM by the IADPSG criteria is 10–15% [28, 29]. When analyzing statistical power of our cohort (*i.e.* GDM, 171 women; NGT, 128 women) using Genetic Power Calculator in the GDM prevalence of 10%, SNPs with MAF > 30% could provide adequate statistical power to detect risk variants with $GRR \geq 1.4$ in our study cohort. Of 45 SNPs examined, three genetic variants (rs266729, rs10811661, and rs9505118) were nominally associated with GDM in Japanese women. Since multiple genes would be involved in the development of GDM, we investigated the combined effects of three genetic variants on GDM. As a result, women with five or more risk alleles showed a 7.32-fold increased risk of GDM, compared with those having no more than one risk allele. Our results suggested the genetic background of GDM in a multi-genetic manner in Japanese women.

Of the three genetic variants, rs266729 (*ADIPOQ*) is a gene involved in insulin sensitivity, while rs10811661 (*CDKN2A/2B*) and rs9505118 (*SSRI-RREB1*) play an important role in insulin secretion. Several studies have shown that a single polymorphism rs266729 is associated with decreased levels of serum adiponectin in GDM as well as T2DM [30, 31]. *CDKN2A/2B* is cyclin-dependent kinases 4 suppressor gene that contributes to the proliferation and maintenance of pancreatic β -cells. Based on previous studies, *CDKN2A/2B* is considered as one of the T2DM susceptibility genes in

Fig. 2 Risk alleles of three genetic variants and the development of gestational diabetes mellitus

(A) Distribution of risk alleles of three genetic variants and in women with gestational diabetes mellitus (GDM) or normal glucose tolerance (NGT). Women with GDM presented significantly more T2DM risk alleles, compared with those with NGT. Black bars represent GDM ($n = 171$), while white bars represent NGT ($n = 128$). (B) Odds ratio for the risk of GDM according to the number of type 2 diabetes mellitus risk alleles carried. Women with five or more risk alleles showed a 7.32-fold increased risk of GDM ($p = 5.6 \times 10^{-5}$, 95% CI: 4.54–11.96), compared with those having no more than one risk allele.

Japanese as well as Europeans [3, 32]. With regard to *SSRI-RREB1*, it is demonstrated that the depletion of RAS-responsive element binding protein 1 (RREB1) encoded by *SSRI* reduces β -cell development and insulin secretion [33]. The meta-analysis of GWAS indicated that rs9505118 in *SSRI-RREB1* was associated with T2DM [34]. Therefore, the risk allele in *SSRI-RREB1* could be related to pancreatic β -cell dysfunction in T2DM. To the best of our knowledge, however, no association between *SSRI-RREB1* variants and risk of GDM has been demonstrated in previous reports. Our findings suggest that *SSRI-RREB1* might be one of risk variants associated with GDM in Japanese women.

It is demonstrated that a potential etiology for GDM is a limitation in beta cell reserves that manifests as maternal hyperglycemia when insulin secretion does not increase to match the escalated insulin needs during pregnancy. With regard to maternal characteristics, Asian women with GDM are less obese than Caucasian and Hispanic women [14, 16]. Thus, decreased insulin secretion in GDM might be more evident in Asians, compared with Caucasians and Hispanics [35]. Our previous investigation has shown that women with Japanese GDM have beta cell dysfunction irrespective of presence or absence of overweight [25]. Regarding the genetic background, several studies revealed risk variants related to insulin secretion in Korean and Chinese population [36-41]. Of the three genetic variants found in this study, two are related to the regulation of insulin secretion (*i.e.* beta cell function). Taken together, beta cell dysfunction might be the core pathophysiology of GDM in Japanese women.

The strength of the present study is that we performed the association analysis using SNPs more than ever before. Most previous studies on GDM risk variants were candidate gene approach using no more than ten variants [42], whereas we used 45 SNPs from 36 genes for analysis. In addition, women with GDM were diagnosed by a single criterion, and those with NGT were fully evaluated for the glucose tolerance status. All women in our cohort were taken care, based on the clinical recommendation by the Japan Society of Obstetrics and Gynecology [17]. The findings that maternal age at delivery, pre-pregnancy BMI and the rate of overweight were comparable between the GDM and NGT groups are important. Therefore, our study cohort is suitable to investigate GDM risk genes, as were suggested in previous reports [8, 40].

There are several limitations in this study. One of the limitations is that we focused on only SNPs with $MAF > 30\%$ since our study cohort was a relatively small panel. Therefore, we may have missed SNPs with $MAF \leq 30\%$ that are associated with GDM in Japanese women because more than 80 susceptibility genes for T2DM have been identified so far [43]. It is also important to replicate and evaluate the present findings in another independent case-control set. In this regard, the results of our study should be interpreted cautiously. In the future, we would conduct the multi-institutional collaborative genetic association study to investigate candidate gene variants for GDM. Ideally, GWAS should be performed to identify all candidate gene variants for GDM in Japanese women.

In conclusion, we performed the association analysis in the context of GDM in Japanese women for the first time and found that genetic variants in *ADIPOQ*, *CDKN2A/2B*, and *SSRI-RREB1* are nominally associated with the development of GDM in Japanese. Since women with GDM are at a high risk of future T2DM, genetic information on GDM would be useful for the T2DM risk classification [38, 41]. Further research using a larger cohort is warranted for better understanding the genetics of GDM in Japanese women.

Disclosure

The authors have no conflict of interest to declare in this study.

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Supplementary Table 1 Genotype information previously reported to be associated with type 2 diabetes or gestational diabetes mellitus

Chr	SNP	Nearby gene	Minor allele	MAF	Risk allele	Candidate gene for GDM	References on GDM	Candidate gene for T2DM	References on T2DM	Reasons for exclusion from our analysis
16	rs3785233	<i>A2BP1(RBFOX1)</i>	G	0.18	C			Yes	Miyake <i>et al.</i> J Hum Genet, 2009	
3	rs4607103	<i>ADAMTS9</i>	T	0.41	C			Yes	Zeggini <i>et al.</i> Nat Genet, 2008	
3	rs6795735	<i>ADAMTS9</i>	C	0.21	C			Yes	Voight <i>et al.</i> Nat Genet, 2010	
3	rs11717195	<i>ADCY5</i>	C	0	C			Yes	Saxena <i>et al.</i> Nat Genet, 2010	No variation in Japanese
3	rs11708067	<i>ADCY5</i>	G	0	A			Yes	Andersson <i>et al.</i> Diabetologia, 2010	No variation in Japanese
3	rs2241766	<i>ADIPOQ</i>	G	0.22	T	Yes	Beltcheva <i>et al.</i> Arch Gynecol Obstet, 2014			
3	rs266729	<i>ADIPOQ</i>	G	0.31	C	Yes	Beltcheva <i>et al.</i> Arch Gynecol Obstet, 2014	Yes	Han <i>et al.</i> Diabetologia, 2011	
8	rs4994	<i>ADRB3</i>	G	0.19	G			Yes	Jing <i>et al.</i> Endocrine, 2012	
20	rs574628	<i>ANGPT4</i>	A	0.37	G			Yes	Miyake <i>et al.</i> J Hum Genet, 2009	
8	rs515071	<i>ANK1</i>	A	0.22	C			Yes	Imamura <i>et al.</i> Hum Mol Genet, 2012	
8	rs516946	<i>ANK1</i>	T	0.16	C			Yes	Morris <i>et al.</i> Nat Genet, 2012	
15	rs2028299	<i>AP3S2</i>	C	0.20	C			Yes	Kooner <i>et al.</i> Nat Genet, 2011	
11	rs1552224	<i>ARAP1</i>	C	0.04	A	Yes	Huerta-Chagoya A <i>et al.</i> PLoS One, 2015	Yes	Voight <i>et al.</i> Nat Genet, 2010	
5	rs702634	<i>ARL15</i>	C	0.12	A			Yes	DIAGRAM Nat Genet, 2014	
16	rs7202877	<i>BCAR1</i>	G	0.21	G			Yes	Morris <i>et al.</i> Nat Genet, 2012	
2	rs243019	<i>BCL11A</i>	T	0.27	C			Yes	MetaboChip®	
2	rs243021	<i>BCL11A</i>	G	0.27	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
2	rs243088	<i>BCL11A</i>	T	0.44	T			Yes	Voight <i>et al.</i> Nat Genet, 2010	
15	rs7163757	<i>C2CD4A</i>	T	0.38	C			Yes	Yamauchi <i>et al.</i> Nat Genet, 2010	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
15	rs7172432	<i>C2CD4A, C2CD4B</i>	G	0.45	A			Yes	Yamauchi <i>et al.</i> Nat Genet, 2010	
10	rs10906115	<i>CDC123, CAMK1D</i>	G	0.49	A			Yes	Shu <i>et al.</i> PLoS Genet, 2010	
10	rs11257655	<i>CDC123, CAMK1D</i>	T	0.41	T			Yes	Voight <i>et al.</i> Nat Genet, 2010	
10	rs12779790	<i>CDC123, CAMK1D</i>	G	0.12	G			Yes	Zeggini <i>et al.</i> Nat Genet, 2008	
6	rs10440833	<i>CDKAL1</i>	A	0.40	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
6	rs7754840	<i>CDKAL1</i>	C	0.41	C	Yes	Zhang <i>et al.</i> Hum Reprod Update, 2013	Yes	Scott <i>et al.</i> Science, 2007	
6	rs7756992	<i>CDKAL1</i>	G	0.46	G	Yes	Cho YM <i>et al.</i> Diabetologia, 2009	Yes	Voight <i>et al.</i> Nat Genet, 2010	
6	rs4712523	<i>CDKAL1</i>	G	0.41	G			Yes	Takeuchi <i>et al.</i> Diabetes, 2009	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
9	rs10811661	<i>CDKN2A, CDKN2B</i>	C	0.48	T	Yes	Cho YM <i>et al.</i> Diabetologia, 2009	Yes	Scott <i>et al.</i> Science, 2007	
9	rs10965250	<i>CDKN2A, CDKN2B</i>	A	0.43	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
9	rs2383208	<i>CDKN2A, CDKN2B</i>	G	0.45	A	Yes	Wang Y <i>et al.</i> PLoS One, 2011	Yes	Takeuchi <i>et al.</i> Diabetes, 2009	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
9	rs13292136	<i>CHCHD9</i>	T	0.13	C			Yes	Voight <i>et al.</i> Nat Genet, 2010	
19	rs10401969	<i>CILP2(SUGPI)</i>	C	0.09	C			Yes	Morris <i>et al.</i> Nat Genet, 2012	
7	rs17168486	<i>DGKB</i>	T	0.41	T			Yes	Dupuis <i>et al.</i> Nat Genet, 2010	
7	rs2191349	<i>DGKB</i>	G	0.27	T			Yes	Dupuis <i>et al.</i> Nat Genet, 2010	
7	rs6960043	<i>DGKB</i>	C/T	0.50	C			Yes	Dupuis <i>et al.</i> Nat Genet, 2010	
X	rs5945326	<i>DUSP9</i>	G	0.38	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
11	rs3740878	<i>EXT2</i>	C	0.36	A			Yes	Takeuchi <i>et al.</i> Diabetes, 2009	
1	rs17106184	<i>FAF1</i>	A	0.06	G			Yes	DIAGRAM Nat Genet, 2014	
12	rs3741872	<i>FAM60A</i>	C	0.27	C			Yes	Miyake <i>et al.</i> J Hum Genet, 2009	
16	rs8050136	<i>FTO</i>	A	0.18	A			Yes	Scott <i>et al.</i> Science, 2007	
16	rs11642841	<i>FTO</i>	A	0.06	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
16	rs9936385	<i>FTO</i>	C	0.12	C			Yes	Voight <i>et al.</i> Nat Genet, 2010	
7	rs17867832	<i>GCC1</i>	G	0.05	T			Yes	Cho <i>et al.</i> Nat Genet, 2012	
7	rs6467136	<i>GCC1</i>	A	0.18	G			Yes	Cho <i>et al.</i> Nat Genet, 2012	
7	rs1799884	<i>GCK</i>	T	0.17	T	Yes	Zhang <i>et al.</i> Hum Reprod Update, 2013			
7	rs4607517	<i>GCK</i>	A	0.20	A	Yes	Mao <i>et al.</i> PLoS One, 2012	Yes	Dupuis <i>et al.</i> Nat Genet, 2010	
2	rs780094	<i>GCKR</i>	C	0.44	C	Yes	Huopio H <i>et al.</i> Eur J Endocrinol, 2013	Yes	Dupuis <i>et al.</i> Nat Genet, 2010	
19	rs8108269	<i>GLPR</i>	T	0.39	G			Yes	Morris <i>et al.</i> Nat Genet, 2012	
9	rs7041847	<i>GLIS3</i>	G	0.47	A			Yes	Cho <i>et al.</i> Nat Genet, 2012	
9	rs11787792	<i>GPSM1</i>	G	0.05	A			Yes	Hara <i>et al.</i> Hum Mol Genet, 2014	

Supplementary Table 1 Cont.

Chr	SNP	Nearby gene	Minor allele	MAF	Risk allele	Candidate gene for GDM	References on GDM	Candidate gene for T2DM	References on T2DM	Reasons for exclusion from our analysis
2	rs13389219	<i>GRB14</i>	T	0.08	C			Yes	Kooner <i>et al.</i> Nat Genet, 2011	
2	rs3923113	<i>GRB14</i>	C	0.09	A			Yes	Kooner <i>et al.</i> Nat Genet, 2011	
10	rs5015480	<i>HHEX</i>	C	0.20	C	Yes	Cho YM <i>et al.</i> Diabetologia, 2009	Yes	Voight <i>et al.</i> Nat Genet, 2010	
10	rs7923837	<i>HHEX</i>	G	0.20	G	Yes	Cho YM <i>et al.</i> Diabetologia, 2009	Yes	Qian <i>et al.</i> PLoS One, 2012	
15	rs7177055	<i>HMG20A</i>	A	0.41	A			Yes	Kooner <i>et al.</i> Nat Genet, 2011	
15	rs7178572	<i>HMG20A</i>	G	0.46	G			Yes	Fukuda <i>et al.</i> PLoS One, 2012	Polymerase chain reaction failures
12	rs2261181	<i>HMGA2(RPSAP52)</i>	T	0.15	T			Yes	Voight <i>et al.</i> Nat Genet, 2010	
12	rs1531343	<i>HMGA2(RPSAP52)</i>	C	0.13	C			Yes	Voight <i>et al.</i> Nat Genet, 2010	
12	rs2612035	<i>HMGA2(RPSAP52)</i>	G	0.13	G			Yes	Voight <i>et al.</i> Nat Genet, 2011	
12	rs12427353	<i>HNF1A</i>	C	0	G			Yes	Langenberg <i>et al.</i> PLoS Med, 2014	No variation in Japanese
17	rs11651755	<i>HNF1B</i>	C	0.29	C			Yes	MetaboChip®	
17	rs11651052	<i>HNF1B</i>	A	0.30	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
17	rs4430796	<i>HNF1B</i>	G	0.36	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
20	rs2144908	<i>HNF4A</i>	A	0.42	A	Yes	Shaat N <i>et al.</i> Diabetologia, 2006	Yes	Chavali <i>et al.</i> J Hum Genet, 2011	
20	rs4812829	<i>HNF4A</i>	A	0.40	A			Yes	Kooner <i>et al.</i> Nat Genet, 2011	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
20	rs6017317	<i>HNF4A</i>	T	0.46	G			Yes	Cho <i>et al.</i> Nat Genet, 2012	
3	rs4402960	<i>IGF2BP2</i>	T	0.30	T	Yes	Mao <i>et al.</i> PLoS One, 2012	Yes	Voight <i>et al.</i> Nat Genet, 2010	
3	rs1470579	<i>IGF2BP2</i>	C	0.33	C			Yes	Saxena <i>et al.</i> Science, 2007	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
3	rs6769511	<i>IGF2BP2</i>	C	0.33	C			Yes	Long <i>et al.</i> Am J Epidemiol, 2012	Polymerase chain reaction failures
2	rs7578326	<i>IRS1</i>	G	0.18	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
2	rs1801278	<i>IRS1</i>	T	0.08	T	Yes	Zhang <i>et al.</i> Hum Reprod Update, 2013	Yes	Alharbi <i>et al.</i> Endocrine, 2014	
2	rs2943640	<i>IRS1</i>	A	0.07	C			Yes	Voight <i>et al.</i> Nat Genet, 2010	
2	rs2943641	<i>IRS1</i>	T	0.07	C			Yes	Rung <i>et al.</i> Nat Genet, 2009	
2	rs7593730	<i>ITGB6-RBMS1</i>	T	0.12	C			Yes	Qi <i>et al.</i> Hum Mol Genet, 2010	
2	rs7569522	<i>ITGB6-RBMS1</i>	A	0.38	A			Yes	Qi <i>et al.</i> Hum Mol Genet, 2010	
7	rs849134	<i>JAZF1</i>	G	0.21	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
7	rs864745	<i>JAZF1</i>	C	0.21	T	Yes	Stuebe AM <i>et al.</i> Am J Perinatol, 2014	Yes	Zeggini <i>et al.</i> Nat Genet, 2008	
7	rs849135	<i>JAZF1</i>	A	0	G			Yes	Langenberg <i>et al.</i> PLoS Med, 2014	No variation in Japanese
11	rs5215	<i>KCNJ11</i>	C	0.34	C			Yes	Scott <i>et al.</i> Science, 2007	
11	rs5219	<i>KCNJ11</i>	T	0.35	T	Yes	Mao <i>et al.</i> PLoS One, 2012	Yes	Sokolova <i>et al.</i> PLoS One, 2014	
6	rs1535500	<i>KCNK17</i>	T	0.40	T			Yes	Cho <i>et al.</i> Nat Genet, 2012	
11	rs231362	<i>KCNQ1</i>	T	0.13	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
11	rs163184	<i>KCNQ1</i>	G	0.42	G	Yes	Huerta-Chagoya A <i>et al.</i> PLoS One, 2015	Yes	Voight <i>et al.</i> Nat Genet, 2010	
11	rs2237892	<i>KCNQ1</i>	T	0.36	C	Yes	Mao <i>et al.</i> PLoS One, 2012	Yes	Yasuda <i>et al.</i> Nat Genet, 2008	
11	rs231361	<i>KCNQ1</i>	C	0.17	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
11	rs2237895	<i>KCNQ1</i>	C	0.3	C	Yes	Mao <i>et al.</i> PLoS One, 2012	Yes	Unoki <i>et al.</i> Nat Genet, 2008	Unique primer design failure
7	rs13233731	<i>KLF14</i>	A	0.29	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
7	rs972283	<i>KLF14</i>	A	0.29	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
12	rs10842994	<i>KLHDC5</i>	T	0.21	T			Yes	Morris <i>et al.</i> Nat Genet, 2012	
12	rs2307027	<i>KRT4</i>	C	0.17	C			Yes	Miyake <i>et al.</i> J Hum Genet, 2009	
4	rs6819243	<i>MAEA</i>	C	0.36	T			Yes	Cho <i>et al.</i> Nat Genet, 2012	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
4	rs6815464	<i>MAEA</i>	G	0.36	C			Yes	Cho <i>et al.</i> Nat Genet, 2012	
18	rs12970134	<i>MC4R</i>	A	0.19	A			Yes	Morris <i>et al.</i> Nat Genet, 2012	
7	rs791595	<i>MIR129-LEP</i>	A	0.10	A			Yes	Hara <i>et al.</i> Hum Mol Genet, 2014	
12	rs4275659	<i>MPHOSPH9(ABCB9)</i>	T	0.33	C			Yes	DIAGRAM Nat Genet, 2014	
11	rs10830963	<i>MTNR1B</i>	G	0.47	G	Yes	Mao <i>et al.</i> PLoS One, 2012	Yes	Dupuis <i>et al.</i> Nat Genet, 2010	
11	rs1387153	<i>MTNR1B</i>	T	0.48	T	Yes	Zhang <i>et al.</i> Hum Reprod Update, 2013	Yes	Voight <i>et al.</i> Nat Genet, 2010	
1	rs10923931	<i>NOTCH2</i>	T	0.02	T			Yes	Zeggini <i>et al.</i> Nat Genet, 2008	
19	rs8182584	<i>PEPD</i>	G	0.36	T			Yes	Cho <i>et al.</i> Nat Genet, 2012	
19	rs3786897	<i>PEPD</i>	G	0.45	A			Yes	Cho <i>et al.</i> Nat Genet, 2012	

Supplementary Table 1 Cont.

Chr	SNP	Nearby gene	Minor allele	MAF	Risk allele	Candidate gene for GDM	References on GDM	Candidate gene for T2DM	References on T2DM	Reasons for exclusion from our analysis
19	rs10425678	PEPD	C	0.27	C			Yes	Cho <i>et al.</i> Nat Genet, 2012	Polymerase chain reaction failures
6	rs3130501	POU5F1	A	0.45	G			Yes	Nair <i>et al.</i> Diabetologia, 2014	Unique primer design failure
3	rs1801282	PPARG	G	0.06	C	Yes	Wu L <i>et al.</i> Sci Rep, 2016	Yes	Saxena <i>et al.</i> Science, 2007	
3	rs13081389	PPARG	G	0.04	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
15	rs12899811	PRCI	A	0.01	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
15	rs8042680	PRCI-ASI	C	0	A			Yes	DIAGRAM Nat Genet, 2014	No variation in Japanese
1	rs2075423	PROX1	T	0.14	G			Yes	Dupuis <i>et al.</i> Nat Genet, 2010	
1	rs340874	PROX1-ASI	C	0.33	C			Yes	Hu <i>et al.</i> PLoS One, 2010	Polymerase chain reaction failures
3	rs12497268	PSMD6(PRICKLE2)	C	0.39	G			Yes	Cho <i>et al.</i> Nat Genet, 2012	
3	rs831571	PSMD6(PRICKLE2)	T	0.31	C			Yes	Cho <i>et al.</i> Nat Genet, 2012	
3	rs13059603	PSMD6(THOC7)	G	0.32	A			Yes	Cho <i>et al.</i> Nat Genet, 2012	
9	rs16927668	PTPRD	T	0.43	T			Yes	Tsai <i>et al.</i> PLoS One, 2010	
9	rs17584499	PTPRD	T	0.15	T			Yes	Tsai <i>et al.</i> PLoS One, 2010	
2	rs7560163	RBM43, RND3	G	0.19	C			Yes	Palmer <i>et al.</i> PLoS One, 2012	
2	rs4410242	RBMS1	A	0.17	G			Yes	MetaboChip®	
17	rs312457	SLC16A13	C	0.07	G			Yes	Hara <i>et al.</i> Hum Mol Genet, 2014	Unique primer design failure
8	rs13266634	SLC30A8	T	0.44	C	Yes	Cho YM <i>et al.</i> Diabetologia, 2009	Yes	Sladek <i>et al.</i> Science, 2007	
8	rs3802177	SLC30A8	A	0.45	G	Yes	Liang Z <i>et al.</i> Diabetes Res Clin Pract, 2010	Yes	Voight <i>et al.</i> Nat Genet, 2010	Gene-based genetic redundancy (pairwise $r^2 > 0.8$)
17	rs391300	SRR	T	0.22	G	Yes	Wang Y <i>et al.</i> PLoS One, 2011	Yes	Tsai <i>et al.</i> PLoS One, 2010	
6	rs9505118	SSRI-RREB1	G	0.41	A			Yes	DIAGRAM Nat Genet, 2014	
3	rs16861329	ST6GAL1	T	0.24	G			Yes	Kooner <i>et al.</i> Nat Genet, 2011	
3	rs17301514	ST6GAL1	A	0.04	A			Yes	Kooner <i>et al.</i> Nat Genet, 2011	
10	rs12255372	TCF7L2	T	0.02	T	Yes	Zhang <i>et al.</i> Hum Reprod Update, 2013	Yes	Tabara <i>et al.</i> Diabetes, 2009	
10	rs7901695	TCF7L2	C	0.04	C	Yes	Huerta-Chagoya A <i>et al.</i> PLoS One, 2015	Yes	Yamauchi <i>et al.</i> Nat Genet, 2010	
2	rs10203174	THADA	T	0.02	C			Yes	Voight <i>et al.</i> Nat Genet, 2010	
2	rs7578597	THADA	C	0.01	T			Yes	Zeggini <i>et al.</i> Nat Genet, 2008	
2	rs11899863	THADA	C	0	C			Yes	Mercader <i>et al.</i> PLoS Genet, 2012	No variation in Japanese
9	rs17791513	TLE4	G	0.08	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
4	rs6813195	TMEM154	T	0.46	C			Yes	DIAGRAM Nat Genet, 2014	
6	rs1800629	TNF	A	0.02	G	Yes	Wu L <i>et al.</i> Sci Rep, 2016	Yes	Boraska <i>et al.</i> BMC Med Genet, 2010	Unique primer design failure
8	rs7845219	TP53INP1	T	0.46	T			Yes	Voight <i>et al.</i> Nat Genet, 2010	
12	rs4760790	TSPAN8, LGR5	A	0.24	A			Yes	Voight <i>et al.</i> Nat Genet, 2010	
12	rs7961581	TSPAN8, LGR5	C	0.23	C	Yes	Stuebe AM <i>et al.</i> Am J Perinatol, 2014	Yes	Zeggini <i>et al.</i> Nat Genet, 2008	
12	rs4760915	TSPAN8, LGR5	T	0.27	T			Yes	MetaboChip®	
12	rs7955901	TSPAN8, LGR5	T	0.30	C			Yes	Voight <i>et al.</i> Nat Genet, 2010	
3	rs7612463	UBE2E2	A	0.15	C	Yes	Kim JY <i>et al.</i> Gynecol Endocrinol, 2013	Yes	Yamauchi <i>et al.</i> Nat Genet, 2010	
3	rs1496653	UBE2E2	G	0.15	A			Yes	Yamauchi <i>et al.</i> Nat Genet, 2010	
3	rs6780569	UBE2E2	A	0.15	G			Yes	Yamauchi <i>et al.</i> Nat Genet, 2010	
10	rs1802295	VPS26A	T	0.12	A			Yes	Kooner <i>et al.</i> Nat Genet, 2011	
10	rs12242953	VPS26A	A	0.05	G			Yes	Kooner <i>et al.</i> Nat Genet, 2011	
4	rs4458523	WFS1	T	0.02	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
4	rs4689388	WFS1	G	0.02	T			Yes	Rung <i>et al.</i> Nat Genet, 2009	
4	rs1801214	WFS1	C	0	T			Yes	Long <i>et al.</i> Am J Epidemiol, 2013	No variation in Japanese
16	rs17797882	WWOX	T	0.21	C			Yes	Sakai <i>et al.</i> PLoS One, 2013	
7	rs10278336	YKT6	G	0.43	A			Yes	Dupuis <i>et al.</i> Nat Genet, 2010	
5	rs4457053	ZBED3	G	0.03	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
5	rs6878122	ZBED3	G	0.02	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
6	rs9470794	ZFAND3	C	0.20	C			Yes	Cho <i>et al.</i> Nat Genet, 2012	
6	rs4299828	ZFAND3(BTBD9)	G	0.06	A			Yes	Cho <i>et al.</i> Nat Genet, 2012	
15	rs11634397	ZFAND6	G	0.09	G			Yes	Voight <i>et al.</i> Nat Genet, 2010	
10	rs12571751	ZMIZ1	G	0.42	G			Yes	Morris <i>et al.</i> Nat Genet, 2012	

The information was retrieved from HapMap JPT as well as previous studies. Chr, Chromosome; SNP, Single nucleotide polymorphism; MAF, Minor allele frequency; T2DM, Type 2 diabetes mellitus; GDM, Gestational diabetes mellitus.

Supplementary Table 2 Primers designed by Assay Design Suite in this study

SNP	Forward primer sequence	Reverse primer sequence	Extension primer sequence
rs10278336	ACGTTGGATGGAACAATCCTGTGGATTGTG	ACGTTGGATGGCACTGTGCTAAAATCCTC	AATCCTCATATGATTGAAAGG
rs10811661	ACGTTGGATGGTCAATAAGCGTCTTGCCC	ACGTTGGATGGATCAGGAGGGTAATAGAC	cccgtAGGGTAATAGACTTACTGTCATG
rs10830963	ACGTTGGATGAGGTCACTCTGTCTATGCTG	ACGTTGGATGCCAGGCAGTTACTGGTTCT	gggcGGCAGTTACTGGTTCTGGATAG
rs10906115	ACGTTGGATGATTGAGGACTCCGTTTGGC	ACGTTGGATGGTTACGTGTATGCGATCCC	cgggACGTGTATGCGATCCCAAGTTTG
rs11257655	ACGTTGGATGTGCAAAAGCACCTACTGCTTC	ACGTTGGATGCCACGGAGATGGTTTCAATG	ttaaGGTTTCATGCCAGTA
rs12497268	ACGTTGGATGAGGCACCCCTTGAAAAACA	ACGTTGGATGAAAACCTGATAGTAGATGCTG	GCTTGATCAGAGCAGGA
rs12571751	ACGTTGGATGGGTGTGTGCATGGTACGTAT	ACGTTGGATGAAACACCTACAGACCCGAG	ttgGGAGGAGGAAAACAGTG
rs13059603	ACGTTGGATGTGACAGACTGCTCAAGCTAC	ACGTTGGATGGTCTCAGTCTCTTCAGATAA	cTTTAAAAATACAACTAATGCTTTC
rs13266634	ACGTTGGATGGCAATCAGTGCTAATCTCCC	ACGTTGGATGTTTCTCTCCGAACCACTTG	tctccCACTTGGCTGTCCC
rs1387153	ACGTTGGATGCTCTCTCTAGAGCTCACAAC	ACGTTGGATGTGTCTGTGGAATGCTAGCAA	CTTTTACAGATAAGAAAATTGAGTT
rs1535500	ACGTTGGATGAGAGATGGGGATCTTCTGAG	ACGTTGGATGAGCTCTGGCTGCTCAGTAGG	aGCGTCAAGGATGGGG
rs163184	ACGTTGGATGTTTGCTCAGTAACGGACTGG	ACGTTGGATGGGTAAAGTGTCTGTGAAAAG	ccGGGGCAAGGGTGGAG
rs16927668	ACGTTGGATGCCATTTTGTGGCCTGTTGG	ACGTTGGATGCACTCTTCAGAACTGGAAGG	gaagaTTCAGAACTGGAAGGAATAGG
rs17168486	ACGTTGGATGGCACCGTGAGGGATATTAAG	ACGTTGGATGTGTCTGATCTGGTTGATCTT	cctgcTCTTGGCAATTTGACACC
rs2144908	ACGTTGGATGACCACGTGCATTGCAAAGAC	ACGTTGGATGCCTGACTAGAGTCAGGAGAT	TCTGTCATTCCCTGGC
rs2237892	ACGTTGGATGCAGATGATGGGAGCTGTAC	ACGTTGGATGTAAGGCATCTGGTGGAGAGG	CTAGGCCCTCACCCC
rs243088	ACGTTGGATGTGAGAGTAGGGTAGGAACAC	ACGTTGGATGTGTGAAAAGGGTAGCTCCG	tGGTAGCTCCGAGAAGA
rs266729	ACGTTGGATGATGTGTGGCTTGCAAGAACC	ACGTTGGATGTGGACTTCTTGGCACGCTC	CGCTCATGTTTGTGTTTGAAG
rs3740878	ACGTTGGATGCAAAAACATACCTGGCTGTC	ACGTTGGATGCACAAAAGATGCAGTGTGG	ccggCACAAGCATGATTTATTGTCTT
rs3786897	ACGTTGGATGAAGCCATCCTGGAAGACCTG	ACGTTGGATGATCTGCATAGGACAGCCCCA	ggagGCCTGGGCTGAGCCCTGAG
rs4275659	ACGTTGGATGAGAGGTGATAAGACTGCTG	ACGTTGGATGTGCTGACGCATGTAAGTGCC	AGACTGCTGAGGCTAA
rs4402960	ACGTTGGATGAGCAGTAAGGTAGGATGGAC	ACGTTGGATGTGGGGCATGTTTGCAAACAC	ggtggGCAAACACAATCAGTATCTT
rs4430796	ACGTTGGATGTGAATACAGAGAGGCAGCAC	ACGTTGGATGCAAGACCCAACAACGCTTG	gggagAGGCAGCACAGACTGGA
rs4607103	ACGTTGGATGTCTAATTCCTCAGGCCAG	ACGTTGGATGGTGTGTACCAAGGACATCCA	AGGCCAGCAGGTTT
rs5215	ACGTTGGATGCTGTGGTCTCTCAAGCTG	ACGTTGGATGACGGACGTTACTCTGTGGAC	GTGTGGGCACCTTTGA
rs5219	ACGTTGGATGTGTTCTTGTGGGCCACGTTG	ACGTTGGATGGCATCATCCCCGAGGAATA	gagaCACGGTACCTGGGCT
rs574628	ACGTTGGATGCTCTTGACCCCATCAAAAG	ACGTTGGATGTCTCAGTGCCTAATCCGGAG	CCACATCAAAGGTCAGG
rs5945326	ACGTTGGATGCAGGGATCTCAGGCTCTTTA	ACGTTGGATGTGTCTCCAGGGCTTTGCAC	GGGGCCGTAGCAATG
rs6017317	ACGTTGGATGAAGAAAAGGCAAGGATCTG	ACGTTGGATGTGGCCATTCTATGTTGTC	TCTATGTTGTCTGTTTGTAG
rs6813195	ACGTTGGATGGGGAGAGGAAGCAAGTAAAC	ACGTTGGATGATGGCAACCACACTCCTGCT	gaggGTAAATACTGGCCTTGC
rs6815464	ACGTTGGATGTCTGCACACATCCTGCTTAG	ACGTTGGATGAGCTCTCACGAGGAAGCAAT	cgggCCGATACCTGTACCCCGGGTTTTG
rs6960043	ACGTTGGATGCCCTTTTGGACTAATAGCTG	ACGTTGGATGGCCCTTGAATGTGAGTTTA	AACCTGCTGTCTCA
rs7041847	ACGTTGGATGGATGCCGGGTGTAAATCAC	ACGTTGGATGCCACCTCATCGCATACATT	TCCTTCCCTTGACCA
rs7172432	ACGTTGGATGCTTTGGGAGATAGGTTCTGC	ACGTTGGATGGCTTAAAGAGGGCTTGGG	AGACAGTTTCTTTGGGAA
rs7177055	ACGTTGGATGCACAGCTTCTACCTTACGTG	ACGTTGGATGCTAGGAGACATCTTACCTG	ccccCCTTACGTGCTGAGAC
rs7569522	ACGTTGGATGCTGTCCCAAATGCTTTCAG	ACGTTGGATGGCCAGTGCATGTATGTAAAT	GTAATAGTTATGGGGATTGAAATA
rs7754840	ACGTTGGATGATCAACTGCTTGTGTTGGG	ACGTTGGATGCAGAGACATCACTGTCTTTT	AAATCCTCTATCAAGTCAAC
rs7756992	ACGTTGGATGGACAATTAATATCCCCCTG	ACGTTGGATGATGCAACCAAGAGAGGTCTG	cattaCCCCCTGATTTTAGTTTT
rs780094	ACGTTGGATGAGGGCCCCAGTTTTTTAGAC	ACGTTGGATGCCCGGCCTCAACAAATGTAT	cttgTAGACCATGACTGACACAT
rs7845219	ACGTTGGATGTTCTTTGGGCTTCGTGTTCC	ACGTTGGATGACCCCTATTGTGGAGCTCTA	CTTCGTGTTCCATTATTCTGAA
rs7955901	ACGTTGGATGATGCATTCATAGACACCACC	ACGTTGGATGTGTTGTGTACATGCACTGGG	gggagGGGAGCCCAAGTGGTT
rs8108269	ACGTTGGATGGGGTCTGATTTCAACACCT	ACGTTGGATGCCCCATTTCTGGATAGGGA	ttAGACATGTCACCCTGA
rs8182584	ACGTTGGATGGCATGACGACAAACACAGAC	ACGTTGGATGTGTCTATTTCAGGCACTCG	GCACTCGGAGCCTCAG
rs831571	ACGTTGGATGGACAAGGCTATTCCATCCTC	ACGTTGGATGGTGACCTAGAGATAGGGCTG	TCTTGACAACAAGATAGGCTTTA
rs9505118	ACGTTGGATGACTTGGTTATTGTACTGCTG	ACGTTGGATGCAGCAGTTTAAAGCGTTTAC	ACTGCTGAAGACACC

SNP, Single nucleotide polymorphism.

Supplementary Table 3 Association analysis results between single nucleotide polymorphisms and the risk of gestational diabetes mellitus

	SNP	Chr	Nearby gene	Insulin sensitivity	Insulin secretion	Risk allele	Japanese major allele	Japanese minor allele	RAF in this study		The present study	
									GDM	NGT	p-value	OR (95%CI)
1	rs266729	3	<i>ADIPOQ</i>	Yes		C	C	G	0.79	0.69	0.013	1.56 (1.10-2.23)
2	rs10811661	9	<i>CDKN2A/2B</i>		Yes	T	T	C	0.58	0.49	0.035	1.46 (1.03-2.08)
3	rs9505118	6	<i>SSR1-RREB1</i>		Yes	A	A	G	0.58	0.50	0.046	1.41 (1.01-1.97)
4	rs7177055	15	<i>HMG20A</i>		Yes	A	G	A	0.39	0.32	0.064	1.41 (0.98-2.01)
5	rs16927668	9	<i>PTPRD</i>	Yes		T	T	C	0.55	0.48	0.083	1.34 (0.96-1.87)
6	rs1535500	6	<i>KCNK17</i>			T	G	T	0.38	0.31	0.087	1.35 (0.96-1.89)
7	rs574628	20	<i>ANGPT4</i>	Yes		G	G	A	0.59	0.64	0.165	0.77 (0.53-1.12)
8	rs5219	11	<i>KCNJ11</i>		Yes	T	C	T	0.36	0.41	0.245	0.81 (0.57-1.15)
9	rs4430796	17	<i>HNF1B</i>		Yes	G	A	G	0.31	0.35	0.279	0.82 (0.56-1.18)
10	rs1387153	11	<i>MTNR1B</i>		Yes	T	C	T	0.49	0.45	0.280	1.21 (0.86-1.71)
11	rs6815464	4	<i>MAEA</i>	Yes		C	C	G	0.68	0.64	0.282	1.22 (0.85-1.77)
12	rs8182584	19	<i>PEPD</i>	Yes		T	T	G	0.62	0.67	0.284	0.83 (0.58-1.17)
13	rs12497268	3	<i>PSMD6(PRICKLE2)</i>			G	G	C	0.65	0.60	0.312	1.19 (0.85-1.67)
14	rs2237892	11	<i>KCNQ1</i>		Yes	C	C	T	0.63	0.67	0.326	0.84 (0.59-1.20)
15	rs6813195	4	<i>TMEM154</i>		Yes	C	T	C	0.48	0.44	0.341	1.18 (0.84-1.64)
16	rs6017317	20	<i>HNF4A</i>		Yes	G	G	T	0.52	0.56	0.357	0.86 (0.62-1.19)
17	rs5215	11	<i>KCNJ11</i>		Yes	C	T	C	0.38	0.42	0.393	0.86 (0.61-1.22)
18	rs2144908	20	<i>HNF4A</i>		Yes	A	G	A	0.46	0.48	0.425	0.86 (0.60-1.24)
19	rs163184	11	<i>KCNQ1</i>		Yes	G	T	G	0.48	0.45	0.430	1.14 (0.82-1.59)
20	rs13059603	3	<i>THOC7</i>			A	A	G	0.66	0.63	0.446	1.14 (0.81-1.61)
21	rs10278336	7	<i>YKT6</i>			A	A	G	0.67	0.70	0.446	0.87 (0.61-1.24)
22	rs7041847	9	<i>GLIS3</i>		Yes	A	G	A	0.47	0.44	0.506	1.12 (0.80-1.57)
23	rs780094	2	<i>GCKR</i>	Yes		G	A	G	0.44	0.47	0.512	0.90 (0.64-1.25)
24	rs17168486	7	<i>DGKB</i>		Yes	T	C	T	0.39	0.41	0.598	0.91 (0.65-1.28)
25	rs10906115	10	<i>CDC123, CAMK1D</i>		Yes	A	A	G	0.58	0.56	0.642	1.08 (0.79-1.48)
26	rs8108269	19	<i>GIPR</i>	Yes		G	G	T	0.68	0.66	0.645	1.09 (0.76-1.56)
27	rs4275659	12	<i>MPHOSPH9(ABCB9)</i>			C	C	T	0.71	0.70	0.687	1.08 (0.74-1.57)
28	rs4607103	3	<i>ADAMTS9</i>	Yes		C	C	T	0.61	0.62	0.716	0.94 (0.67-1.32)
29	rs7754840	6	<i>CDKAL1</i>		Yes	C	G	C	0.45	0.44	0.737	1.06 (0.77-1.45)
30	rs12571751	10	<i>ZMIZ1</i>			G	A	G	0.45	0.46	0.738	0.95 (0.69-1.31)
31	rs5945326	X	<i>DUSP9</i>	Yes		A	A	G	0.65	0.66	0.769	0.95 (0.68-1.35)
32	rs7955901	12	<i>TSPAN8, LGR5</i>		Yes	C	C	T	0.68	0.69	0.807	0.96 (0.66-1.38)
33	rs7845219	8	<i>TP53INP1</i>		Yes	T	C	T	0.31	0.32	0.814	0.96 (0.67-1.37)
34	rs243088	2	<i>BCL11A</i>	Yes		T	A	T	0.32	0.33	0.830	0.96 (0.68-1.36)
35	rs7172432	15	<i>C2CD4A/4B</i>		Yes	A	A	G	0.59	0.58	0.852	1.03 (0.75-1.41)
36	rs3740878	11	<i>EXT2</i>		Yes	A	A	G	0.63	0.64	0.876	0.97 (0.68-1.38)
37	rs10830963	11	<i>MTNR1B</i>		Yes	G	C	G	0.48	0.47	0.880	1.03 (0.73-1.45)
38	rs11257655	10	<i>CDC123, CAMK1D</i>		Yes	T	C	T	0.47	0.46	0.882	1.03 (0.73-1.44)
39	rs7756992	6	<i>CDKAL1</i>		Yes	G	A	G	0.49	0.48	0.893	1.02 (0.75-1.39)
40	rs831571	3	<i>PSMD6(PRICKLE2)</i>			C	C	T	0.67	0.32	0.918	1.02 (0.72-1.44)
41	rs6960043	7	<i>DGKB</i>		Yes	C	C	T	0.51	0.51	0.931	0.99 (0.71-1.38)
42	rs13266634	8	<i>SLC30A8</i>		Yes	C	C	T	0.61	0.61	0.961	0.99 (0.71-1.38)
43	rs7569522	2	<i>ITGB6-RBMS1</i>	Yes		A	G	A	0.34	0.34	0.963	1.01 (0.72-1.42)
44	rs3786897	19	<i>PEPD</i>	Yes		A	A	G	0.58	0.58	0.982	1.00 (0.70-1.44)
45	rs4402960	3	<i>IGF2BP2</i>		Yes	T	G	T	0.32	0.31	0.987	1.00 (0.69-1.45)

SNP, Single nucleotide polymorphism; Chr, Chromosome; GDM, Gestational diabetes mellitus; RAF, Risk allele frequency; OR, Odds ratio; CI, confidence interval.

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