Replication of previous genome-wide association studies of HKDC1, BACE2, SLC16A11 and TMEM163 SNPs in a gestational diabetes mellitus case–control sample from Han Chinese population

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Background: Four novel glucose metabolism risk loci (HKDC1 rs4746822, BACE2 rs6517656, SLC16A11 rs13342232 and TMEM163 rs998451) were identified in recent genome-wide association studies (GWAS) of Afro-Caribbean, European, Hispanic, Thai, Mexican, Latin American and Indian populations. None of the abovementioned SNPs has been reported in a Han Chinese population.

Aim: To replicate the relationships between HKDC1 rs4746822, BACE2 rs6517656, SLC16A11 rs13342232 and TMEM163 rs998451 with gestational diabetes mellitus (GDM) in a Han Chinese population.

Methods: This was a case–control study which enrolled 334 pregnant women with GDM and 367 pregnant women with normal glucose tolerance. The linear regression and logistic regression were used to estimate the association between SNPs with the risk of GDM, HOMA-IR and fasting insulin levels. The fasting insulin concentration and HOMA-IR were log10 transformed before analysis.

Results: No significant differences in the alleles and genotypes of SLC16A11 rs13342232, HKDC1 rs4746822 and BACE2 rs6517656 were observed between cases and controls. After adjusting the weekly BMI growth, pre-pregnancy BMI and maternal age, under the additive model, SLC16A11 rs13342232 was associated with log10 fasting serum insulin (Beta=-0.046, p=0.016), log10 HOMA-IR level (Beta=-0.061, p=0.003) and fasting plasma glucose level (Beta=0.016, p=0.011); HKDC1 rs4746822 was associated with OGTT 2-hr plasma glucose level (Beta=0.023, p=0.016) and BACE2 rs6517656 was associated with log10 fasting serum insulin (Beta=-0.053, p=0.044) and log10 HOMA-IR level (Beta=-0.060, p=0.048). After correction for multiple testing, the associations of SLC16A11 and HKDC1 with glucose metabolism remained statistically significant. The A allele of TMEM163 rs998451 was not detected in this population.

Conclusion: HKDC1 rs4746822, BACE2 rs6517656 and SLC16A11 rs13342232 are associated with glucose metabolism in pregnant women of Han Chinese.

Keywords: gestational diabetes mellitus, SLC16A11, HKDC1, BACE2, TMEM163

Introduction
Gestational diabetes mellitus (GDM) is defined as glucose intolerance first detected during pregnancy.1 It is estimated by the International Diabetes Federation that 21.3 million women (16.2% of live births) in 2017 had some form of hyperglycemia in pregnancy, and of these, 86.4% were due to GDM.2 During pregnancy, insulin
resistance is enhanced physiologically and can be further promoted by other factors such as obesity, leading to a high risk of GDM.3-5 Genome-wide association studies (GWAS) have led to the identification of 8 common-penetrance loci (CDKAL1, GCKR, G6PC2, PCSK1, PPAR3B, MTNR1B, HKDC1 and BACE2) for GDM, principally through 2 GWAS carried out among women of Afro-Caribbean, European, Hispanic, Thai and Korean descent.6,7 In replication studies, most (but not all) risk alleles have been shown to confer similar effects in different ethnic populations.8-16

The study by Hayes et al identified two novel significant genome-wide associations: 2-hr plasma glucose with HKDC1 rs5030937 and rs4746822 (top associated SNP) and fasting C-peptide with BACE2 rs6517656 in women with hyperglycemia and adverse pregnancy outcomes (HAPO).6 HKDC1 encodes hexokinase domain containing 1 and is a member of the hexokinase family.17 A follow-up study to the GWAS demonstrated that hexokinase domain containing 1 has hexokinase activity and that lower levels of HKDC1 expression are associated with higher levels of maternal 2-hr glucose.18 In the only replication study of this locus, the T allele of HKDC1 rs4746822 showed a significant association with GDM in a south Indian population.8 BACE2, which encodes β-site amyloid polypeptide cleaving enzyme 2, is expressed in human pancreatic beta cells, where its protein product is located in endocytic vesicles and has been shown to both augment and inhibit insulin secretion and/or production in human islet.19,20 BACE2 rs6517656 has not been studied in different ethnic GDM populations.

In this replication study, we not only analyzed the association between HKDC1 rs4746822 and BACE2 rs6517656 with GDM risk but also included two genes which were revealed to be significantly genome-wide associated with Type 2 diabetes mellitus (T2DM). The SIGMA Type 2 Diabetes Consortium analyzed 9.2 million SNPs in Mexican and Latin American populations and identified a novel locus associated with T2DM at chromosome 2q21. The strongest signal on the newly identified locus 2q21 mapped to TMEM163, which encodes a probable vesicular transporter in nerve terminals. The association of TMEM163 variants (rs6723108 and rs998451) with reduced fasting plasma insulin levels and Homeostasis model assessment of insulin resistance (HOMA-IR) indicates that it might modulate susceptibility to T2DM by affecting insulin secretion.23 The association between specific gene with the risk of the same disease may vary among different races. Therefore, the results of GWAS need to be verified in different ethnic groups, especially when GWAS did not include these ethnic groups. To the best of our knowledge, there have been no association studies on the association between HKDC1 rs4746822, BACE2 rs6517656, SLC16A11 rs13342232 and TMEM163 rs998451 with GDM risk in a Chinese population to date. Therefore, we aimed to study the associations between the 4 newly identified glucose metabolism GWAS SNPs with GDM risk in a Han Chinese population.

Materials and methods

Ethics statement

The “Central-South University’s Ethical and Confidentiality Committee” reviewed and approved the study protocol (document reference number: CTTYX-13003). We got written informed consent from all participants. This study was conducted in accordance with the Declaration of Helsinki.

Study design and statistical analysis

The research population and most part of the statistical methods of this study were completely consistent with our previous articles,24,25 so the same content is not repeated here (Full version of the materials and methods are available as supplementary file). Briefly, this was a case-control study which enrolled 334 pregnant women with GDM and 367 pregnant women with normal glucose tolerance who visited prenatal clinics regularly and underwent oral glucose tolerance test (OGTT) during 24–28 weeks. The boundaries of OGTT were 5.1 mmol/L, 10.0 mmol/L and 8.5 mmol/L for fasting glucose and 1 and 2 hrs after 75 g oral glucose intake. When one or more OGTT indicators reached or exceeded the above-mentioned boundaries, the pregnant woman was diagnosed with GDM. The following information were collected on the OGTT morning: maternal age, gestational age, parity, height, weight, fasting insulin levels, systolic blood pressure and diastolic blood pressure. We also collected the information of family diabetes history. Relatives included the paternal grandfather, paternal grandmother, maternal grandfather, maternal grandmother, father, mother, brothers, sisters, and brothers and
sisters of the father and mother. One or more relatives were diagnosed with diabetes and the pregnant woman was judged to have a family history of diabetes. Positive family diabetes history rate=number of cases (controls) with family diabetes history/number of cases (controls), we calculated the positive rate in cases and controls, respectively.

Four SNPs (HKDC1 rs4746822, BACE2 rs6517656, SLC16A11 rs13342232 and TMEM163 rs998451) were genotyped in this study. Genomic DNA was extracted from whole blood using a TIANamp Blood DNA Kit (DP318-03, TIANGEN, Beijing), which is based on silica membrane technology and uses a special buffer system for DNA extraction from fresh or frozen whole blood. SNPs were genotyped with the SEQUENOM MassARRAY iPLEX platform. The assay consists of an initial locus-specific PCR reaction, followed by single-base extension and matrix-assisted laser desorption/ionization–time of flight mass spectrometry to identify the SNP allele.

Table 1 shows the functional consequence, alleles, HWE p-value of controls and the MAF of Han Chinese from HapMap project of the SNPs.

Table 2 shows the 5’ UTR and 3’ UTR region primers of the SNPs in PCR reaction.

The chi-square test was used to compare the distribution of genotypes between the case and control groups. In the analysis of the association between SNPs and disease risk, GWAS used additive models to assign the SNPs (wild-type homozygotes=0, heterozygous assignments=1, and mutant homozygotes=2, continuity variable). Therefore, this study also used the additive model to analyze the association between SNPs and GDM risk and glucose metabolism levels. Logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of each SNP adjusted by maternal age, pre-pregnancy BMI and weekly BMI growth. Linear regression was used to estimate the relationship between SNPs and the OGTT, fasting insulin and HOMA-IR levels, adjusted by maternal age, pre-pregnancy BMI and weekly BMI growth. HOMA-IR=Fasting insulin (mIU/L)*fasting blood glucose (mmol/L)/22.5. The fasting insulin concentration and HOMA-IR were log10 transformed before analysis. Weekly BMI growth=(BMI on the OGTT morning-pre-pregnancy BMI)/gestational age (weeks). The fasting insulin concentration and HOMA-IR were log10 transformed before analysis. Three SNPs were finally included in the analysis; therefore, \( \alpha \) was equal to 0.017 (0.017=0.05/3).

Results
Base information
Table 3 shows the cases’ and controls’ clinical characteristics. Positive family diabetes history rate \( (p<0.001) \), weekly BMI growth \( (p<0.001) \), pre-pregnancy BMI \( (p<0.001) \), diastolic blood pressure \( (p<0.001) \) and systolic blood pressure \( (p<0.001) \) were higher in case group than control group.

Hardy–Weinberg equilibrium
The SNP genotyping detection rate was 99.5%. Hardy–Weinberg equilibrium (HWE) was observed in the control group for all SNPs.

Table 1 The functional consequence, alleles, HWE p-value of controls and the MAF of Han Chinese from HapMap project of the SNPs

Table 2 The 5’ UTR and 3’ UTR region primers of the SNPs in PCR reaction
Association between alleles and genotypes with GDM

As shown in Table 4, no significant differences in the alleles and genotypes of SLC16A11 rs13342232, HKDC1 rs4746822 and BACE2 rs6517656 were observed between cases and controls; after adjusting for the weekly BMI growth, pre-pregnancy BMI and maternal age, the results were the same (Table 5). The A allele of TMEM163 rs998451 was not detected in this population.

Association analysis of genetic variants in SLC16A11 rs13342232, HKDC1 rs4746822 and BACE2 rs6517656 with OGTT, HOMA-IR and fasting serum insulin levels

Besides the fasting plasma glucose level, 1 hr and 2 hrs plasma glucose levels after oral glucose intake, the fasting plasma insulin and HOMA-IR levels are also important to evaluate the level of glucose metabolism. The results of Hayes et al GWAS\(^6\) that needed to be replicated were the relationships assessed with linear regressions between genotypes and glycemic traits. Therefore, in this study, we not only analyzed the association between the SNPs and GDM risk but also analyzed the association between the SNPs and glycemic traits (fasting plasma insulin levels, etc.).

As shown in Table 5, the results of the linear regression analysis revealed that under the additive model, SLC16A11 rs13342232 was associated with fasting plasma glucose levels ($\beta=0.164$, $p=0.011$), log\(_{10}\)fasting serum insulin levels ($\beta=0.046$, $p=0.016$) and log\(_{10}\)HOMA-IR levels ($\beta=0.061$, $p=0.003$); HKDC1 rs4746822 was associated with OGTT 2-hr plasma glucose levels ($\beta=0.239$, $p=0.016$); and BACE2 rs6517656 was associated with log\(_{10}\)fasting serum insulin levels ($\beta=−0.053$, $p=0.044$) and log\(_{10}\)HOMA-IR levels ($\beta=−0.060$, $p=0.048$), after adjusting for the weekly BMI growth, pre-pregnancy BMI and maternal age. The $p$-values of the associations between SLC16A11 rs13342232 with fasting plasma glucose levels ($p=0.011$), log\(_{10}\)fasting serum insulin levels ($p=0.016$) and log\(_{10}\)HOMA-IR levels ($p=0.003$); and between HKDC1 rs4746822 with OGTT 2-hr plasma glucose levels ($p=0.016$) were lower than the $\alpha$ value ($\alpha=0.017$) after correction for multiple testing. We inferred that the SLC16A11 rs13342232 G allele, the HKDC1 rs4746822 T allele and the BACE2 rs6517656 G allele may be risk alleles for glucose metabolism in pregnant Chinese women.

Discussion

In this study, we identified six significant associations: fasting plasma glucose with SLC16A11 rs13342232, 2-hr plasma glucose with HKDC1 rs4746822, fasting serum insulin and HOMA-IR levels with SLC16A11 rs13342232 and BACE2 rs6517656 in a pregnant Han Chinese population. The A allele of TMEM163 rs998451 was not detected in this population.

In their GWAS, Hayes et al identified two novel genome-wide significant associations: 2-hr plasma glucose with HKDC1 rs4746822 and fasting C-peptide with BACE2
rs6517656 in pregnant women of Afro-Caribbean, European, Hispanic and Thai ancestry. Our results show that the T allele of HKDC1 rs4746822 is associated with higher 2-hr plasma glucose; the G allele of BACE2 rs6517656 is associated with higher fasting serum insulin and higher HOMA-IR levels. We did not measure C-peptide; however, previous study revealed that peripheral insulin and C-peptide concentrations correlated well with each other.

Our results indicate that the T allele of HKDC1 rs4746822 and the G allele of BACE2 rs6517656 are not only associated with glucose metabolism in HAPO population but also associated with glucose metabolism in pregnant women of Han Chinese. Several studies have explored possible mechanisms by which HKDC1 and BACE2 affect glucose metabolism. In the follow-up study to the GWAS, the authors demonstrated that HKDC1 is a novel human hexokinase gene. HKDC1 rs4746822 lies within a region of the genome exhibiting chromatin modifications consistent with active gene regulation across diverse tissues. HKDC1 rs4746822 influences maternal glucose metabolism by altering the activity of regulatory elements that control HKDC1 expression. BACE2 (Beta-Site APP-Cleaving Enzyme 2, 21q22.3) encodes an integral membrane glycoprotein cleaving the amyloid

### Table 4 The distribution of alleles and genotypes of rs13342232, rs4746822, rs6517656 and rs998451

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### Table 5 The association of rs13342262, rs4746822 and rs6517656 with GDM risk, OGTT, fasting insulin and HOMA-IR levels

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<th>p</th>
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<th>log₁₀ Fasting insulin</th>
<th>log₁₀ HOMA-IR</th>
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<td>(0.496,1.496)</td>
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<td>-0.086</td>
<td>0.377</td>
<td>-0.207</td>
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Note: Covariates in the logistic regression analyses and linear regression analyses were maternal age, pre-pregnancy BMI and weekly BMI growth. Bold font means the p-value was less than 0.05.

Abbreviations: BG, blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance.
precursor protein into the amyloid beta peptide. In the normal human pancreas, BACE2 expression was restricted to beta-cells, where it is located in endocytic vesicles. When BACE2 was pharmacologically inhibited, BACE2 content in clathrin-coated vesicles was increased. The insulin internalization rate was reduced, insulin receptor beta-subunit (IR beta) expression was decreased at the plasma membrane and increased in the Golgi apparatus, and a significant reduction in insulin gene expression was detected. Similar results were obtained after specific BACE2 silencing in MIN6 cells. All these data point to a role for BACE2 in IR beta trafficking and insulin signaling. Esterhazy et al identified BACE2 as the sheddase of the pro-proliferative plasma membrane protein Tmem27 in murine and human β cells. Mice with functionally inactive BACE2 exhibit reduced blood glucose levels, improved intraepithelial glucose tolerance and increased β cell mass. Pharmacological inhibition of BACE2 increases β cell mass and improves glycemic control in mice with obesity-related insulin resistance.

In the previous replication study of SLC16A11 rs13342232, the authors did not analyze the association between SLC16A11 rs13342232 and glucose metabolism indicators and indicated that SLC16A11 rs13342232 is not associated with GDM in Mexican women. Our study also showed negative results when we compared cases and controls with logistic regression analysis; however, we showed that the A allele of SLC16A11 rs13342232 is associated with higher fasting plasma glucose, higher fasting serum insulin and higher HOMA-IR levels with linear regression analysis. SLC16A11 is a proton-coupled monocarboxylate transporter. The T2DM risk coding variants (including rs13342232) disrupt protein–protein interactions responsible for correct SLC16A11 function to affect the amount of SLC16A11 transport activity.

In this study, the A allele of TMEM163 rs998451 was not detected in Han Chinese population. According to the search results of the SNPedia website (https://www.snpedia.com/index.php/Rs998451), only the CEU European population from the HapMap project has been able to identify a population with the A allele present for the SNP rs998451; The A allele was not present in Han Chinese and other east Asian populations.

To the best of our knowledge, this is the first study that has focused on the associations between SLC16A11 rs13342232, HKDC1 rs4746822 and BACE2 rs6517656 with glucose metabolism in a Han Chinese population. However, this study has certain limitations. First, we did not obtain any positive results in the logistic regression analysis comparing cases and controls, which may be due to an insufficient sample size. It is necessary to increase the sample size in subsequent studies to verify the results. Second, the association between these SNPs and other important glucose metabolism indicators, such as C-peptide, 1-hr serum insulin, 2-hr serum insulin, etc., needs further study in pregnant women of Han Chinese.

**Acknowledgments**

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**Disclosure**

The authors report no conflicts of interest in this work.

**References**


