Positive Association Between Type 2 Diabetes Risk Alleles Near CDKAL1 and Reduced Birthweight in Chinese Han Individuals

Xiao-Fang Sun1,2, Xin-Hua Xiao1, Zhen-Xin Zhang1, Ying Liu1, Tao Xu1, Xi-Lin Zhu1, Yun Zhang1, Xiao-Pan Wu1, Wen-Hui Li1, Hua-Bing Zhang1, Miao Yu1
1Department of Endocrinology, Key Laboratory of Endocrinology, Ministry of Health, Peking Union Medical College Hospital, Diabetes Research Center of Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
2Department of Endocrinology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, China

Abstract

Background: Fetal insulin hypothesis was proposed that the association between low birth weight and type 2 diabetes is principally genetically mediated. The aim of this study was to investigate whether common variants in genes CDKAL1, HHEX, ADCY5, SRR, PTPRD that predisposed to type 2 diabetes were also associated with reduced birthweight in Chinese Han population.

Methods: Twelve single nucleotide polymorphisms (rs7756992/rs10946398 in CDKAL1, rs1111875 in HHEX, rs391300 in SRR, rs17584499 in PTPRD, rs1170806/rs9883204/rs4678017/rs9881942/rs7641344/rs677397/rs6226243 in ADCY5) were genotyped in 1174 unrelated individuals born in Peking Union Medical College Hospital from 1921 to 1954 by TaqMan allelic discrimination assays, of which 645 had normal glucose tolerance, 181 had developed type 2 diabetes and 348 impaired glucose regulation. Associations of these 12 genetic variants with birthweight and glucose metabolism in later life were analyzed.

Results: Birthweight was inversely associated with CDKAL1-rs10946398 (β = −41 g [95% confidence interval [CI]: −80, −3], P = 0.034), common variants both associated with increased risk of impaired glucose metabolism and decreased insulin secretion index later in life. After adjusting for sex, gestational weeks, parity and maternal age, the risk allele of CDKAL1-rs7756992 was associated with reduced birthweight (β = −36 g [95% CI: −72, −0.2], P = 0.048). The risk allele in SRR showed a trend toward a reduction of birthweight (P = 0.085).

Conclusions: This study identified the association between type 2 diabetes risk variants in CDKAL1 and birthweight in Chinese Han individuals, and the carrier of risk allele within SRR had the trend of reduced birthweight. This demonstrates that there is a clear overlap between the genetics of type 2 diabetes and fetal growth, which proposes that lower birth weight and type 2 diabetes may be two phenotypes of one genotype.

Key words: Birthweight; Chinese Han; Genetic Polymorphisms; Impaired Glucose Metabolism

INTRODUCTION

Recently, a series of epidemiological studies have found that reduced birthweight was associated with impaired glucose tolerance and type 2 diabetes later in life. But the pathogenic mechanisms behind this association are poorly understood. There are two explanations for it, which are “thrifty phenotype hypothesis” and “fetal insulin hypothesis. Insulin is important for fetal growth and metabolism throughout life.

Fetal insulin hypothesis was proposed that the association between low birth weight and type 2 diabetes is principally genetically mediated. Genetic variants affecting pancreatic beta cell function or insulin sensitivity result in low-insulin mediated fetal growth (that is low birth weight) and the risk of type 2 diabetes in later life.[1]

In recent years, many international studies on the association between birth weight and type 2 diabetes risk gene variants have been reported, which are strong evidence of a fetal insulin hypothesis. As we known, there is a racial difference...
in gene polymorphisms. To explore the low birth weight risk gene variants in Chinese Han population, in 2009, we analyzed the association between type 2 diabetes risk gene variants in or near TCF7L2, SLC30A8, KCNQ1, and PANK4 in Chinese Han individuals born in Peking Union Medical College Hospital (PUMCH), then found that birth weight was positively associated with KCNQ1 rs2074196 (β = −40 g, [95% confidence interval [CI]: −71, −0.1], P = 0.04), and did not observe association between birth weight and TCF7L2, SLC30A8, and PANK4.[2]

In this study, we aimed to further explore the relationship between birth weight and other type 2 diabetes risk gene variants in Chinese people. We selected variants in or near CDKAL1, HHEX, and ADCY5, recently identified the association with reduced birthweight in European, and SRR and PTPRD, which were recently identified through type 2 diabetes genome-wide association studies in Chinese Han population and have not been investigated in relation to birth weight.

**Methods**

**Study population**

A cohort of 2019 participants born in PUMCH from 1921 to 1954 were recruited during May 2003 and April 2005, for the study of the association between low birthweight and later diabetes and impaired glucose regulation (IGR), detailed information has been published previously.[3] Among them, 1174 subjects with blood samples drawn entered this study, 564 males and 610 females, aged 50–85 years (average age 59 years). Written informed consent was obtained from each participant, and the scanned document was submitted. The study was approved by the Institutional Review Board of PUMCH (No. S-002) on January 9, 2003.

Standard oral glucose tolerance testing was performed in all the participants except those who had already been diagnosed with diabetes. Type 2 diabetes was defined as the presence of one or more of the following: Fasting plasma glucose (FPG) ≥7.0 mmol/L, 2-h plasma glucose (2hPG) ≥11.1 mmol/L, or a definite history of diabetes with or without medicine. The criteria for IGR were FPG ≥5.6 to <7.0 mmol/L and/or 2hPG on the oral glucose tolerance test of ≥7.8 to <11.1 mmol/L.[4] Insulin resistance was determined by homeostasis model assessment (HOMA-IR): HOMA-IR = FPG × FINS/22.5; pancreatic β cell function was determined by homeostasis model assessment (HOMA-B): HOMA-B = 20 × FINS/ (FPG−3.5). FPG: (mmol/L), FINS: (μIU/ml).[5] Ponderal index was calculated as birthweight (kg)/birth length (m^3).

**Single nucleotide polymorphism genotyping**

The loci previously reported to be associated with reduced birthweight at a genome-wide significance level in European were selected, including CDKAL1 (rs7756992 rs10946398), HHEX (rs1111875) and ADCY5 (rs 1170806 rs9883204), 5 TagSNPs (rs4678017/rs9881942/rs7641344/rs6777397/ rs6226243) in ADCY5, rs391300 in SRR and rs17584499 in PTPRD which have not been investigated in relation to birth weight were also selected. Genotyping was performed using Taqman allelic discrimination assays. The quality value was set as 95% during data analysis using the Sequence Detection System version 2.4 software (Applied Biosystems, Foster City, CA, USA). Genotyping quality control was performed in 10% of the samples by duplicate checking (rate of concordance in duplicates 99%). All genotyping success rates were >99% with an error rate of <0.5%.

**Statistical analysis**

Data are presented as means ± standard deviation or median (interquartile range) for nonnormally distributed variables. Differences among groups were assessed by analysis of variance for normally distributed continuous variables, by nonparametric tests (Kruskall–Wallis test) for nonnormally distributed continuous variables (HOMA-IR, the number of pregnancies, and parity) and by a χ^2 test for frequencies. The effect of the genetic variant on birthweight, length at birth, and ponderal index was assessed by linear regression adjusting for sex, gestational age, parity, and maternal age. Consequently for each variant, only participants with complete data were included in the analysis. Type 2 diabetes risk was assessed by logistic regression analysis, after adjusting for age, sex, and body mass index (BMI). Statistical analyses were performed by SPSS 13.0 software (Inc., Chicago, IL, USA). A nominal P < 0.05 was considered statistically significant.

**Results**

**Baseline and clinical characteristics**

A total of 1174 participants, 645 (50.0%) had normal glucose tolerance (NGT), 181 (15.4%) had developed type 2 diabetes and 348 (29.6%) IGR, respectively. Table 1 shows the baseline characteristics of the study participants.

| Variable                  | IGM     | NGT     | P      |
|---------------------------|---------|---------|--------|
| n                         | 529     | 645     |        |
| Measurements at birth     |         |         |        |
| Birth weight (g)*         | 3077.8 ± 439.6 | 3154.4 ± 456.2 | <0.001 |
| Birth length (cm)*        | 49.3 ± 2.3 | 49.6 ± 2.4 | 0.010  |
| Ponderal index (kg/m^3)   | 25.6 ± 2.7 | 25.8 ± 3.0 | 0.079  |
| Gestational weeks         | 39.3 ± 1.8 | 39.3 ± 2.0 | 0.709  |
| Parity*                   | 2.0 (1.0, 4.0) | 2.0 (1.0, 3.0) | 0.001  |
| Maternal age (years)      | 28.1 ± 5.7 | 27.3 ± 5.3 | 0.060  |
| Adult measurements        |         |         |        |
| Age (years)*              | 60.1 ± 8.0 | 57.1 ± 7.4 | <0.001 |
| Waist circumference*      | 92.1 ± 10.9 | 87.7 ± 10.6 | <0.001 |
| BMI (kg/m^2)*             | 25.9 ± 3.6 | 24.5 ± 3.5 | <0.001 |
| HbA1c (%)                 | 5.9 ± 0.9 | 5.4 ± 0.5 | <0.001 |
| FPG (mmol/L)*             | 103.6 ± 25.7 | 84.3 ± 8.1 | <0.001 |
| 2hPG (mmol/L)*            | 178.7 ± 64.6 | 105.7 ± 19.9 | <0.001 |

*Data are shown as mean ± SD or median (interquartile range). *Represent the significance of differences between IGM group and NGT group. The statistical tests of the difference between the IGM and NGT groups in this table are not adjusted for confounding factors. Ponderal index: Birth weight/length^2; BMI: Body mass index; FPG: Fasting plasma glucose; 2hPG: 2-h plasma glucose; SD: Standard deviation; NGT: Normal glucose tolerance; IGM: Impaired glucose metabolism.
## Table 2: Effect of genetic variants on birth weight

| T2D risk variant | T2D risk allele (%) | Mean birth weight (g) per genotype (number of T2DM risk alleles) | Per risk allele (g) | P* |
|------------------|----------------------|------------------------------------------------------------------|---------------------|----|
|                  |                      | 0 | 1  | 2              |                                |                        |                     |
| CDKAL1-rs7756992| G (54.3)             | 3126.3 ± 450.3 | 3126.5 ± 464.7 | 3067.1 ± 469.9 | −36 (−72, −0.2) | 0.048 |
|                  | C (42.1)             | 3138.0 ± 454.7 | 3107.9 ± 459.7 | 3051.6 ± 484.5 | −29 (−64, 7.0)  | 0.118 |
| HHEX-rs1111875  | G (30.6)             | 3124.5 ± 475.2 | 3087.3 ± 454.6 | 3121.0 ± 455.4 | −16.7 (−54, 21) | 0.387 |
| SRR-rs391300    | G (69.7)             | 3201.9 ± 499.9 | 3093.0 ± 450.8 | 3103.8 ± 468.2 | −34 (−72, 5.0)  | 0.085 |
| ADCY5-rs16478017| A (28.0)             | 3096.3 ± 471.9 | 3111.1 ± 437.4 | 3155.9 ± 532.4 | 13 (−26, 53)   | 0.508 |
| ADCY5-rs9881942 | G (66.9)             | 3136.0 ± 377.6 | 3084.4 ± 462.0 | 3127.5 ± 481.2 | 12 (−26, 50)   | 0.531 |
| ADCY5-rs7641344 | G (60.3)             | 3124.3 ± 430.6 | 3122.9 ± 460.8 | 3087.6 ± 482.2 | −18 (−54, 18)  | 0.327 |
| ADCY5-rs6777397 | A (17.6)             | 3119.2 ± 464.5 | 3085.5 ± 453.9 | 3121.0 ± 507.3 | −10 (−56, 37)  | 0.685 |
| ADCY5-rs6226243 | G (33.6)             | 3097.0 ± 476.4 | 3122.2 ± 444.4 | 3102.1 ± 496.9 | 25 (−14, 63)   | 0.204 |

*Means ± SD stratified by T2DM risk genotypes; **Effect in gram (95% CI); *Linear regression, adjusted for gestational sex, parity, gestational weeks and maternal age. T2DM: Type 2 diabetes mellitus; SD: Standard deviation; CI: Confidence interval.

## Table 3: Genotype distributions and allele frequencies of all the 11 SNPs

| SNP       | Group | Genotype | Genotype (n %) | P* | Allele (n %) | OR† (95% CI) | Allele (n %) | P* | OR† (95% CI) |
|-----------|-------|----------|----------------|----|--------------|--------------|--------------|----|--------------|
| CDKAL1    |       | AA       | 248 (48.2)     | 0.257 | 452 (43.9)   | 0.875 (0.741–1.033) | 578 (56.1)   | 0.114 | 0.875 (0.741–1.033) |
|           |       | AG       | 240 (46)       | 0.004 | 354 (33.9)   | 1.325 (1.109–1.582) | 690 (66.1)   | 0.002 | 1.325 (1.109–1.582) |
|           |       | GG       | 225 (43.1)     | 0.339 | 307 (29.7)   | 0.951 (0.795–1.138) | 725 (70.3)   | 0.586 | 0.951 (0.795–1.138) |
| SRR       |       | AA       | 219 (41.9)     | 0.072 | 299 (28.6)   | 0.071 (0.087–1.265) | 747 (71.4)   | 0.571 | 0.071 (0.087–1.265) |
|           |       | AG       | 211 (42.3)     | 0.084 | 332 (31.9)   | 0.235 (0.756–1.071) | 710 (68.1)   | 0.092 | 0.235 (0.756–1.071) |
|           |       | GG       | 225 (43.8)     | 0.333 | 404 (38.8)   | 0.435 (0.790–1.107) | 636 (61.2)   | 0.586 | 0.435 (0.790–1.107) |
| ADCY5     |       | AA       | 219 (41.9)     | 0.072 | 299 (28.6)   | 0.071 (0.087–1.265) | 747 (71.4)   | 0.571 | 0.071 (0.087–1.265) |
|           |       | AG       | 211 (42.3)     | 0.084 | 332 (31.9)   | 0.235 (0.756–1.071) | 710 (68.1)   | 0.092 | 0.235 (0.756–1.071) |
|           |       | GG       | 225 (43.8)     | 0.333 | 404 (38.8)   | 0.435 (0.790–1.107) | 636 (61.2)   | 0.586 | 0.435 (0.790–1.107) |

*P values were calculated by Fisher’s exact test; †OR: Odds ratio for risk allele; risk allele, allele with higher frequency in cases compared to controls. IGM: Impaired glucose metabolism; NGT: Normal glucose tolerance; CI: Confidence interval.
shows the baseline characteristics of the study subjects and the statistical test of the differences between the impaired glucose metabolism (IGM, including type 2 diabetes and IGR) and NGT groups. There were no significant sex differences between the two groups (not shown). However, the birthweight and birth length of IGM patients were smaller than NGT groups (P < 0.001 and P = 0.01, respectively). About adult measurements, there were significant differences in age, waist, BMI, FPG, and 2hPG in the two groups (P < 0.001).

**Effect of genetic variants on birth weight**

All genotypes obeyed Hardy–Weinberg equilibrium in non-diabetic patients except PTPRD rs17584499 (P = 0.005). The risk C allele of CDKAL1-rs10946398 was associated with reduced birthweight (per allele β = −41 g [95% CI: −80, −3], P = 0.034), after adjusting for sex, gestational weeks, parity and maternal age, there were no significant association (P = 0.118). While the risk G allele of CDKAL1-rs7756992 was associated with reduced birthweight (per allele β = −36 g [95% CI: −72, −0.2], P = 0.048). The risk G allele of SRR-rs391300 showed a tendency toward lower birth weight (β = −34 g [95% CI: −72, 5], P = 0.085) after adjusting for sex, gestational weeks, parity, and maternal age [Table 2]. However, all studied variants were not independently associated with birth length and ponderal index (data not shown).

**Effect of genetic variants on impaired glucose metabolism**

The risk G allele of the HHEX-rs1111875 was significantly associated with increased risk of IGM (odds ratio [OR]: 1.325 [95% CI: 1.109–1.582], P = 0.002). CC genotype of the CDKAL1-rs10946398 was significantly associated with increased IGM compared with AA genotype (OR: 1.575 [95% CI: 1.097–2.261], P = 0.014). Other studied variants were not independently associated with increased risk of IGM. We did not analyze the association between ADCY5-rs1708067/rs9883204 and the risk of IGM, because the frequency of the risk alleles of which were below 1% (G = 0.4% and T = 0.5%, respectively) [Tables 3 and 4].

**Effect of genetic variants on insulin secretion and sensitivity**

The risk alleles (C and G) of CDKAL1-rs10946398 and ADCY5-rs7641344 were associated with impaired beta cell function (HOMA-B: P = 0.008 and P = 0.02; FINS: P = 0.085 and P = 0.05) compared with non-risk alleles. None of the risk variants was associated with reduced insulin secretion and sensitivity [Table 5].

**Discussion**

This is the first genetic study on the association between birthweight and glucose metabolism in Chinese Han population. The major finding in this study is that CDKAL1 rs10946398/rs7756992 are associated with reduced birthweight. Studies on European by Freathy et al. and Zhao et al. supported our results. The C allele of single nucleotide polymorphism (SNP) rs10946398 is associated with a 41 g reduction in birthweight, common variants both associated with increased risk of IGM and decreased insulin secretion index. Insulin is important for fetal growth and metabolism throughout life, so variants in CDKAL1 might affect pancreatic beta cell function resulting in low-insulin mediated fetal growth and the risk of type 2 diabetes in later life, which is a strong evidence for fetal insulin hypothesis. CDKAL1 is located on chromosome 6p22.3 and encodes a 65-kDa protein. The function of CDKAL1 is not yet clear. Previous studies found that CDKAL1 was a member of methyl sulfur transferase family, expressed in human pancreatic islet, might associated with insulin secretion of pancreatic beta cell induced by cyclin-dependent kinase 5 (CDK5).[9] The down-regulation of CDKAL1 expression might increase the activity of CDK5, resulting in decreased insulin secretion,[10] while the exact mechanisms are not clear. In the future, we need further study to explore the function of CDKAL1 on insulin secretion and glucose metabolism.

In the present study, SRR-rs391300 is nominally associated with reduced birthweight, carrier of G allele had a trend of birthweight reduction. SRR was identified as a special risk gene of type 2 diabetes mellitus in the Han Chinese other than the other race.[11] The function of SRR is not yet clear. Basic research showed SRR affected glutamate metabolism, followed secretion of the pancreatic beta cell.[12] So SRR may be the Chinese Han population characteristic and potential risk gene of type 2 diabetes associated with birth weight. In
Table 5: Effect of genetic variants on insulin secretion and sensitivity

| Gene/SNP   | Minor/major allele (MAF) | Variable | Minor allele homozygotes | Heterozygotes | Major allele homozygotes | P     |
|------------|--------------------------|----------|--------------------------|---------------|--------------------------|-------|
| **CDKAL1** |                          |          |                          |               |                          |       |
| rs7756992  | A/G (45.7)               | FINS     | 6.0 (4.0, 9.5)           | 6.2 (4.2, 10.3)| 6.3 (4.2, 11.7)          | 0.328 |
|           |                          | HOMA-IR  | 25.2 (16.8, 42.8)        | 25.7 (16.2, 44.1)| 26.4 (15.7, 50.5)        | 0.750 |
|           |                          | HOMA-B   | 1.4 (0.9, 2.0)           | 1.4 (1.0, 2.1) | 1.4 (1.0, 2.6)           | 0.117 |
| rs10946398 | C/A (42.1)               | FINS     | 5.7 (4.1, 8.8)           | 6.2 (4.2, 10.3)| 6.4 (4.2, 10.9)          | 0.085 |
|           |                          | HOMA-IR  | 24.6 (16.6, 42.2)        | 25.8 (16.4, 44.0)| 26.0 (16.0, 48.8)        | 0.557 |
|           |                          | HOMA-B   | 1.2 (0.9, 1.9)           | 1.4 (1.0, 2.2) | 1.4 (1.0, 2.4)           | 0.008 |
| **HHEX**  |                          |          |                          |               |                          |       |
| rs1111875  | G/A (30.6)               | FINS     | 5.9 (4.1, 9.7)           | 6.4 (4.3, 10.4)| 6.0 (4.1, 10.4)          | 0.328 |
|           |                          | HOMA-IR  | 25.7 (16.0, 42.6)        | 27.0 (16.4, 46.6)| 24.9 (16.2, 43.6)        | 0.750 |
|           |                          | HOMA-B   | 1.4 (0.9, 1.9)           | 1.4 (1.0, 2.2) | 1.4 (1.0, 2.3)           | 0.117 |
| **SRR**   |                          |          |                          |               |                          |       |
| rs391300   | A/G (30.3)               | FINS     | 7.1 (4.3, 12.3)          | 6.2 (4.2, 10.6)| 6.1 (4.2, 10.6)          | 0.445 |
|           |                          | HOMA-IR  | 29.0 (16.1, 49.0)        | 26.2 (16.9, 45.0)| 25.3 (16.1, 43.8)        | 0.539 |
|           |                          | HOMA-B   | 1.5 (1.0, 2.3)           | 1.4 (1.0, 2.2) | 1.3 (1.0, 2.1)           | 0.342 |
| **ADCY5** |                          |          |                          |               |                          |       |
| rs4678017  | A/C (28.0)               | FINS     | 6.2 (0.9, 10.1)          | 6.2 (4.0, 10.4)| 6.4 (4.4, 10.5)          | 0.509 |
|           |                          | HOMA-IR  | 23.52 (14.7, 41.3)       | 25.6 (16.3, 46.1)| 26.4 (16.9, 44.9)        | 0.367 |
|           |                          | HOMA-B   | 1.31 (1.0, 2.1)          | 1.4 (1.0, 2.12)| 1.4 (1.0, 2.3)           | 0.429 |
| rs9881942  | A/G (33.1)               | FINS     | 6.0 (4.3, 10.9)          | 6.2 (4.2, 10.2)| 6.2 (4.0, 10.2)          | 0.849 |
|           |                          | HOMA-IR  | 25.2 (15.8, 44.9)        | 25.6 (16.6, 44.7)| 25.9 (16.0, 45.2)        | 0.997 |
|           |                          | HOMA-B   | 1.4 (1.1, 2.4)           | 1.4 (1.0, 2.1) | 1.4 (1.0, 2.1)           | 0.508 |
| rs7641344  | A/G (39.7)               | FINS     | 6.8 (4.6, 12.1)          | 6.2 (4.1, 10.4)| 6.0 (4.0, 9.6)           | 0.050 |
|           |                          | HOMA-IR  | 27.7 (18.3, 51.1)        | 25.7 (15.8, 44.9)| 25.3 (16.9, 42.6)        | 0.179 |
|           |                          | HOMA-B   | 1.5 (1.1, 2.5)           | 1.4 (1.0, 2.2) | 1.3 (0.9, 2.1)           | 0.020 |
| rs6777397  | A/G (17.6)               | FINS     | 6.2 (4.0, 11.1)          | 6.3 (4.1, 10.2)| 6.2 (4.2, 10.3)          | 0.988 |
|           |                          | HOMA-IR  | 29.5 (15.4, 50.5)        | 26.3 (16.4, 45.8)| 25.6 (16.3, 44.3)        | 0.950 |
|           |                          | HOMA-B   | 1.2 (0.9, 2.3)           | 1.4 (1.0, 2.1) | 1.4 (1.0, 2.2)           | 0.863 |
| rs6226243  | G/C (33.6)               | FINS     | 6.0 (4.0, 11.2)          | 6.2 (4.0, 10.3)| 6.2 (4.4, 10.2)          | 0.990 |
|           |                          | HOMA-IR  | 27.2 (16.8, 50.0)        | 25.5 (15.8, 45.9)| 26.4 (16.9, 43.1)        | 0.675 |
|           |                          | HOMA-B   | 1.3 (0.9, 2.4)           | 1.4 (1.0, 2.3) | 1.4 (1.0, 2.1)           | 0.891 |

Data are shown as median (interquartile range), which was stratified by T2DM risk genotypes. MAF: Minor allele frequency; FINS: Fasting insulin level; HOMA-IR: Homeostasis model assessment for insulin resistance; HOMA-B: Homeostasis model assessment for β cell function; T2DM: Type 2 diabetes mellitus.

The future, further study on this association should be carried on in a large sample number and different races.

ADCY5 was newly identified as a risk gene of type 2 diabetes mellitus in many large meta-analysis studies.[12-15] Freathy et al. reported a meta-analysis of genome-wide association studies in European followed by replication studies showing that the C allele of rs9883204 in ADCY5 was associated with lower birthweight ($P = 7 \times 10^{-15}$).[6] Andersson et al. showed the inverse association between risk allele of ADCY5-rs9883204/rs7756992 and birthweight in Danish Inter99 population.[16] According to HapMap, the risk allele frequency of these two SNPs was 21.7% in European while below 1% in this present study. Hu et al. reported a meta-analysis of genome-wide association studies in Chinese Han population showing that there was no association between risk allele of rs11708067 and risk of type 2 diabetes.[17] Hence, it is possible that there are other SNPs of ADCY5 associated with risk of type 2 diabetes in Chinese Han population. ADCY5-rs7641344 may be the choice because the risk genotype was associated with reduced insulin secretion of pancreatic beta cell in this study and rs7641344 is a Tag SNP of ADCY5, which is in linkage disequilibrium with six SNPs rs9840967, rs7614840, rs6794936, rs9841543, rs7616545, rs7641344 (HapMap CEU phase III $r^2 = 1.0$). So rs7641344 may be the special variants of ADCY5 associated with type 2 diabetes in Chinese Han individuals. Further study on this association should be carried on in a large sample number and different races.

We confirmed the association between risk of IGM and variant in rs1111875 of HHEX,[18-22] which was not associated with fasting insulin, HOMA-B and HOMA-IR.

In conclusion, this study identified the association between risk of IGM and variant in $CDKAL1$ and reduced birthweight in Chinese Han individuals for the first time, and the carrier of risk allele within SRR had the trend of reduced birth weight. The polymorphism of ADCY5 had significant racial difference, variant of rs7641344 in ADCY5 was associated with reduced insulin secretion, which may be the
special variants of ADCY5 associated with type 2 diabetes in Chinese Han individuals. Our study demonstrated that there was a clear overlap between the genetics of type 2 diabetes and fetal growth, supporting the fetal insulin hypothesis, which proposed that lower birth weight and type 2 diabetes could be two phenotypes of one genotype. Hence, we can deeply explore the molecular genetic mechanism of type 2 diabetes in the future.

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