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

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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/rs6777397/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 ($\beta = -41$ 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 ($\beta = -36$ 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

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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

Table 1: 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^3; 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)[a] per genotype (number of T2DM risk alleles)			Effect	
		0	1	2	Per risk alle (g)[b]	*P**
CDKAL1-rs7756992	G (54.3)	3126.3 ± 450.3	3126.5 ± 464.7	3067.1 ± 469.9	−36 (−72, −0.2)	0.048
CDKAL1-rs10946398	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-rs4678017	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	3152.4 ± 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

[a]Means ± SD stratified by T2DM risk genotypes; [b]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 (*n* %)			*P**	Allele (*n* %)		*P**	*OR*† (95% *CI*)
		AA	AG	GG		A	G		
CDKAL1									
rs7756992	IGM	102 (19.8)	248 (48.2)	165 (32.0)	0.257	452 (43.9)	578 (56.1)	0.114	0.875 (0.741–1.033)
	NGT	138 (22.1)	313 (50.2)	173 (27.7)		589 (47.2)	659 (52.8)		
		CC	CA	AA		C	A		
rs10946398	IGM	108 (21.3)	231 (45.5)	169 (33.3)	0.104	447 (44.0)	569 (56.0)	0.092	1.156 (0.977–1.368)
	NGT	99 (16.3)	294 (48.4)	215 (35.4)		492 (40.5)	724 (59.5)		
		GG	GA	AA		G	A		
HHEX									
rs1111875	IGM	57 (10.9)	240 (46)	225 (43.1)	0.004	354 (33.9)	690 (66.1)	0.002	1.325 (1.109–1.582)
	NGT	56 (8.8)	242 (38.2)	336 (53.0)		354 (27.9)	914 (72.1)		
		AA	AG	GG		A	G		
SRR									
rs391300	IGM	43 (8.3)	221 (42.8)	252 (48.8)	0.339	307 (29.7)	725 (70.3)	0.586	0.951 (0.795–1.138)
	NGT	67 (10.7)	251 (40.2)	307 (49.1)		385 (30.8)	865 (69.2)		
		AA	AC	CC		A	C		
ADCY5									
rs4678017	IGM	40 (7.6)	219 (41.9)	264 (50.5)	0.726	299 (28.6)	747 (71.4)	0.571	1.054 (0.878–1.265)
	NGT	49 (7.7)	251 (39.6)	334 (52.7)		349 (27.5)	919 (72.5)		
		AA	AG	GG		A	G		
rs9881942	IGM	46 (8.8)	240 (46.1)	235 (45.1)	0.197	332 (31.9)	710 (68.1)	0.235	0.899 (0.756–1.071)
	NGT	77 (12.1)	281 (44.2)	278 (43.7)		435 (34.2)	837 (65.8)		
		AA	AG	GG		A	G		
rs7641344	IGM	86 (16.5)	232 (44.6)	202 (38.8)	0.533	404 (38.8)	636 (61.2)	0.435	0.935 (0.790–1.107)
	NGT	103 (16.7)	294 (47.6)	221 (35.8)		500 (40.5)	736 (59.5)		
		AA	AG	GG		A	G		
rs6777397	IGM	17 (3.3)	163 (31.4)	339 (65.3)	0.251	197 (19.0)	841 (81)	0.106	1.194 (0.963–1.481)
	NGT	17 (2.7)	172 (27.4)	439 (69.9)		206 (16.4)	1050 (83.6)		
		GG	GC	CC		G	C		
rs6226243	IGM	64 (12.2)	238 (45.5)	221 (42.3)	0.242	366 (35.0)	680 (65.0)	0.205	1.18 (0.941–1.33)
	NGT	58 (9.2)	294 (46.6)	279 (44.2)		410 (32.5)	852 (67.5)		
		GG	GA	AA		G	A		
rs11708067	IGM	0	4 (0.8)	519 (99.2)	0.976	4 (0.4)	1042 (99.6)	0.977	0.980 (0.263–3.660)
	NGT	0	5 (0.8)	636 (99.2)		5 (0.4)	1277 (99.6)		
		TT	CT	CC		C	T		
rs9883204	IGM	0	5 (1)	519 (99)	0.973	1043 (99.5)	5 (0.5)	0.973	1.021 (0.311–3.355)
	NGT	0	6 (0.9)	636 (99.1)		1278 (99.5)	6 (0.5)		

**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 nondiabetic participants 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 risk of 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*-rs11708067/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 nonrisk-alleles. None of the risk variants was associated with reduced insulin sensitivity [Table 5].

Table 4: Association between nine genetic variants and the risk of IGM

Gene/SNP	Genotype	*P*	*P**	*OR*	95% *CI*
CDKAL1					
rs7756992	GG	0.134	0.213	1.252	0.879–1.785
	GA	0.656	0.897	1.022	0.739–1.411
rs10946398	CC	0.058	0.014	1.575	1.097–2.261
	CA	0.998	0.839	0.971	0.733–1.287
HHEX					
rs1111875	GG	0.043	0.037	1.574	1.028–2.408
	GA	0.002	0.006	1.445	1.114–1.875
SRR					
rs391300	GG	0.248	0.126	1.415	0.908–2.207
	GA	0.143	0.108	1.445	0.922–2.266
ADCY5					
rs4678017	AA	0.888	0.885	1.036	0.644–1.664
	AC	0.425	0.330	1.136	0.879–1.468
rs9881942	GG	0.093	0.088	1.446	0.946–2.209
	GA	0.083	0.142	1.374	0.900–2.097
rs7641344	GG	0.606	0.617	1.097	0.763–1.576
	GA	0.740	0.567	0.902	0.635–1.282
rs6777397	AA	0.461	0.784	0.903	0.435–1.875
	AG	0.118	0.151	1.222	0.929–1.608
rs6226243	GG	0.102	0.113	1.403	0.923–2.132
	GC	0.862	0.884	0.981	0.756–1.273

**P* values were assessed by logistic regression after adjusted by sex, age, and BMI. *OR*: Odds ratio; *CI*: Confidence interval; BMI: Body mass index; IGM: Impaired glucose metabolism.

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.[6,7] 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).[8] The down-regulation of *CDKAL1* expression might increase the activity of CDK5, resulting in decreased insulin secretion,[9] 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.[10] The function of SRR is not yet clear. Basic research showed SRR affected glutamate metabolism, followed secretion of the pancreatic beta cell.[11] 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 10.0)	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)	6.2 (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 type 2 diabetes mellitus risk variants 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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