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Association of the *CD36* gene with impaired glucose tolerance, impaired fasting glucose, type-2 diabetes, and lipid metabolism in essential hypertensive patients

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ABSTRACT. Essential hypertension is a common disorder that can increase the risk of type 2 diabetes (T2D). *CD36* has been studied in patients with diabetes and hypertension extensively; however, few studies have focused on the relationship of the *CD36* gene with impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) or T2D in essential hypertension patients. To identify *rs1049673* and *rs1527483* in the *CD36* gene conferring susceptibility to IFG/IGT and T2D, we conducted a case-control study in 1257 essential hypertension

patients among the Han Chinese population (control: 676; IGT/IFG: 468; T2D: 113). We also evaluated the impact of two loci on insulin sensitivity, glucose tolerance and serum lipid. The major findings of this study were that *rs1049673* was found associated with IFG/IGT and T2D in essential hypertension patients (*P*co = 0.028; *P*dom = 0.015). The *rs1049673 G* carriers showed significant higher Glu0 (βdom = 0.08 (0.01~0.16), *P*dom = 0.045) and Lp(a) (βco = 0.04 (0.002~0.07), *P*co = 0.041; βdom = 0.06 (0.01~0.12), *P*dom = 0.032), and lower HDL by the linear regression with the adjustment for gender, age, BMI, and mean blood pressures. These findings provided evidence that the *CD36* gene may play some role in the pathogenesis of IFG/IGT and T2D in essential hypertension patients.

Key words: *CD36*; IGT/IFG; Lipid metabolism; T2D

INTRODUCTION

Essential hypertension (EH) and type 2 diabetes mellitus (T2D) are both common chronic conditions that affect a major proportion of the general population. Genetic epidemiological investigations have confirmed the contributions of genetic and environmental determinants of EH and T2D (Wang and Snieder, 2010; Yamauchi et al., 2010); in addition, linkage and candidate gene studies have suggested the genetic background overlap of two disorders (Gurnell et al., 2003). EH accompanying T2D nearly double the risk for stroke, myocardial infarction and mortality (Almgren et al., 2007), and are more difficult to control by antihypertensive treatment. Recently, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have been considered as the pre-diabetic state of dysglycemia (Osei et al., 2004), and have been related to increased risk of cardiovascular pathology (Pontiroli et al., 2004). It is therefore necessary to elucidate the mechanism underlying the pathogenesis of IFG/IGT and T2D in EH patients, in order to intervene in the progress of EH accompanying T2D.

The membrane protein CD36 has been extensively studied in patients with T2D and EH (Pravenec and Kurtz, 2002; Lepretre et al., 2004), because of its role in facilitating fatty acid (FA) uptake and oxidation (Harasim et al., 2008). The *CD36* gene is located at 7q11.2, which is translated into an 88-kDa membrane protein composed of one large extracellular hydrophobic domain and two short cytoplasmic tails (Coburn et al., 2000; Hajri and Abumrad, 2002). It has been reported that *CD36* deficiency may be associated with insulin resistance, defective FA metabolism and hypertriglyceridemia in spontaneously hypertensive rats and may be important in the pathogenesis of human insulin-resistance syndromes (Aitman et al., 1999). Furthermore, the single nucleotide polymorphisms (SNPs) in *CD36* have been associated with the susceptibility to T2D (Love-Gregory et al., 2008), obesity (Bokor et al., 2010) and metabolic syndrome, separately (Han et al., 2007); however, there is still little research focused on the effect of *CD36* on the development of IFG/IGT or T2D in EH patients.

Accordingly, we developed the following hypotheses: 1) that *CD36* would increase the susceptibility to IFG/IGT and T2D in EH patients and influence the glucose metabolic

phenotypes; 2) that this gene may influence the progress of lipid metabolism in EH patients. To identify SNPs conferring susceptibility to IFG/IGT and T2D, we conducted a case-control study in EH patients with normal glucose tolerance (NGT), IFG/IGT and T2D among a Han Chinese population. To determine the influence of the gene on metabolic index, moreover, we evaluated the impact of SNPs on insulin sensitivity, glucose tolerance and serum lipids.

MATERIAL AND METHODS

Participants

The participants involved in the present study were from the EH inpatients at the Division of Hypertension of Ruijin hospital affiliated with Shanghai Jiao Tong University from January 2000 to October 2004. All of them were of Han Chinese ancestry from the Shanghai metropolitan area. The hypertensive status was determined according to a systolic blood pressure (SBP) more than 140 mmHg or diastolic blood pressure (DBP) more than 90 mmHg, or taking antihypertensive medication. Oral glucose tolerance test (OGTT) was applied to estimate the status of NGT, IGT, IFG, and T2D based on American Diabetes Association criteria. Subjects who had a history of diabetes and who at the time of their clinical examination were taking either insulin or oral antidiabetic were also considered to have diabetes, regardless of their plasma glucose values. The patients who had taken antihypertensives influencing glucose metabolism in past two weeks, such as β-receptor blockers and thiazine diuretic, were excluded. Thus, a total of 1257 EH patients were enrolled, including 676 with NGT, 468 with IGT or IFG, and 113 with T2D. The association study was performed among three groups. While, to estimate the effect of *CD36* on glucose metabolism and serum lipids, the patients with T2D were excluded from the quantitative study; therefore, only the EH patients with NGT and IGT/IFG were considered. All individuals were of Chinese Han origin and gave written informed consent to donating blood samples for genetic analysis and related assays. This study was approved by the Ethics Committee of the Ruijin Hospital.

Study parameters

OGTT and calculation of insulin sensitivity were performed as previously described (Zhou et al., 2010). Glu0, Glu30, Glu60, Glu120, Glu180, Ins0, Ins30, Ins60, Ins120, and Ins180 represented the plasma glucose and insulin concentrations at 0, 30, 60, 120, and 180 min, separately. The serum lipid level was estimated by several criteria, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A (apoA), apolipoprotein B (apoB), and lipase A (Lp(a)). At the same time, the baseline index of age, height, weight, and 24-h blood pressure were recorded.

SNP genotyping

Genomic DNA was extracted from peripheral blood leukocytes using the standard phenol/chloroform procedure for genetic analysis. SNPs were selected for genotyping based

on published associations and linkage disequilibrium to sample different genetic blocks (Bokor et al., 2010; Noel et al., 2010). MassARRAY SNP genotyping system (Sequenom, San Diego, CA, USA) was used to determine the genotypes of *rs1527483* and *rs1049673* in *CD36* based on matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS). Primers for PCR amplification and subsequent extension reactions were designed using the SpectroDESIGNER assay design software (Sequenom). The primer sequences were as follows: *rs1527483* forward: 5'-ACGTTGGATGAAGCCAATTAGAATCACTTC-3', reverse: 5'-ACGTTGGATGCACATTCTTGAAAGTTACTGA-3', extension: 5'-AAAGTTACTGAA ACTTAGGTC-3'; *rs1049673* forward: 5'-ACGTTGGATGACTTCAGAGAGAAAATTAGG -3', reverse: 5'-ACGTTGGATGTCTTCCTTAAATTCCTGTGC-3', extension: 5'-CCTGTGC TTTTTCTAGTTCCT-3'. PCR conditions and extensive protocol design are described elsewhere. Genotypes were automatically called by the SpectroTyper software (Sequenom), and each genotype was manually inspected and verified. Fifty quality control individuals were placed randomly throughout the plates and accuracy was nearly 99%.

Statistical analysis

The chi-square (χ^2) goodness-of-fit test was applied to test for Hardy-Weinberg equilibrium for genotypic distributions among NGT, IGT/IFG and T2D, separately. Multinomial regression analyses were performed to examine the association between the genotypes in NGT, IGT/IFG and T2D subjects in codominant (11 *vs* 12 *vs* 22), dominant (11 *vs* 12 + 22) and recessive (11 + 12 *vs* 22) models. The relative risks of IGT/IFG or T2D were estimated as odds ratios (ORs) with associated 95% confidence intervals (95%CI). Linear regression analyses (standardized coefficient β) were performed to study the associations of insulin sensitivity, glucose tolerance, and serum lipids with genotypic groups in both subjects besides T2D. The values are reported as means ± SD. Logarithmic transformation was used for variables that were not normally distributed. The logistic and linear regression analyses were both adjusted for gender, age, body mass index (BMI), mean SBP (MSBP) and mean DBP (MDBP). The data were analyzed using the SPSS statistical software (version 13.0; SPSS Inc., Chicago, IL, USA), and the level of statistical significance was set at 5%. The power of the present study was about 94% with an α error of 5% and effect size of 0.1 by G power 3.0.10.

RESULTS

Comparison of characteristics in NGT, IGT/IFG and T2D groups

Table 1 summarizes the demographic and clinical data of EH patients with NGT, IGT/IFG and T2D. It is apparent that the IGT/IFG or T2D individuals had a higher age, BMI, MSBP, Glu0, Glu30, Glu60, Glu120, Glu180, Ins0, Ins30, Ins60, Ins120, Ins180, insulin sensitivity index, TG and apoB. However, the homeostatic model assessment of insulin resistance (HOMA-IR), Cederholm index, and HDL of the IGT/IFG or T2D group was significantly lower compared to the NGT group. No significant difference was found for gender, MDBP, HOMA index β (HOMA-β), TC, LDL, apoA and Lp(a) between the three groups.

Table 1. Demographic and clinical data of subjects.

	NGT	IGT/IFG	DM	P
Gender (male/female)	402/274	282/186	68/45	0.960
Age (years)	53.2 ± 11.8	55.7 ± 11.2	59.5 ± 10.8	**0.000**
BMI (kg/m^2)	25.0 ± 3.4	26.3 ± 5.6	26.3 ± 3.4	**0.000**
MSBP (mmHg)	129.6 ± 13.8	131.3 ± 15.5	135.4 ± 17.2	**0.002**
MDBP (mmHg)	82.1 ± 10.4	81.7 ± 11.2	80.2 ± 11.7	0.193
Glu0 (mM)	5.2 ± 0.5	5.8 ± 0.5	6.7 ± 1.0	**0.000**
Glu30 (mM)	8.9 ± 1.5	10.3 ± 1.6	12.1 ± 2.3	**0.000**
Glu60 (mM)	8.6 ± 2.0	11.3 ± 1.9	13.9 ± 2.7	**0.000**
Glu120 (mM)	6.0 ± 1.0	8.9 ± 1.1	11.6 ± 2.8	**0.000**
Glu180 (mM)	4.5 ± 0.9	5.6 ± 1.3	8.5 ± 3.4	**0.000**
Ins0 (mU/L)	7.9 ± 6.1	10.5 ± 10.1	11.8 ± 11.6	**0.000**
Ins30 (mU/L)	74.5 ± 50.4	69.7 ± 24.1	50.2 ± 41.8	**0.000**
Ins60 (mU/L)	89.8 ± 61.0	105.4 ± 60.8	72.2 ± 55.8	**0.000**
Ins120 (mU/L)	49.0 ± 41.0	100.7 ± 68.6	79.9 ± 61.6	**0.000**
Ins180 (mU/L)	14.0 ± 15.4	33.1 ± 29.4	40.6 ± 38.6	**0.000**
HOMA-IR (mmol·mU^{-1}·L^{-2})	14.9 ± 2.4	12.8 ± 2.3	9.8 ± 3.5	**0.000**
ISI	3.5 ± 0.8	3.8 ± 0.8	4.1 ± 0.8	**0.000**
Cederholm index	14.9 ± 2.4	12.8 ± 2.3	9.8 ± 3.5	**0.000**
HOMA-β (U/mmol)	98.5 ± 92.4	87.5 ± 167.7	109.8 ± 151.3	0.452
TG (mM)	2.0 ± 1.3	2.3 ± 1.4	2.5 ± 2.4	**0.000**
TC (mM)	4.8 ± 0.9	4.9 ± 1.0	5.0 ± 1.2	0.138
HDL (mM)	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.4	**0.000**
LDL (mM)	2.8 ± 0.8	2.9 ± 0.8	2.9 ± 0.9	0.470
apoA (g/L)	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	0.926
apoB (g/L)	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.3	**0.020**
Lp(a) (g/L)	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.057

Data are reported as means ± SD for continuous variables. NGT = normal glucose tolerance; IGT = impaired glucose tolerance; IFG = impaired fasting glucose; DM = diabetes mellitus; BMI = body mass index; MSBP = 24-h mean systolic blood pressure; MDBP = 24-h mean diastolic blood pressure; Glu0, Glu30, Glu60, Glu120, Glu180, Ins0, Ins30, Ins60, Ins120, and Ins180 represent the plasma glucose and insulin concentrations at 0, 30, 60, 120, and 180 min, separately. HOMA-β = homeostatic model assessment index β; HOMA-IR = HOMA insulin resistance; ISI = insulin sensitivity index; TG = triglycerides; TC = total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; apoA = apolipoprotein A; apoB = apolipoprotein B; LP(a) = lipase A. P values less than 0.05 are shown in bold and italics.

Association of genotypes with IFG/IGT and T2D

The χ^2 goodness-of-fit test showed that the genotypic distributions of *rs1527483* and *rs1049673* did not deviate from Hardy-Weinberg equilibrium in all three groups. In the case-control study involving NGT, IFG/IGT and T2D patients with EH, no association of *rs1527483* with IFG/IGT or T2D was found using any genotypic model. In the multinomial regression study, a significant difference of *rs1049673* distribution was found between the NGT, IFG/IGT and T2D groups under both the 2-d.f. codominant model (*P*co = 0.028) and dominant model (*P*dom = 0.015) with adjustment for age, gender, BMI, MSBP, and MDBP (see Table 2). In the codominant model, compared to the NGT group, the subjects carrying the *rs1049673 C/G* genotype can increase the susceptibility of IFG/IGT with an adjusted OR = 1.43 (P = 0.023, 95%CI = 1.05-1.96); the *rs1049673 G/G* genotype was associated with the T2D with an adjusted OR = 2.36 (P = 0.011, 95%CI = 1.22-4.56). In the dominant model, the EH patients with the G allele showed significant association with both IFG and IGT (P = 0.034, OR = 1.38, 95%CI = 1.03-1.85) and T2D (P = 0.021, OR = 1.97, 95%CI = 1.11-3.51). When we combined the T2D and IFG/IGT as one group compared to NGT, there was no significant difference between the two groups. There was also no meaningful difference between the IFG and IGT groups (data not shown).

Table 2. Association of *rs1527483* and *rs1049673* with impaired glucose tolerance (IGT) and diabetes mellitus (DM).

Variant	Gene	NGT	IGT	DM	Codominant model[a]	Dominant model[b]	Recessive model[b]
rs1527483	*G/G*	373	281	66	$\chi^2 = 4.932$	$\chi^2 = 1.874$	$\chi^2 = 4.276$
	A/G	244	154	39	*P*co = 0.294	*P*dom = 0.392	*P*rec = 0.118
	A/A	46	21	6			
rs1049673	*C/C*	180	104	18	$\chi^2 = 10.839$	$\chi^2 = 8.427$	$\chi^2 = 3.558$
	C/G	322	248	57	*P*co = **0.028**	*P*dom = **0.015**	*P*rec = 0.169
	G/G	165	106	36			

Data are reported as number of subjects with each genotype (% of each group). P values compare genotype distributions between normal glucose tolerance (NGT), IGT and DM subjects applying a codominant (*P*co), dominant (*P*dom), or recessive (*P*rec) logistic regression model with adjustment for age, gender, BMI, MSBP, and MDBP. [a]d.f. = 4; [b]d.f. = 2. The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

Association of genotypes with glucose tolerance and insulin sensitivity

In the comparison of glucose tolerance and insulin sensitivity among EH patients with different *rs1527483* and *rs1049673* genotypes, we found an association of *rs1527483* with any index of glucose metabolism in any genetic model (data not shown). However, SNP *rs1049673* showed a significant association with Glu0 in the dominant model with adjustment for age, gender, BMI, MSBP and MDBP (see Table 3). The EH patients with the G allele of *rs1049673* displayed higher Glu0 (*P*dom = 0.045).

Table 3. Association of rs1049673 with glucose tolerance, insulin sensitivity and serum lipids in impaired glucose tolerance and normal glucose tolerance subjects with essential hypertension.

rs1049673	C/C	C/G	G/G	Codominant		Dominant		Recessive	
				β (95%CI)	*P*co	β (95%CI)	*P*dom	β (95%CI)	*P*rec
Glu0 (mM)	5.4 ± 0.6	5.5 ± 0.6	5.4 ± 0.6	0.02 (-0.03~0.08)	0.733	0.08 (0.01~0.16)	**0.045**	-0.03 (-0.07-0.01)	0.125
Glu30 (mM)	9.4 ± 1.6	9.5 ± 1.8	9.5 ± 1.6	0.02 (-0.13~0.17)	0.823	0.05 (-0.20~0.30)	0.666	-0.01 (-0.13-0.12)	0.940
Glu60 (mM)	9.6 ± 2.3	9.7 ± 2.4	9.6 ± 2.4	0.07 (-0.14~0.27)	0.531	0.17 (-0.16~0.50)	0.316	0.00 (-0.17~0.17)	0.998
Glu120 (mM)	7.1 ± 1.7	7.3 ± 1.8	7.2 ± 1.7	0.01 (-0.01~0.02)	0.234	0.01 (-0.01~0.03)	0.165	0.02 (-0.01~0.01)	0.586
Glu180 (mM)	4.9 ± 1.2	5.1 ± 1.3	4.8 ± 1.1	-0.002 (-0.01~0.01)	0.609	0.01 (-0.01~0.02)	0.544	-0.01 (-0.01~0.01)	0.140
Ins0 (mU/L)	8.7 ± 7.8	9.2 ± 9.0	8.8 ± 7.8	-0.003 (-0.06~0.07)	0.923	0.007 (-0.10~0.12)	0.900	0.01 (-0.06~0.06)	0.977
Ins30 (mU/L)	74.4 ± 49.9	70.6 ± 44.3	74.7 ± 51.3	-0.003 (-0.03~0.02)	0.821	-0.02 (-0.06~0.02)	0.317	0.01 (-0.02~0.03)	0.510
Ins60 (mU/L)	92.5 ± 58.9	95.4 ± 61.5	100.3 ± 64.2	0.02 (-0.01~0.04)	0.123	0.01 (-0.03~0.05)	0.617	0.02 (-0.01~0.04)	0.118
Ins120 (mU/L)	68.5 ± 60.5	69.6 ± 58.3	72.2 ± 62.6	0.02 (-0.01~0.04)	0.309	0.01 (-0.04~0.07)	0.624	0.02 (-0.01~0.04)	0.238
Ins180 (mU/L)	21.2 ± 24.0	22.4 ± 25.3	20.9 ± 21.6	0.03 (-0.01~0.06)	0.207	0.03 (-0.03~0.10)	0.299	0.02 (-0.02~0.05)	0.307
HOMA-IR ($mmol \cdot mU \cdot L^{-2}$)	2.1 ± 1.3	2.1 ± 1.3	2.1 ± 1.4	0.001 (-0.03~0.03)	0.937	0.01 (-0.04~0.06)	0.789	-0.01 (-0.27~0.02)	0.885
ISI	3.6 ± 0.8	3.6 ± 0.8	3.6 ± 0.7	0.01 (-0.05~0.08)	0.712	0.03 (-0.08~0.14)	0.641	0.01 (-0.05~0.06)	0.896
Cederholm index	14.2 ± 2.5	13.9 ± 2.6	14.3 ± 2.6	0.01 (-0.03~0.04)	0.857	-0.03 (-0.08~0.02)	0.183	0.02 (-0.01~0.05)	0.094
HOMA-β (U/mmol)	95.0 ± 82.2	96.8 ± 97.4	88.0 ± 85.5	0.001 (-0.03~0.03)	0.966	0.02 (-0.01~0.04)	0.514	0.01 (-0.02~0.03)	0.459
TG (mM)	2.1 ± 1.3	2.1 ± 1.3	2.1 ± 1.4	0.01 (-0.01~0.03)	0.367	0.01 (-0.02~0.04)	0.500	0.01 (-0.01~0.02)	0.423
TC (mM)	4.8 ± 0.9	4.8 ± 1.0	4.9 ± 1.0	0.004 (-0.01~0.01)	0.343	0.002 (-0.01~0.01)	0.817	0.01 (-0.01~0.01)	0.183
HDL (mM)	1.21 ± 0.28	1.18 ± 0.32	1.16 ± 0.29	-0.01 (-0.03~-0.001)	**0.033**	-0.02 (-0.04~0.01)	0.078	-0.01 (-0.02~0.01)	0.052
LDL (mM)	2.8 ± 0.7	2.8 ± 0.8	2.9 ± 0.8	0.005 (-0.01~0.02)	0.323	0.004 (-0.01~0.02)	0.694	0.005 (-0.01~0.14)	0.268
apoA (g/L)	1.4 ± 0.3	1.3 ± 0.2	1.4 ± 0.3	0.002 (-0.005~0.01)	0.609	-0.003 (-0.01~0.01)	0.485	0.004 (-0.01~0.01)	0.212
apoB (g/L)	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	0.008 (-0.01~0.02)	0.146	0.009 (-0.01~0.05)	0.286	0.006 (-0.00~0.01)	0.190
LP(a) (g/L)	0.16 ± 0.18	0.18 ± 0.16	0.19 ± 0.16	0.04 (0.002~0.07)	**0.041**	0.06 (0.01~0.12)	**0.032**	0.02 (-0.01~0.04)	0.237

Data are reported as means ± SD. P values compare measurements among essential hypertension patients with different genotypes applying a codominant (*P*co), dominant (*P*dom), or recessive (*P*rec) linear regression model with adjustment for age, gender, BMI, MSBP, and MDBP. P values were obtained from $\log_{10}$-transformed variables. P values less than 0.05 are shown in bold. For other abbreviations, see legend to Table 1.

Association of genotypes with serum lipids

There was no significant difference found between the genotypes of *rs1527483* with any serum lipid measurements (data not shown). However, *rs1049673* displayed a significant association with HDL and Lp(a) (see Table 3) by the linear regression with adjustment for age, gender, BMI, MSBP, and MDBP. In the codominant model, the subjects carrying *G/G* significantly showed the lowest HDL (*P*co = 0.033, *G/G* = 1.16 ± 0.29, *C/G* = 1.18 ± 0.32, *C/C* = 1.21 ± 0.28) and highest Lp(a) (*P*co = 0.041, *G/G* = 0.19 ± 0.16, *C/G* = 0.18 ± 0.16, *C/C* = 0.16 ± 0.18) (see Table 3). Furthermore, in the dominant model, the *rs1049673 G* allele carriers showed significantly higher Lp(a) concentration (*P*dom = 0.032).

DISCUSSION

To our knowledge, the present study is the first report showing the association of the *CD36* gene and IFG/IGT and T2D in EH patients. Here, we found that *rs1049673* at 3'-UTR of *CD36* was associated with the susceptibility of IFG/IGT and T2D in EH patients of a Chinese population with an adjustment of gender, age, BMI and mean blood pressures. Moreover, the *rs1049673 G/G* carriers displayed a significant association with the lowest HDL and the highest Lp(a), which was in accordance with the findings of Love-Gregory et al. (2008) who showed that SNPs at 3'-UTR of the *CD36* gene was associated with metabolic syndrome and HDL. However, Ma et al. (2004) did not detect any relationship between *rs1049673* and HDL level but displayed the association of a haplotype including *rs1049673* with free FA. Such difference may be primarily attributed to ethnic heterogeneity, as the deficiency or mutation of the *CD36* gene in European populations is much lower than in persons of African or Asian descent (3-5%), which may be related to the high incidence of malaria in Africa and Asia (Susztak et al., 2005). In addition, the inconsistency of criteria used for including patients may also influence the results. Here, we mainly focused on the tendency of EH patients with IGT/IFG and diabetes mellitus, while others mostly paid attention to common subjects or susceptibility to diabetes and metabolic syndrome.

Of course, there were some limitations in the study. First, the sample size of the T2D group was suboptimal, which may have weakened the statistical power of the study. Therefore, the results need further verification in another larger population. Second, we only chose two SNPs reported associated with IFG/IGT or T2D, which cannot give the full coverage of the *CD36* gene. Also, the added effect of SNP *rs1049673* on the progress of IFG/IGT or T2D in EH could not be determined by the present study. However, it showed us some cue for further research, including; 1) to determine and confirm an association signal meeting genome wide significance; 2) to fine map the best candidate SNP(s) in the associated linkage disequilibrium block, and 3) to perform functional studies.

CONCLUSION

In the present study, we found that *rs1049673* in the *CD36* gene was associated with a susceptibility to IFG/IGT and T2D in EH patients, Glu0, and serum lipid concentration. However, the precise mechanism needs further functional study, as well as genetic analysis in different populations and prospective studies.

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