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Lack of association of functional *UCP2* -866G/A and Ala55Val polymorphisms and type 2 diabetes in the Chinese population based on a case-control study and a meta-analysis

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ABSTRACT. Uncoupling protein 2 (UCP2) is a mitochondrial transporter protein and can affect the function of β-cells. We investigated a possible association between functional *UCP2* -866G/A and Ala55Val polymorphisms and type 2 diabetes in 715 Hubei Han Chinese. No significant association was found, either for the -866G/A polymorphism (allele, P = 0.254; genotype, P = 0.508) or for the Ala55Val polymorphism (allele, P = 0.250; genotype, P = 0.896). Then, we reviewed the association of *UCP2* -866G/A and Ala55Val polymorphisms with type 2 diabetes susceptibility in the Chinese population with a meta-analysis. Our meta-analysis, which included 3643 Chinese, further confirmed a lack of association of -866G/A and Ala55Val with type 2 diabetes (additive model: -866G/A, odds ratio = 1.09, 95% confidence interval = 0.94-1.27, P = 0.25; Ala55Val, odds ratio = 1.21, 95% confidence interval = 0.85-1.72, P = 0.28).

Based on our case-control study and meta-analysis, we conclude that *UCP2* Ala55Val and -866G/A polymorphisms are not significantly associated with type 2 diabetes risk in the Chinese population.

Key words: Association study; UCP2; Meta-analysis; Type 2 diabetes

INTRODUCTION

Type 2 diabetes is a complex disease that is affected by the environment and multiple genes and their interaction. The incidence of type 2 diabetes has been rising for the past few years. The number of type 2 diabetes patients is 346 million all over the world according to the World Health Organization in 2011, and the number was about 92.4 million in China in 2010 (Yang et al., 2010). Type 2 diabetes can cause injuries to the kidney, eyes, heart, and so on, where it is seriously harmful to human health. The identification of susceptible genes of type 2 diabetes will help the diagnosis, prevention, and treatment of this disease.

Uncoupling protein 2 (UCP2) belongs to a family of mitochondrial transporter proteins, including UCP1-UCP5. The *UCP2* gene is located on the human chromosome 11q13, and was found to be a novel gene linked to obesity and hyperinsulinemia (Fleury et al., 1997). It is ubiquitously expressed in skeletal muscle, brown adipose tissue, brain, lung, kidney, and pancreas. The structure of UCP2, determined by NMR in 2011, closely resembles the bovine ADP/ATP carrier (Berardi et al., 2011). The physiological functions of UCP2 are still under debate (Dalgaard, 2011). A number of studies have reported that it can mediate proton leak, which can uncouple respiration and ATP synthesis, leading to energy consumed in the form of heat. It is also involved in the differentiation of human pluripotent stem cells (Zhang et al., 2011). UCP2 plays a very important part in continued clearance of apoptotic cells (Park et al., 2011). Studies have indicated that UCP2 can affect the function of β-cells (Gimeno et al., 1997; Zhang et al., 2001; Yang et al., 2010). UCP2 mRNA expression is dependent on glucose metabolism in pancreatic islets of mice (Dalgaard, 2012). Overexpression of UCP2 causes the suppression of insulin secretion (Chan et al., 2001). It has been proven that microRNA-15a positively regulates insulin synthesis by inhibiting UCP2 expression in mouse β-cells (Sun et al., 2011). UCP2 may be a microRNA-133a target. High microRNA-133a levels result in a decrease in insulin biosynthesis rates in human islets (Fred et al., 2010).

The -866G/A (rs659366) polymorphism is situated in the promoter in the *UCP2* gene and putatively changes binding sites of the transcription factors IPF1 and PAX6 (Krempler et al., 2002). Ala55Val (rs660339) polymorphism is situated in exon 4 in the *UCP2* gene. Numerous studies have examined the association between genetic variability in the *UCP2* gene and the risk of type 2 diabetes. Most replication studies focused on the functional -866G/A and Ala55Val polymorphisms and contradictory results were reported (Zheng et al., 1999; Xiu et al., 2004; Shen et al., 2007; Gu et al., 2007; Li et al., 2008; Wang et al., 2009; Liu et al., 2009; She, 2009; Yang et al., 2009; Hu et al., 2010). The purpose of this study was to first examine the association of the -866G/A and Ala55Val polymorphisms in the *UCP2* gene with type 2 diabetes in 715 Hubei Han Chinese, and then systematically review the association of the -866G/A and Ala55Val polymorphisms with type 2 diabetes risk in Chinese population via meta-analysis.

MATERIAL AND METHODS

Subjects

The present study included 715 individuals of Hubei Han Chinese recruited between 2006 and 2009 from the Yiling Hospital in Yichang, China, which have been previously described (Dehwah et al., 2010). Type 2 diabetes is defined according to the 1997 American Diabetes Association criteria as follows: fasting blood glucose (FBG) ≥7.0 mM (126 mg/dL) and 2-h postprandial blood glucose (PBG) ≥11.1 mM (200 mg/dL). The subjects with a family history of maturity onset diabetes of the young, maternally inherited diabetes, gestational diabetes, mitochondrial diabetes, type 1 diabetes, and other obvious chronic diseases, such as hypertension, coronary heart disease, and cancer, were excluded. All healthy controls had FBG <6.1 mM (110 mg/dL) and 2-h PBG <7.8 mM, no family history of type 2 diabetes in first-degree relatives, normal blood pressure, normal liver and kidney functions, and no chronic heart and lung disease. Signed inform consent was obtained from the subjects for the survey and sampling.

Phenotyping

Weight, height, and waist and hip circumference were measured in all individuals. Body mass index (BMI) and waist-to-hip ratio were separately calculated as weight (kg)/height $(m)^2$ and waist (cm)/hip (cm). Clinical parameters measured included FBG, 2-h PBG, systolic blood pressure (SBP) and diastolic blood pressure (DBP), total cholesterol, triacylglycerol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and fasting insulin (Table 1).

Genotyping

Genomic DNA was obtained from whole blood leukocytes using the standard phenol/chloroform method. The -866G/A (rs659366) polymorphism in the *UCP2* gene was examined by PCR-RFLP with the primers 5'-CAC GCT GCT TCT GCC AGG AC-3' (forward) and 5'-AGG CGT CAG GAG ATG GAC CG-3' (reverse). The 360-bp PCR product contains one *Mlu*I restriction site (290 + 70 bp) for the G allele and none for the A allele. Following enzymatic digestion, PCR products were resolved by 1.5% agarose gel electrophoresis and visualized by ethidium bromide staining. The SNP Ala55Val (rs660339) of the *UCP2* gene was examined by PCR-RFLP with the primers 5'-GGC CAG TGC GCG CTA CGG-3' (forward) and 5'-ATT GTA GAG GCT TCG GGG GCC C-3' (reverse). The PCR product was digested with *Hae*III. C/C (Ala/Ala) homozygotes consisted of a 95-bp fragment, T/T (Val/Val) homozygotes consisted of 77- and 18-bp fragments, and T/C (Val/Ala) heterozygotes consisted of 95-, 77-, and 18-bp fragments. Following enzymatic digestion, PCR products were resolved by 3.5% agarose gel electrophoresis and visualized by ethidium bromide staining.

Statistical analysis

The genotype distribution in cases and controls were separately tested for Hardy-Wein-

berg equilibrium using the χ^2 test before association analysis. All continuous variables are reported as means ± standard deviation. The Student *t*-test was used to compare differences in the continuous variables between the type 2 diabetes and non-diabetic control groups. The genotypic and allelic frequencies between type 2 diabetes patients and controls were compared using the χ^2 test. The genotype-disease association analyses were performed by logistic regression analysis with or without adjustment for covariates. $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed using the SPSS software (version 11.5) for Windows.

Meta-analysis

PubMed, vipbrowser database, and Wanfang database online were searched using "UCP2" and "type 2 diabetes" or "T2D" as key words. The references of all computer-identified publications were searched for additional studies. Without any language restriction, we only selected published manuscripts. All of the studies were carefully identified. First, each study had case-control groups and had been published as an original study. Second, numbers in case and control groups had to be reported for each genotype. Third, if the data were duplicated and had been published more than once, the most recent and complete study was chosen. The odds ratios (ORs) were calculated using 2x2 contingency tables for each study. The Stata 10.0 software was used to evaluate the heterogeneity between studies and publication bias. Pooled ORs were computed by the fixed-effect method of Mantel-Haenszel (Peto method) under no heterogeneity between studies. If significant heterogeneity existed between studies, the DerSimonian-Laird random-effect model (D-L method) was then applied to combined data. The conservative Egger regression analysis was used to evaluate publication bias.

RESULTS

Clinical characteristics of subjects

Clinical characteristics of subjects are summarized in Table 1. The independent *t*-test analysis showed that weight, waist circumference, SBP, DBP, BMI, triacylglycerol, and fasting insulin in type 2 diabetes patients were significantly higher than those of the control group ($P < 0.05$). These results suggested that weight, waist circumference, SBP, DBP, and BMI were independent risk factors for type 2 diabetes in the study population. The covariates that showed significant differences between cases and controls were adjusted in the subsequent logistic regression analysis as indicated in Table 2. Notably, age and HDL cholesterol in the control group were higher than in type 2 diabetes patients. The older age of the control subjects decreased the risk for controls to develop type 2 diabetes in subsequent years, although they had no clinical symptoms at the time of investigation, lowering misclassification bias.

Association study in a Hubei Han Chinese population

Genotypic distributions of the *UCP2* -866G/A and Ala55Val polymorphisms were in Hardy-Weinberg equilibrium in both type 2 diabetes patients and the control group. We found no statistically significant ($P < 0.05$) associations between type 2 diabetes and *UCP2* -866G/A polymorphism using an additive model (allele: $\chi^2 = 1.3$, $P = 0.254$; genotype: $\chi^2 = 1.4$, $P =$

0.508), dominant model (genotype: $\chi^2 = 0.81$, P = 0.369), and recessive model (genotype: $\chi^2 = 0.66$, P = 0.417). Moreover, we also found no evidence of association by logistic regression with or without adjustment for covariates (Table 2).

Table 1. Clinical characteristics of the study subjects.

Characteristics	Case group	Control group	P value
Gender (male/female)	172/180	193/170	0.625
Age (years)	54.32 ± 10.36	63.19 ± 12.60	<0.001*
Height (cm)	159.98 ± 9.54	158.22 ± 9.20	0.789
Weight (kg)	75.06 ± 20.27	70.79 ± 24.09	<0.001*
Waist circumference (cm)	74.12 ± 13.55	65.66 ± 10.94	<0.001*
Hip circumference (cm)	88.64 ± 11.59	83.13 ± 10.27	0.06
SBP (mmHg)	133.83 ± 23.55	129.54 ± 30.02	0.024*
DBP (mmHg)	83.45 ± 13.36	79.74 ± 17.62	0.039*
BMI (kg/m^2)	28.08 ± 9.59	20.74 ± 3.27	<0.001*
WHR	0.84 ± 0.20	0.79 ± 0.20	0.587
Total cholesterol	5.56 ± 1.29	6.75 ± 25.35	0.498
Triacylglycerol	2.49 ± 3.11	1.13 ± 0.64	<0.001*
HDL cholesterol	1.56 ± 0.51	1.69 ± 0.42	0.004*
LDL cholesterol	2.52 ± 1.31	2.17 ± 3.09	0.120
Fasting insulin	13.25 ± 8.99	6.02 ± 3.63	<0.001*

Parameters adjusted as covariates in logistic regression analysis (P < 0.05). SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; WHR = waist-to-hip ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2. Logistic regression analysis of *UCP2* -866G/A and Ala55Val and type 2 diabetes.

Locus	Genotype	Groups		Unadjusted			After adjustment		
		Cases	Controls	OR	95%CI	P	OR	95%CI	P
-866G/A	GG	88	102	1.00	-	-	1.00	-	-
	GA	184	187	0.88	0.62-1.25	0.46	0.71	0.31-1.60	0.41
	AA	82	74	0.78	0.51-1.19	0.25	0.60	0.23-1.56	0.29
Ala55Val	CC	55	59	1.00	-	-	1.00	-	-
	TC	147	203	1.25	0.82-1.90	0.31	0.66	0.19-2.32	0.52
	TT	90	107	1.04	0.66-1.65	0.87	0.50	0.13-1.88	0.30

Adjustment for covariates with P < 0.05 in Table 1.

Likewise, the allele and genotype frequencies of the Ala55Val polymorphism did not differ significantly between case and control groups, either by additive (allele: $\chi^2 = 2.77$, P = 0.25; genotype: $\chi^2 = 0.017$, P = 0.896), dominant (genotype: $\chi^2 = 0.74$, P = 0.39), or recessive (genotype: $\chi^2 = 0.18$, P = 0.67) models. Logistic regression with or without adjustment for covariates further confirmed the lack of association between the *UCP2* Ala55Val polymorphism and type 2 diabetes in our study population (Table 2).

Meta-analysis in Chinese

We identified eight studies for the *UCP2* -866G/A and four studies for the *UCP2* Ala55Val, including our current study. Tables 3 and 4 summarize the characteristics of these published association studies of *UCP2* -866G/A and Ala55Val with type 2 diabetes in Chinese populations. The Egger regression analysis indicated no publication bias.

Table 3. Characteristics of case-control studies included in the meta-analysis of the *UCP2* -866G/A polymorphism.

Study	Population	Group	Gender (male/female)	Age (years)	BMI (kg/m²)	Sample size	rs659366 GG/GA/AA	Allele A (%)	Genotype P	Allele P
Shen et al. (2007)	Nanjing	Case	122/107	54 ± 10	25.5 ± 3.3	229	65/117/47	46.1	0.038	0.012
	Chinese	Control	98/98	52 ± 10	23.2 ± 3.1	196	77/91/28	37.5		
Gu et al. (2007)	Tianjin	Case	139/139	58 ± 8	25.2 ± 3.5	278	80/134/64	47.1	0.245	0.088
	Chinese	Control	76/86	53 ± 7	-	162	37/78/47	53.1		
Li et al. (2008)	Northern	Case	116/76	55 ± 12	25.3 ± 3.1	192	44/103/45	50.3	0.298	0.391
	Chinese	Control	73/28	58 ± 12	24.2 ± 2.8	101	31/46/24	46.5		
Wang et al. (2009)	Beijing	Case	246/224	58 ± 13	-	470	124/248/98	47.2	0.538	0.301
	Chinese	Control	90/127	58 ± 11	-	217	52/112/53	50.2		
Liu et al. (2009)	Dalian	Case	53/62	62.4 ± 11.6	25.6 ± 4.1	115	42/36/37	47.8	0.038	0.008
	Chinese	Control	49/27	60.4 ± 10.2	24.1 ± 3.6	76	36/28/12	34.2		
She (2009)	Hunan	Case	185/185	49.8 ± 10.7	24.7 ± 3.3	370	113/169/88	46.6	0.792	0.729
	Chinese	Control	95/71	48.6 ± 11.3	24.2 ± 4.4	166	55/71/40	45.4		
Yang et al. (2009)	Chinese	Case	83/116	49.1 ± 10.1	25.6 ± 3.4	199	56/124/19	40.7	0.939	0.807
	Han	Control	92/68	44.6 ± 11.5	21.3 ± 3.7	155	41/99/15	41.6		
Qin et al. (2013)	Hubei	Case	173/181	54.0 ± 10.2	27.8 ± 9.2	354	88/184/82	49.2	0.508	0.254
	Chinese	Control	193/170	63.7 ± 12.3	25.7 ± 9.3	363	102/187/74	46.1		

Table 4. Characteristics of case-control studies included in the meta-analysis of the *UCP2* Ala55Val polymorphism.

Study	Population	Group	Gender (male/female)	Age (years)	BMI (kg/m²)	Sample size	SNP rs660339 CC/CT/TT	Allele T (%)	Genotype P	Allele P
Hu et al. (2010)	Gansu	Case	-	-	24.4 ± 3.5	104	43/48/13	35.6	0.827	0.402
	Chinese	Control	-	-	24.05 ± 3.8	114	43/57/14	37.3		
Xiu et al. (2004)	Chinese	Case	76/97	57 ± 12	21.9 ± 2.0	173	52/80/41	46.8	0.001	0.000
		Control	68/109	56 ± 8	21.9 ± 1.9	177	82/81/14	30.8		
Zheng et al. (1999)	Shanghai	Case	75/91	56 ± 10	26.76 ± 3.7	166	43/88/35	47.6	0.615	0.403
	Chinese	Control	84/109	53 ± 12	25.61 ± 4.3	90	28/46/16	43.3		
Qin et al. (2013)	Hubei	Case	151/141	55 ± 10	28.8 ± 9.6	292	55/147/90	56.0	0.896	0.250
	Chinese	Control	195/174	64 ± 14	26.9 ± 9.3	369	59/203/107	56.5		

Figure 1A presents the forest plot of risk allele OR of each individual study and meta-analysis for association between *UCP2* -866G/A and type 2 diabetes in 2207 type 2 diabetes patients and 1436 control subjects from the eight studies. A pooled OR was 1.09 (95%CI = 0.94-1.27, P = 0.25; heterogeneity P = 0.026, random-effect model) in additive model, and 1.12 (95%CI = 0.97-1.30, P = 0.12; heterogeneity P = 0.152, fixed-effect model) in dominant model and 1.07 (95%CI = 0.91-1.26, P = 0.42; heterogeneity P = 0.138, fixed-effect model) in recessive model. Two studies in our meta-analysis deviated from Hardy-Weinberg equilibrium (P < 0.05) (Yang et al., 2009; She, 2009). After the exclusion of these two studies, the association remained nonsignificant: additive (OR = 1.13, 95%CI = 0.93-1.38, P = 0.23), dominant (OR = 1.15, 95%CI = 0.97-1.37, P = 0.10), and recessive (OR = 1.09, 95%CI = 0.91-1.32, P = 0.34) models. We further combined genotype data of all 8 studies. The chi-square test of pooled data showed no significant association between *UCP2* -866G/A and type 2 diabetes by additive (allele: $\chi^2 = 2.23$, P = 0.14; genotype: $\chi^2 = 2.48$, P = 0.29), dominant (genotype: $\chi^2 = 2.11$, P = 0.14), and recessive (genotype: $\chi^2 = 0.86$, P = 0.35) models.

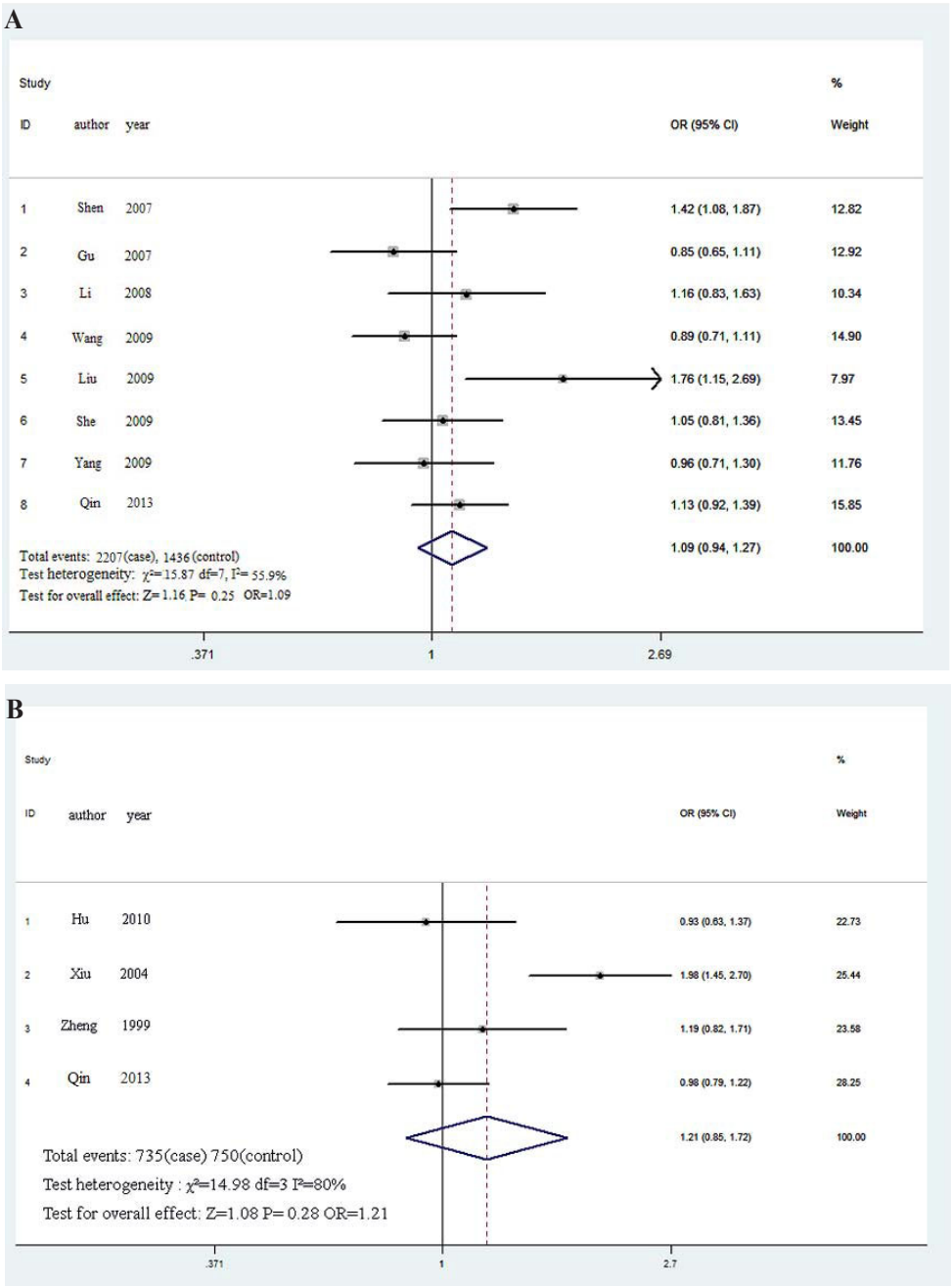

Figure 1. Forest plots of meta-analysis of the association of *UCP2* -866G/A (**A**) and Ala55Val (**B**) polymorphisms with type 2 diabetes in the Chinese population. Estimations of odds ratios (OR) and 95% confidence intervals (CI) in each study are displayed as closed squares and horizontal lines, respectively. The size of the black squares reflects the weight of the study in the meta-analysis. The diamond represents the combined OR, calculated using a random- or fixed-effect model, with its 95%CI.

Figure 1B presents the forest plot of risk allele OR of each individual study and meta-analysis for association between *UCP2* Ala55Val and type 2 diabetes in 735 type 2 diabetes patients and 750 control subjects from the four studies. Because of the significant heterogeneity in the three models, a random-effect model was used and generated a combined allelic OR of 1.21 (95%CI = 0.85-1.72, P = 0.28; heterogeneity P = 0.002) in additive, 0.86 (95%CI = 0.55-1.34, P = 0.50; heterogeneity P = 0.017) in dominant, and 0.68 (95%CI = 0.39-1.18, P = 0.17; heterogeneity P = 0.012) in recessive models. We pooled our data with the three previously published studies (Zheng et al., 1999; Xiu et al., 2004; Hu et al., 2010). The allele and genotype frequencies did not differ significantly between the case and control groups in additive (allele: $\chi^2 = 2.76$, P = 0.096; genotype: $\chi^2 = 3.88$, P = 0.14), recessive (genotype: $\chi^2 = 0.18$, P = 0.67), and dominant (genotype: $\chi^2 = 0.74$, P = 0.39) models.

DISCUSSION

In our study of Hubei Han Chinese, no association was observed between *UCP2* -866G/A and Ala55Val variants and type 2 diabetes, by either additive, dominant, or recessive model and logistic regression with or without adjustment for covariates. This finding is further confirmed by our meta-analysis including 3643 Chinese. Our results do not support an association between *UCP2* -866G/A and Ala55Val variants and type 2 diabetes in the Chinese population. Although our sample size was relatively small, results of pooled data of all eligible studies showed no evidence of association between *UCP2* -866G/A and Ala55Val polymorphisms and type 2 diabetes. To our knowledge, the present study is the first to systematically evaluate the *UCP2* -866G/A and Ala55Val polymorphisms in relation to type 2 diabetes in the Chinese population.

Seven small studies previously conducted in the Chinese population examined the *UCP2* -866G/A polymorphism in relation to type 2 diabetes with inconsistent results (Shen et al., 2007; Gu et al., 2007; Li et al., 2008; Wang et al., 2009; Liu et al., 2009; She, 2009; Yang et al., 2009). Two studies (Shen et al., 2007; Liu et al., 2009) found statistically significant associations. It is noteworthy that in the two above-mentioned studies, the frequencies of the A allele in the controls were the lowest (37.5 and 34.2%, respectively), and sample size in the study by Liu et al. (2009) was the smallest (191). Only three previous studies (Zheng et al., 1999; Xiu et al., 2004; Hu et al., 2010) looked at *UCP2* Ala55Val variant and type 2 diabetes in the Chinese population. One study (Xiu et al., 2004) with the lowest frequency (30.8%) of the T allele in controls found statistically significant associations.

Xu et al. (2011) recently performed a meta-analysis to assess the association between the *UCP2* -866G/A and Ala55Val polymorphisms and type 2 diabetes susceptibility. No significant association was observed for the *UCP2* -866G/A polymorphism either in participants of Asian or European descendant. In contrast, the *UCP2* Ala55Val polymorphism showed significant association with type 2 diabetes risk in participants of Asian descendant (OR = 1.15, 95%CI = 1.03-1.28), but not in Europeans. However, no study of the Chinese population was included in their meta-analysis of the *UCP2* Ala55Val polymorphism.

Despite strong functional evidence for the relevance of the *UCP2* -866G/A and Ala55Val polymorphisms (Krempler et al., 2002), we did not detect any association with type 2 diabetes susceptibility. Notably, -866G/A and Ala55Val polymorphisms are located in a low linkage disequilibrium region in the *UCP2* gene (Figure 2). Therefore, the lack of

association between -866G/A and Ala55Val polymorphisms and type 2 diabetes susceptibility in Chinese population cannot rule out the role of the *UCP2* gene in the pathophysiology of type 2 diabetes. Comprehensive assessment of variation across the *UCP2* gene (gene-based association) in large samples should be conducted in the future.

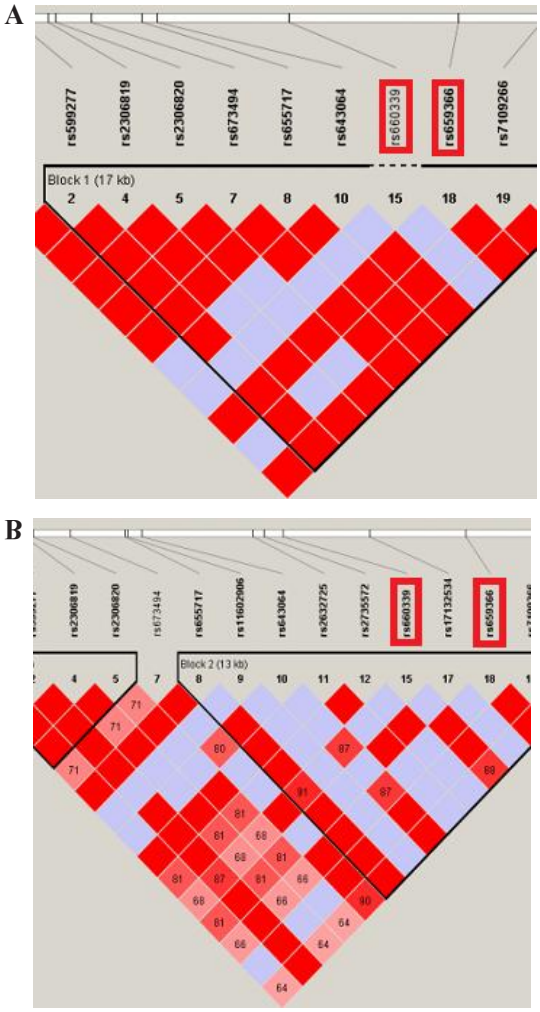

Figure 2. Linkage disequilibrium pattern and r^2 values between the -866G/A (rs659366), Ala55Val (rs660339), and the SNPs nearby in Chinese ($r^2 = 0.017$) (**A**) and European ($r^2 = 0.833$) (**B**).

A previous meta-analysis revealed that ethnicity was the only covariate likely to have made an important contribution to the overall between-study heterogeneity (Xu et al., 2011). Although we limited our meta-analysis to Chinese Han populations, meta-analysis still revealed significant between-study heterogeneity for the Ala55Val polymorphism. This was likely because only four studies are available for meta-analysis of this locus. There can be

large uncertainty in a meta-analysis about the presence or not of between-study heterogeneity and its extent when the meta-analysis includes few studies (Huedo-Medina et al., 2006).

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