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RESEARCH ARTICLE

Smoking modifies the effect of two independent SNPs rs5063 and rs198358 of *NPPA* on central obesity in the Chinese Han population

HUAN ZHANG[1,2], XINGBO MO[1,2,3], ZHENGYUAN ZHOU[4], ZHENGBAO ZHU[1,2], XINFENG HUANGFU[1,2], TAN XU[1,2], AILI WANG[1,2], ZHIRONG GUO[1,2] and YONGHONG ZHANG[1,2]*

[1]*Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, Soochow University, Suzhou, Jiangsu, People's Republic of China*
[2]*Department of Epidemiology, School of Public Health, Medical College of Soochow University, Suzhou, Jiangsu, People's Republic of China*
[3]*Center for Genetic Epidemiology and Genomics, School of Public Health, Medical College of Soochow University, Suzhou, Jiangsu, People's Republic of China*
[4]*Changshu Center of Disease Control and Prevention, Suzhou, Jiangsu, People's Republic of China*
*For correspondence. E-mail: yhzhang@suda.edu.cn.

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Abstract. Obesity is the third most risk factors of death in the middle-income and high-income countries. Whether DNA polymorphisms in *CORIN* and *NPPA* genes were associated with obesity, and if these associations could be modified by smoking in the Chinese Han population were unknown, hence a group of 1507 participants were recruited and genotyped for 12 tag single-nucleotide polymorphisms (SNPs) of *CORIN* and *NPPA* genes. Regression models were used to test the associations of SNPs with obesity. The potential SNP–smoking interactions were detected in regression models. *NPPA* SNPs rs5063 and rs198358 were associated with the body mass index (BMI) ($P = 0.0053$ and 0.0037, respectively). Rs198358 was associated with obesity in both univariate- and multivariable-adjusted analyses ($P = 0.0138$ and 0.0173, respectively). Rs5063 was associated with central obesity in both univariate- and multivariable-adjusted analyses ($P = 0.0454$ and 0.0361, respectively). Significant interactions between cigarette smoking and rs5063 and rs198358 were detected ($P = 0.0019$ and 0.0006, respectively). In subgroup analyses, rs5063 and rs198358 were associated with central obesity in smokers ($P = 0.0081$ and 0.0037, respectively). The results of our study demonstrated that the effect of *NPPA* SNPs rs5063 and rs198358 on central obesity might be modified by smoking in the Chinese Han population. Further studies are needed to confirm the associations and elucidate the underlying mechanisms.

Keywords. corin; atrial-natriuretic peptides; obesity; genetic association; smoking.

Introduction

Obesity is the third most risk factors of death in middle-income and high-income countries (Narayan *et al.* 2010). By 2030, the respective numbers of overweight and obese adults are projected to be 1.35 billion and 573 million individuals (Kelly *et al.* 2008). In China, the total number of overweight men and women will exceed the established market economies by 2030 (Kelly *et al.* 2008). It is known that the higher the body mass index (BMI), the greater the risk of comorbidities such as diabetes mellitus, hypertension, dyslipidaemia, cardiovascular diseases, obstructive sleep apnea, cancers and overall mortality (Hensrud and Klein 2006). The causes of obesity have been recognized and are largely related to a genetic predisposition and an environmental susceptibility to gain weight due to increased energy intake and decrease energy expenditures (Lifshitz and Lifshitz 2014). The genetic aspects of obesity lead to mutations in various genes responsible for controlling appetite and metabolism. Over the past two decades, several strategies, including genomewide association studies (GWAS) have been employed for the identification of genetic determinants of obesity and loci in the human genome

that link with obesity (Thorleifsson *et al.* 2009; Willer *et al.* 2009; Speliotes *et al.* 2010; Okada *et al.* 2012; Wen *et al.* 2012; Yang *et al.* 2012; Wen *et al.* 2014; Shungin *et al.* 2015; Ried *et al.* 2016; Wahl *et al.* 2017). Even then, the knowledge of underlying risk factors for obesity is still limited.

The natriuretic peptide system may have a potential role in obesity. An atrial-natriuretic peptide (ANP) is a cardiac hormone with potent cardiovascular and metabolic effects (Levin *et al.* 1998). ANP was also reported to induce a strong lipolytic effect in cultured human adipocytes with potency similar to catecholamine activation of the β-adrenergic receptors (Sengenes *et al.* 2000). The Framingham Heart Study has shown that the plasma ANP level was lower in subjects with obesity and those with metabolic risk factors (Wang *et al.* 2004, 2007). Corin, a type II transmembrane serine protease, found in cardiomyocytes, converts the precursor molecules of ANP into active proteins (Chan *et al.* 2005). Corin acts downstream of agouti gene expression as a suppressor of the agouti pathway, indicating a potential role of corin in obesity (Enshell-Seijffers *et al.* 2008). Our previous study has detected the association of serum soluble corin levels in obesity (Peng *et al.* 2015).

Genetic variants of the *NPPA* gene, which encodes the ANP precursor, were associated with hypertension, stroke, coronary artery disease, heart failure and obesity (Song *et al.* 2015). The human *CORIN* gene is located on chromosome 4p12-13 (Yan *et al.* 1999). *CORIN* gene variants have been identified to alter corin protein conformation and inhibited corin zymogen activation and contribute to hypertension, and heart diseases (Dries *et al.* 2005; Dong *et al.* 2013; Zhou and Wu 2014). Whether genetic variants in *NPPA*, or the convertase coding gene *CORIN* can affect risk of obesity has not been determined in the Chinese populations.

Cigarette smoking is one of the leading causes of preventable morbidity and mortality. The association between smoking and obesity has been extensively investigated in diverse populations (Chiolero *et al.* 2007; Xu *et al.* 2007; Mackay *et al.* 2013). Besides, the potential for smoking to influence genetic associations with obesity has also been explored (Fesinmeyer *et al.* 2013; Johnson *et al.* 2014). However, whether the associations between the DNA polymorphisms in the *CORIN* and *NPPA* genes, and obesity could be modified by smoking in the Chinese population is unclear. We have examined the associations between single-nucleotide polymorphisms (SNPs) in the *CORIN* and *NPPA* genes and obesity, and the interaction effect of the SNPs with smoking on obesity in this study. Our results may lead to better understanding of the combined effects of *CORIN* or *NPPA* variants and smoking on obesity among Chinese Han individuals.

Methods

Study population

A group of 1507 adults were randomly selected from a large cohort study in community population of Jiangsu Province and judged to be free of hypertension, cardiovascular diseases, diabetes mellitus, renal or hepatic diseases. Standard questionnaire were used by trained interviewers to obtain data on demographic characteristics, lifestyle risk factors, personal medical history, and family history of hypertension for all participants. Three sitting blood pressure (BP) measurements were taken and the mean of the three BP measurements was used in analyses. Body weight and height were measured by using standard methods, and the BMI was calculated as the weight in kilograms divided by the square of the height in meters. The waist circumference (WC) was measured two times at 1 cm above the umbilicus at minimal respiration by trained observers with the subjects standing and breathing normally during the physical examination. In this study, overweight was defined as $24 \leq \text{BMI} < 28$ kg/m^2, obesity was defined as BMI$\geq$28 kg/m^2 and central obesity was defined as WC$\geq$85 cm for men and as WC$\geq$80 cm for women based on the recommendations of the Working Group on Obesity in China (Zhou 2002). Cigarette smoking was defined as having smoked at least 100 cigarettes (Pierce *et al.* 1998; He *et al.* 2007). Alcohol consumption was defined as consuming any type of alcohol beverage at least 12 times during the past 1 year (Bazzano *et al.* 2007; Xiao *et al.* 2015). Written informed consent was obtained from all study participants. This study was approved by the ethics committee at Soochow University in China.

Biochemical measurements

Blood samples were collected in the morning after at least 8 h of fasting. All plasma samples were frozen at −80°C until laboratory testing was performed. Fasting plasma glucose (FPG) was measured using an oxidase enzymatic method. The concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were assessed enzymatically using an automatic biochemistry analyser (Hitachi, Tokyo, Japan) and commercial reagents. The Friedewald equation was used to calculate the low-density lipoprotein cholesterol (LDL-C) from TC, HDL-C and TG. All analyses were performed in the same lab.

DNA extraction, SNP selection and genotyping

Genomic DNA was isolated from the white blood cells according to a standard procedure using a DNA extraction kit (Tiangen Biotech, Beijing, China). We selected tag-SNPs from these genes with pairwise r^2 thresholds

of 0.8. Haploview software (ver. 4.2, http://www.broad.mit.edu/mpg/haploview) was used to conduct tag-SNP selection (Barrett *et al.* 2005). A total of 12 tag-SNPs were included in the current study. Detailed information on all tag-SNPs, including the chromosome position, minor allele frequency (MAF), and Hardy–Weinberg equilibrium (HWE) *P* values has been searched and calculated. The selected tag-SNPs have been genotyped by using SNPscan technology, a custom-by-design 48-Plex SNPscan kit based on double ligation and multiplex fluorescence polymerase chain reaction (PCR) (Cat#: G0104; Genesky Biotechnologies, Shanghai, China) (Chen *et al.* 2012; Jin *et al.* 2015). This kit was developed according to patented SNP genotyping technology by Genesky Biotechnologies, which was based on double ligation and multiplex fluorescence PCR. Briefly, 100–200 ng of DNA sample was first denatured at 98°C for 5 min in a 10-mL reaction mixture containing 1× DNA lysis buffer and then mixed well with a 10-mL ligation premix composed of 2 mL 103 ligase buffer, 0.5 mL ligase, 1 mL probe mix and 7.5 mL Milli-Q water. The ligation reaction was carried out in an ABI2720 thermal cycler. Two 48-plex fluorescence PCR reactions were performed for each ligation product. PCR reactions were prepared in a 20-mL mixture containing 1× PCR master mix, 1 mL primer mix set A or set B, and 1 mL ligation product. PCR products were separated and detected by capillary electrophoresis in an ABI3730XL sequencer. Raw data were analysed according to the information obtained for the labelling dye colour and fragment size of the allele-specific ligation-PCR product.

Statistical analysis

The differences in mean levels of risk factors in individuals with and without overweight or obesity, as well as in participants with and without central obesity were compared using a student's *t*-test for continuous variables and χ^2 tests for categorical variables. Linear regression was used to test the association between the SNPs and BMI, and WC. Logistic regression models were used to estimate odds ratio (OR) and 95% confidence intervals (CI) of obesity and central obesity with the tested SNPs. The SNP was analysed as 0, 1 or 2 copies of the minor allele in an additive genetic model. Considering adjustment for multiple testing corrections, a significance level of 0.004 was used. The potential covariates such as age, sex, systolic blood pressure (SBP), lipid levels and FPG were included in the multivariable models. To detect the potential SNP–smoking interactions, an extra interaction term of the genotype × smoking was included in the regression model. We also performed subgroup analyses according to the smoking status of the participants. Statistical analyses were conducted using SAS statistical software ver. 9.2 (SAS, Cary, USA).

Results

Baseline characteristics

There were 578 (38.4%) male and 929 (61.6%) female participants in this study. The average age of these participants was 53 years, ranged from 21 to 89 years. Among them, 342 (22.7%) and 63 (4.2%) participants were overweight and obese, respectively, and 449 (30.0%) participants were central obese. The characteristics of the participants are presented in table 1. It seemed that obese participants were younger than the normal weight participants. The frequencies of smokers and alcoholics between the obesity and normal weight participants were not different. Compared with normal BMI, obese participants had higher levels of SBP, diastolic blood pressure (DBP), TC, TG and LDL-C, and a lower level of HDL-C. Central obese individuals were more likely to be women, and have higher levels of SBP, DBP, TC, TG, LDL-C and FPG, and a lower level of HDL-C than those without central obesity.

Association between genotypes and obesity

The HWE of the 12 SNPs (MAF>10%) was tested with the Fisher's exact test and no departures were observed (table 2). Table 2 also shows the results of association between the SNPs and BMI and obesity. No *CORIN* SNP was associated with BMI. Rs17654423 seemed to be associated with obesity ($P = 0.0395$) but the association was not significant in multivariable-adjusted analysis. For *NPPA* SNPs, rs5063 and rs198358 were associated with BMI in univariate analyses ($P = 0.0053$ and 0.0037, respectively). Rs5063 was associated with obesity in univariate analyses ($P = 0.0398$). Rs198358 was associated with obesity in both univariate- and multivariable-adjusted analyses ($P = 0.0138$ and 0.0173, respectively).

Association between genotypes and central obesity

We investigated the associations between the *CORIN* and *NPPA* SNPs and WC and central obesity in the 1507 participants. The results are presented in table 3. No *CORIN* SNP was associated with WC or central obesity. For *NPPA* SNPs, rs5063 was associated with WC in univariate analyses ($P = 0.0231$). After adjusted for covariates, this association was not significant ($P = 0.0586$). Rs5063 was also associated with central obesity in both univariate- and multivariable-adjusted analyses ($P = 0.0454$ and 0.0361, respectively).

Interaction between cigarette smoking and SNPs

Weak evidence of interaction between cigarette smoking and rs1866689 and rs10008014 on obesity was detected ($P = 0.0236$ and 0.0157, respectively) (table 4). In

Table 1. Characteristics of study participants.

Characteristics	BMI				WC		
	Obesity ($n = 63$)	Overweight ($n = 342$)	Normal weight ($n = 1102$)	P value	Central obesity ($n = 449$)	Normal WC ($n = 1058$)	P value
Age, years	49.05 ± 11.69	50.23 ± 11.79	53.90 ± 12.90	<0.0001	52.03 ± 12.40	53.22 ± 12.84	0.0968
Male, %	30.16	36.26	39.47	0.2220	34.08	40.17	0.0261
Smokers, %	23.81	26.02	30.13	0.2258	26.95	29.77	0.2688
Drinkers, %	14.29	22.51	21.23	0.3406	21.16	21.27	0.9625
SBP, mmHg	125.0 ± 9.13	124.4 ± 9.17	121.6 ± 10.65	<0.0001	125.1 ± 8.96	121.2 ± 10.69	<0.0001
DBP, mmHg	79.59 ± 6.79	78.35 ± 6.40	74.42 ± 7.58	<0.0001	78.04 ± 6.58	74.46 ± 7.65	<0.0001
TC, mmol/L	4.78 ± 1.01	4.67 ± 0.96	4.48 ± 0.96	0.0003	4.72 ± 1.00	4.44 ± 0.94	<0.0001
TG, mmol/L	1.78 ± 0.89	1.88 ± 1.45	1.33 ± 0.80	<0.0001	1.86 ± 1.32	1.31 ± 0.80	<0.0001
HDL-C, mmol/L	1.16 ± 0.34	1.20 ± 0.42	1.37 ± 0.48	<0.0001	1.20 ± 0.41	1.37 ± 0.49	<0.0001
LDL-C, mmol/L	2.68 ± 0.89	2.56 ± 0.81	2.46 ± 0.78	0.0227	2.62 ± 0.85	2.44 ± 0.77	0.0002
FPG, mmol/L	5.21 ± 0.99	5.07 ± 0.88	5.07 ± 1.00	0.5660	5.19 ± 1.10	5.03 ± 0.91	0.0032

subgroup analyses by separating the study population into smokers and nonsmokers, we found no significant association between the two SNPs and obesity. For central obesity, significant interactions between cigarette smoking and rs5063 and rs198358 were detected ($P = 0.0019$ and 0.0006, respectively). In subgroup analyses, these two SNPs were associated with central obesity in smokers ($P = 0.0081$ and 0.0037, respectively), but not in nonsmokers (table 4). Smokers carrying minor alleles of rs5063 and rs198358 seemed to have low risk of obesity; OR (95% CI) for rs5063 and rs198358 were 0.50 (0.29, 0.83) and 0.48 (0.30, 0.79), respectively.

Discussion

This is the first study to evaluate the associations of *CORIN* and *NPPA* gene SNPs with obesity and central obesity, and the interaction effect of the SNPs with smoking on obesity and central obesity in the Chinese Han population. We found that *NPPA* gene SNPs rs5063 and rs198358 were associated with obesity and central obesity. Significant interactions between these two SNPs and smoking on central obesity were detected. Our study suggested that the effect of the two independent SNPs rs5063 and rs198358 of *NPPA* on central obesity might be modified by smoking in the Chinese Han population. Human ANP plays an important role in lipolysis (Sengenes *et al.* 2000). The Framingham Heart Study has shown that the plasma levels of ANPs were lower in subjects with obesity and those with metabolic risk factors (Wang *et al.* 2004, 2007). The *NPPA* gene encodes the ANP precursor. The potential relationships between the *NPPA* genetic polymorphism and essential hypertension have been widely explored (Wang *et al.* 2016). However, no study has been reported the relationship between the DNA polymorphisms in *NPPA* genes and obesity, including GWAS. We showed for the first time that *NPPA* SNPs rs5063 and rs198358 were associated with obesity in the Chinese Han population. Our data also suggested that smokers carrying one or two minor alleles of rs5063 or rs198358 might have lower risk of central obesity. Conversely, major allele homozygote smokers might have higher risk. This means that these two SNPs are protective for smokers with central obesity. Rs5063 is a missense mutation in exon 1 of the *NPPA* gene, while rs198358 is located at the downstream region. The underlying mechanisms of these two SNPs on obesity need to elucidate in future studies.

It is known that nicotine has a direct effect on adipose tissue metabolism (Carney and Goldberg 1984). Besides, it has been shown that the mechanism by which smoking regulates adiposity likely involves appetite suppression via neural pathways (Mineur *et al.* 2011). Although, genetic associations with obesity may differ by the smoking status (Fesinmeyer *et al.* 2013), the precise mechanisms by which

Table 2. Association between the *CORIN*/*NPPA* gene polymorphisms and BMI and obesity.

SNPs	Position	MAF, %	HWE*	BMI			Obesity		
				P	$P\_adj^{\#}$	OR (95% CI)	*P*	$OR\_adj^{\#}$ (95% CI)	*P*_adj
CORIN									
rs2289433	Exon 1	34.3	0.075	0.0836	0.4147	0.97 (0.82, 1.16)	0.7624	0.98 (0.82, 1.17)	0.8089
rs1866689	Intron 1	43.5	0.870	0.2376	0.6872	1.01 (0.85, 1.18)	0.9501	1.03 (0.87, 1.22)	0.7308
rs10008014	Intron 6	24.6	0.289	0.1080	0.6504	1.03 (0.85, 1.24)	0.7833	1.02 (0.84, 1.25)	0.8208
rs17654423	Intron 6	26.6	0.670	0.1710	0.1009	1.21 (1.01, 1.46)	0.0395	1.18 (0.99, 1.43)	0.0825
rs10517195	Exon 9	15.7	0.167	0.5588	0.8438	1.02 (0.82, 1.28)	0.8448	1.10 (0.87, 1.39)	0.4155
rs2271037	Intron 9	38.7	0.551	0.5192	0.9437	1.06 (0.90, 1.25)	0.5174	1.12 (0.95, 1.33)	0.1860
rs2351784	Intron 11	23.0	0.335	0.5168	0.5187	1.03 (0.85, 1.25)	0.7680	1.05 (0.85, 1.28)	0.6722
rs12509275	Intron 17	13.8	0.064	0.5377	0.2594	1.13 (0.89, 1.43)	0.3140	1.20 (0.94, 1.53)	0.1498
rs3749585	Exon 22	48.0	0.774	0.4685	0.5912	0.99 (0.85, 1.16)	0.9084	0.96 (0.82, 1.14)	0.6646
NPPA									
rs632793	Upstream	14.4	0.604	0.8337	0.9924	0.94 (0.75, 1.17)	0.5583	0.93 (0.74, 1.17)	0.5408
rs5063	Exon 1	11.6	0.981	0.0053	0.1128	0.77 (0.60, 0.99)	0.0398	0.78 (0.60, 1.01)	0.0565
rs198358	Downstream	10.0	0.583	0.0037	0.1336	0.74 (0.58, 0.94)	0.0138	0.74 (0.58, 0.95)	0.0173

HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency.
*P value for the HWE using the Fisher's exact test.
#Adjusted for age, SBP and lipid levels.

Table 3. Association between the *CORIN*/*NPPA* gene polymorphisms and WC and central obesity.

SNPs	WC			Central obesity		
	P	$P\_adj^{\#}$	OR (95% CI)	*P*	$OR\_adj^{\#}$ (95% CI)	*P*_adj
			CORIN			
rs2289433	0.2576	0.6018	0.97 (0.82, 1.15)	0.7199	0.98 (0.82, 1.17)	0.7884
rs1866689	0.6918	0.8837	0.97 (0.83, 1.14)	0.6913	0.99 (0.84, 1.17)	0.8912
rs10008014	0.2064	0.3150	1.10 (0.91, 1.33)	0.9310	1.12 (0.92, 1.36)	0.2763
rs17654423	0.3752	0.2500	1.09 (0.91, 1.30)	0.3657	1.07 (0.89, 1.28)	0.5031
rs10517195	0.6952	0.9942	0.92 (0.74, 1.14)	0.4463	0.97 (0.77, 1.21)	0.7686
rs2271037	0.2535	0.5789	0.95 (0.81, 1.12)	0.5370	1.00 (0.84, 1.18)	0.9777
rs2351784	0.5216	0.4345	1.00 (0.83, 1.21)	0.9915	1.02 (0.83, 1.24)	0.8849
rs12509275	0.3663	0.6342	1.04 (0.83, 1.30)	0.7486	1.07 (0.84, 1.36)	0.5916
rs3749585	0.2840	0.8347	1.00 (0.85, 1.16)	0.9616	0.97 (0.82, 1.14)	0.6756
			NPPA			
rs632793	0.9980	0.6666	0.91 (0.74, 1.14)	0.4209	0.91 (0.72, 1.14)	0.3995
rs5063	0.0231	0.0586	0.78 (0.61, 1.00)	0.0454	0.76 (0.58, 0.98)	0.0361
rs198358	0.0642	0.1063	0.82 (0.65, 1.04)	0.1011	0.81 (0.63, 1.04)	0.0965

HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency.
*P value for the HWE using the Fisher's exact test.
#Adjusted for age, sex, SBP, lipid levels and FPG.

the interaction of genetic variants with smoking affects obesity are still largely unknown. In the current study, we observed that the effect of rs5063 or rs198358 on central obesity might be modified by smoking, which has not been reported in previous studies. Smokers carrying the major alleles of rs5063 or rs198358 might have higher risk of central obesity. This effect could not be seen in nonsmokers. We still cannot determine if smoking affects the function of rs5063 or rs198358, or if the SNPs could change smoking behaviour. In view of the effect of ANP and smoking on adipose metabolism, future studies are needed to determine if smoking could influence the circulating ANP levels, and whether this change is associated with the food intake and energy expenditure.

Corin is a converting enzyme in the natriuretic peptide system. Recent studies have shown the association of circulating soluble corin and heart failure (Dong *et al.* 2010), acute coronary syndrome (Peleg *et al.* 2013), osteoporosis (Zhou *et al.* 2013), pregnant hypertension (Zaki *et al.* 2012) and obesity (Peng *et al.* 2015). *CORIN* gene variants have been identified to alter corin protein conformation and inhibited corin zymogen activation and contribute to hypertension and heart disease (Dries *et al.* 2005; Dong *et al.* 2013; Zhou and Wu 2014). The present study

Table 4. Association between the *CORIN*/*NPPA* gene polymorphisms and obesity or central obesity in smokers and nonsmokers.

	Smokers ($n = 436$)				Nonsmokers ($n = 1071$)				
	OR (95% CI)	*P*	OR_adj[#] (95% CI)	*P*_adj	OR (95% CI)	*P*	OR_adj[#] (95% CI)	*P*_adj	*P*_interaction
Obesity									
rs1866689	1.29 (0.92, 1.79)	0.1351	1.35 (0.94, 1.95)	0.1060	0.93 (0.77, 1.12)	0.4519	0.94 (0.78, 1.14)	0.5346	0.0236
rs10008014	1.46 (0.98, 2.19)	0.0645	1.44 (0.93, 2.23)	0.1040	0.92 (0.74, 1.15)	0.4584	0.92 (0.74, 1.15)	0.4569	0.0157
Central obesity									
rs5063	0.52 (0.33, 0.81)	0.0041	0.50 (0.29, 0.83)	0.0081	0.92 (0.68, 1.24)	0.5820	0.91 (0.67, 1.24)	0.5557	0.0019
rs198358	0.49 (0.32, 0.75)	0.0010	0.48 (0.30, 0.79)	0.0037	1.03 (0.77, 1.37)	0.8617	1.03 (0.76, 1.40)	0.8269	0.0006

[#]Adjusted for age, sex, SBP, lipid levels and FPG.

evaluated for the first time the associations between the *CORIN* gene SNPs and obesity in Chinese individuals. Unfortunately, we did not detect a significant association. The effect sizes of genetic variants in the *CORIN* gene on obesity may be much smaller than those of the *NPPA* gene, or the mutations may not have an effect on obesity risk.

This study has some potential limitations. First, the sample size of this study is relatively small. This means that some SNPs especially with weaker genetic effects would not be detected in our study. Moreover, the associations between the small effect SNPs and obesity was not significant when adjusted for age, BP and lipid levels, which has much larger effect sizes. Second, no association between the *CORIN* polymorphism and obesity was likely due to the small sample size. Besides, only several tag-SNPs of *CORIN* have tested in the present study. Thus it cannot conclude that *CORIN* gene variants were not associated with obesity. Finally, there were 21 (4.8%) men and 42 (6.3%) women with central obesity in the BMI normal group (435 men and 667 women), which could not be considered as normal for comparison against obese and overweight individuals. However, the proportion was very small. When excluded these individuals from the analyses of obesity, the results did not vary.

In summary, the results of our study demonstrated that *NPPA* SNPs rs5063 and rs198358 were associated with obesity, and the effect of these SNPs on central obesity might be modified by smoking in the Chinese Han population. Smokers carrying the major alleles of rs5063 or rs198358 might have higher risk of central obesity. Further studies are needed to confirm the associations and elucidate the underlying mechanisms.

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