CLINICAL STUDY

Genetic variants associated with persistent central obesity and the metabolic syndrome in a 12-year longitudinal study

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Abstract

Objective: Central obesity predisposes to various cardiometabolic diseases and is a key component of the metabolic syndrome (MetS). We have previously demonstrated that three obesity-susceptible single nucleotide polymorphisms (SNPs), rs10938397 (*GNPDA2*), rs8050136 (*FTO*) and rs17782313 (*MC4R*), were associated with obesity and waist circumference in cross-sectional studies in the Chinese population. In this study, we investigate whether these SNPs could also predict the persistence of central obesity and MetS in subjects from the Hong Kong Cardiovascular Risk Factors Prevalence Study (CRISPS) cohort.

Design and methods: We genotyped these SNPs in i) 354 subjects with and 994 subjects without central obesity at both baseline and a 12-year follow-up, ii) 2214 subjects (816 cases and 1398 controls) in an MetS cross-sectional case–control study and iii) 225 subjects with and 1221 subjects without MetS at both baseline and the 12-year follow-up.

Results: Both *FTO* rs8050136 ($P_{\text{age, sex-adjusted}} = 0.019$; odds ratio (OR) (95% confidence intervals (CI)): 1.35 (1.05, 1.73)) and *GNPDA2* rs10938397 ($P_{\text{age, sex-adjusted}} = 3 \times 10^{-3}$; OR (95% CI): 1.34 (1.11, 1.63)) were significantly associated with persistent central obesity. *GNPDA2* rs10938397 was also significantly associated with MetS ($P_{\text{age, sex-adjusted}} = 0.011$, OR (95% CI): 1.20 (1.04, 1.38)) in the case–control study. However, none of these SNPs showed an individual association with persistent MetS. In the combined genetic risk analyses for persistent central obesity and persistent MetS, the combined genetic risk score of the three SNPs showed an OR of 1.25 (95% CI: 1.10, 1.42; $P_{\text{age, sex-adjusted}} = 4.92 \times 10^{-3}$) and 1.19 (95% CI: 1.03, 1.38; $P_{\text{age, sex-adjusted}} = 0.019$) for each additional risk allele respectively.

Conclusion: This study demonstrated that *FTO* and *GNPDA2* variants predicted persistent central obesity in the Chinese population, further supporting their importance as obesity-susceptible genes.

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Introduction

Obesity, with a rapidly increasing prevalence all over the world, is now recognised as a global epidemic (1). Obesity, whether general or central obesity, is associated with an increased risk of developing various cardiometabolic diseases such as type 2 diabetes mellitus (T2DM), hypertension and cardiovascular diseases (CVD) (2). Using the Asian criterion for general obesity (body mass index (BMI) $\geq 27.5 \text{ kg/m}^2$) (3), our group recently replicated the associations of three obesity-susceptible genetic variants identified from

previous Caucasian genome-wide association studies (4, 5) with obesity in a Chinese case–control study involving 470 obese (BMI $\geq 27.5 \text{ kg/m}^2$) cases and 700 normal weight controls. Three single nucleotide polymorphisms (SNPs), rs10938397 (*GNPDA2*), rs8050136 (*FTO*) and rs17782313 (*MC4R*), were found to be strongly associated with obesity in our Southern Chinese cohort (6). In the same study, we also observed significant associations of these three SNPs with BMI, and in the females we also observed significant associations with waist circumference (WC) in a cross-sectional extension study

based on 1938 Southern Chinese subjects from the Hong Kong Cardiovascular Risk Factors Prevalence Study (CRISPS) cohort (6). The significant associations of the GNPDA2 SNP rs10938397 and *FTO* SNP rs6499640 ($r^2=1$ with rs8050136 on the HapMap for Han Chinese) with obesity were further replicated in another separate study in the Chinese population (7).

Epidemiological studies in recent years have suggested that central obesity, as indicated by an increased WC or waist-hip ratio, may be more important than general obesity, as reflected by BMI, in predicting the risk of the metabolic syndrome (MetS) and CVD (8–11). Indeed, central obesity is recognised as a key component of the MetS (12), a cluster of inter-related cardiometabolic abnormalities, which also include hypertension, hyperglycaemia and dyslipidaemia (hypertriglyceridaemia and reduced high-density lipoprotein cholesterol (HDLc)) (13, 14). It has been suggested that central obesity plays a causative role in the pathogenesis of MetS (12, 15, 16).

We hypothesised that individuals persistently affected by a particular condition may be under a strong influence from genetic susceptibility. Similarly, individuals who are persistently unaffected by a condition may be influenced by the protective effects conferred by certain genes. The CRISPS cohort, with 12-year longitudinal data, has allowed us to identify two such groups of individuals whom we hypothesise are likely to be genetically distinct. In this study, our major objective is to further establish the clinical significance of the three previously identified obesity-associated SNPs (rs10938397, rs8050136 and rs17782313) by evaluating their association with the persistence of central obesity and MetS. We carried out i) a longitudinal study on persistent central obesity, ii) a cross-sectional case-control study on MetS and iii) a longitudinal study on persistent MetS in a 12-year longitudinal study in Southern Chinese population.

Methods

Subjects

CRISPS is a population-based longitudinal study of cardiovascular risk factors, in which subjects were randomly selected from the general population in Hong Kong. Details of the CRISPS cohort were previously described (17–22). Briefly, in 1995–1996, 2895 Hong Kong Chinese (1412 males and 1483 females, aged 25–74 years) were recruited randomly using their telephone numbers (baseline). In 2000–2004, 1944 subjects (901 males, 1043 females, mean age: 52 ± 12 years, retention rate: 67.2%) returned for follow-up study (CRISPS2) (22). In the years 2005–2008, 1803 subjects (839 males, 964 females, mean age: 56 ± 11

years, retention rate of baseline cohort: 62.3%) enrolled in the latest follow-up study (CRISPS3).

In this study, out of the 2895 subjects at baseline, we only included those who had returned either to CRISPS2 or CRISPS3.

Twelve-year longitudinal study for persistent central obesity

- Persistent central obesity ($n=354$) included subjects who had central obesity at baseline and continued to have central obesity at CRISPS3.
- Persistent absence of central obesity ($n=994$) included subjects without central obesity at baseline, who remained free of central obesity at CRISPS3 (Table 1).

Cross-sectional case-control study for the MetS

- Cases ($n=816$) included subjects who documented to have MetS at either baseline or CRISPS2 or CRISPS3.
- Controls ($n=1398$) included subjects without MetS at baseline and subsequent follow-up visit(s) (Table 2).

Twelve-year longitudinal study for persistent MetS

- Persistent MetS ($n=225$) included subjects who had MetS at baseline and continued to have MetS at CRISPS3.
- Persistent absence of MetS (non-MetS) ($n=1221$) included subjects without MetS at baseline who remained free of MetS at CRISPS3 (Table 2).

From the cross-sectional case-control study cohort, the subsets of cases ($n=225$, ~28%) and controls ($n=1221$, ~87%) who showed persistence in their phenotypes (i.e. persistent MetS or persistent absence of

Table 1 Baseline clinical characteristics of subjects in the longitudinal study for persistent central obesity. Data as mean $\pm$ s.d.

Baseline parameter	Persistent central obesity		P value
	Present	Absent	
Number	354	994	–
Sex (male %)	37.6	52.6	<0.001
Age (years)	48.6 ± 11.1	42.9 ± 11.4	<0.001
BMI (kg/m^2)	28.6 ± 3.1	22.3 ± 2.5	<0.001
Waist circumference (cm)			
Male	96.2 ± 5.2	78.4 ± 6.5	<0.001
Female	87.5 ± 5.9	69.1 ± 5.3	<0.001
Fasting glucose (mmol/l)	5.6 ± 1.4	5.2 ± 1.0	<0.001
Two hours post-OGTT glucose (mmol/l)	8.0 ± 3.5	6.2 ± 2.4	<0.001
Fasting insulin ($\mu\text{U/ml}$) ^a	$7.7 (5.1\text{--}10.8)$	$4.2 (2.7\text{--}5.9)$	<0.001

^aNatural-log-transformed before analysis.

Table 2 Baseline clinical characteristics of subjects in the cross-sectional case–control study for MetS and longitudinal study for persistent MetS. Data as mean $\pm$ s.d. or median (interquartile range). Cases are defined as the presence of MetS in either baseline or CRISPS2 or CRISPS3 follow-up. Controls are defined as the absence of MetS in both baseline and subsequent follow-up(s).

Baseline parameter	Cross-sectional case–control study for MetS			Longitudinal study for persistent MetS		
	Case	Control	P value	Persistent MetS	Persistent non-MetS	P value
Number	816	1398	–	225	1221	–
Sex (male %)	47.7	46.3	0.527	47.3	47.6	0.934
Age (years)	50.0 $\pm$ 12.1	43.0 $\pm$ 11.4	<0.001	50.4 $\pm$ 10.7	42.3 $\pm$ 10.9	<0.001
BMI (kg/m ²)	26.4 $\pm$ 3.4	22.9 $\pm$ 3.0	<0.001	27.9 $\pm$ 3.0	23.0 $\pm$ 3.0	<0.001
Waist circumference (cm)						
Male	89.4 $\pm$ 8.5	79.6 $\pm$ 7.8	<0.001	93.0 $\pm$ 6.5	80.0 $\pm$ 7.6	<0.001
Female	81.9 $\pm$ 8.6	71.6 $\pm$ 7.3	<0.001	86.3 $\pm$ 7.6	71.5 $\pm$ 7.4	<0.001
Fasting glucose (mmol/l)	5.8 $\pm$ 1.7	5.1 $\pm$ 0.9	<0.001	6.2 $\pm$ 1.8	5.1 $\pm$ 0.7	<0.001
Two hours post-OGTT glucose (mmol/l)	8.3 $\pm$ 4.0	5.9 $\pm$ 1.9	<0.001	9.2 $\pm$ 4.3	5.9 $\pm$ 1.7	<0.001
Fasting insulin (μ U/ml) ^a	6.6 (4.6–9.9)	4.1 (2.8–6.0)	<0.001	8.3 (5.7–11.3)	4.2 (2.9–6.2)	<0.001

^aNatural-log-transformed before analysis.

MetS) from baseline to CRISPS3 were therefore included respectively as the cases and controls of the 12-year longitudinal study for persistent MetS (Table 2).

Anthropometric and biochemical measurements

All subjects were assessed after an overnight 10 h fast. The anthropometric (including blood pressure, weight, height, BMI, WC and hip circumference) and biochemical parameters (including plasma glucose, insulin and lipids) were measured as previously described (10, 22–25). All subjects, except those with diagnosed diabetes on medical treatment, underwent a 75 g oral glucose tolerance test (OGTT). Venous blood samples were taken for clinical biochemistry and genetic analyses. All participants gave written informed consent, and the study protocol was approved by the ethics committee of the University of Hong Kong.

Definition of central obesity and MetS

Central obesity was defined by WC $\geq$ 90 cm in men or $\geq$ 80 cm in women as suggested for Asian populations (26). MetS was defined according to the modified criteria proposed in the joint scientific statement by the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (27). An individual would be classified as having MetS if three out of the five following criteria were fulfilled:

- WC $\geq$ 90 cm in men or $\geq$ 80 cm in women.
- Triglyceride concentration $\geq$ 150 mg/dl (1.7 mmol/l).

- HDLC concentration < 40 mg/dl (1.0 mmol/l) in males or < 50 mg/dl (1.3 mmol/l) in females.
- Systolic blood pressure $\geq$ 130 mmHg and/or diastolic blood pressure $\geq$ 85 mmHg.
- Fasting blood glucose $\geq$ 100 mg/dl ($\geq$ 5.6 mmol/l).

Individuals receiving specific treatment for a criterion were considered as fulfilling that criterion.

Genetic analysis

The three SNPs, rs10938397 (GNPDA2), rs8050136 (FTO) and rs17782313 (MC4R), that showed the most promising associations with obesity in our previous case–control study (6) were examined for association with persistent central obesity and MetS in this study. Genomic DNA was extracted from available buffy coat samples by the standard phenol–chloroform extraction procedures. Genotypes of the three SNPs from 1938 subjects were obtained from our previous study (6). The three SNPs were genotyped in the remaining subjects by the TaqMan Pre-designed SNP Genotyping Assay (rs10938397: assay ID: C_1594245_10; rs8050136: assay ID: C_031259_10; rs17782313: assay ID: C_32667060_10; Applied Biosystems, Foster City, CA, USA). PCRs were performed in the GeneAmpPCR System 9700 thermal cycler according to the manufacturer's protocols, and assay products were analysed using Applied Biosystems PRISM 7000 Sequence Detection System for fluorescence intensity detection. At least two negative controls (without DNA) were included for the identification of contaminations in each 96-well plate. The Hardy–Weinberg equilibrium (HWE) for each SNP was examined by the De Finetti program available at <http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>. HWE P values were > 0.05 in the case and control subjects for all three SNPs. Average successful genotyping call rate and concordance rate were 99.46 and 98.33% respectively.

Statistical analysis

All statistical analyses were performed with SPSS (Version 16.0; Chicago, IL, USA). All continuous variables are expressed as mean $\pm$ s.d. or median with interquartile range as appropriate. All variables that did not follow a normal distribution in the Kolmogorov–Smirnov test were log-transformed before the analysis. Logistic regressions under the additive model were used to estimate the associations of each SNP with central obesity and MetS. A two-tailed *P* value of <0.05 was considered as statistically significant. The expected power of study was calculated using the Genetic Power Calculator available at <http://pngu.mgh.harvard.edu/~purcell/gpc/> (28). The combined genetic risk score (GRS) for the three SNPs studied were calculated by the simple count (count GRS) method (i.e. counting the number of risk alleles where 0, 1, 2 correspond to genotypes containing zero, one and two risk alleles respectively and a sum score was created out of the maximum number of six risk alleles for three variants) (29). Thirty-four subjects with missing genotypes for any of the three SNPs were excluded from the combined genetic risk analyses (25 controls and 9 cases from the MetS case–control study; 17 subjects from the persistent central obesity longitudinal study; and 24 subjects from the persistent MetS longitudinal study). The receiver operating characteristic curves were generated and the corresponding area under the curves (AUCs) were calculated with SPSS (Version 16.0).

Results

The three previously identified obesity-associated SNPs (rs10938397, rs8050136 and rs17782313) were genotyped in subjects from the population-based CRISPS cohort and examined for their associations with i) persistent central obesity, ii) MetS and iii) persistent MetS. The baseline clinical characteristics of subjects in these three studies were shown in Tables 1 and 2.

Association with persistent central obesity in the longitudinal prospective study

This study involved 354 subjects with persistent central obesity and 994 subjects with persistent absence of central obesity. Table 3 shows the results of the association analyses of the three SNPs and the combined GRS with persistent central obesity. Significant associations with persistent central obesity were observed in the *FTO* SNP rs8050136 ($P_{\text{age, sex-adjusted}} = 0.019$; odds ratio (OR) (95% confidence intervals (CI)): 1.35 (1.05, 1.73)) and *GNPDA2* SNP rs10938397 ($P_{\text{age, sex-adjusted}} = 3 \times 10^{-3}$; OR (95% CI): 1.34 (1.11, 1.63)). After Bonferroni correction for multiple testing, the association of the *GNPDA2* SNP rs10938397 remained significant ($P = 9 \times 10^{-3}$) and there was a

Table 3 Longitudinal study of the three single nucleotide polymorphisms (SNPs) and their combined genetic risk score (GRS) with persistent central obesity.

CHR	Nearest gene	SNP	Effect allele (1)	Other allele (2)	EAF case	EAF control	Genotype count		OR (95% CI)	$P_{\text{age, sex-adjusted}}$ (two-tailed)
							Case (1/12/22)	Control (1/12/22)		
4	<i>GNPDA2</i>	rs10938397	G	A	0.339	0.275	(155/158/41)	(520/400/73)	1.34 (1.11, 1.63)	3×10^{-3}
16	<i>FTO</i>	rs8050136	A	C	0.161	0.124	(13/88/253)	(11/225/758)	1.35 (1.05, 1.73)	0.019
18	<i>MC4R</i>	rs17782313	C	T	0.165	0.146	(8/100/243)	(15/255/708)	1.12 (0.87, 1.44)	0.372
Combined count GRS of <i>GNPDA2</i> SNP rs10938397, <i>FTO</i> SNP rs8050136 and <i>MC4R</i> SNP rs17782313									1.25 (1.10, 1.42)	4.92×10^{-3}

SNPs ranked by chromosome number. Significant associations are highlighted in bold. CHR, chromosome; EAF, effect allele frequency; MetS, metabolic syndrome.

Figure 1 Forest plot showing the risk of persistent central obesity and persistent MetS. OR (95% CI) for association of the *GNPDA2* SNP rs10938397, *FTO* SNP rs8050136 and *MC4R* SNP rs17782313 and their combined GRS with (a) persistent central obesity and (b) persistent MetS.

trend for association of the *FTO* SNP rs8050136 with persistent central obesity ($P=0.057$). In the combined genetic risk analysis, the combined GRS showed an OR of 1.25 (95% CI: 1.10, 1.42; $P_{\text{age, sex-adjusted}} = 4.92 \times 10^{-3}$, $\text{AUC}=0.565$) for each additional risk allele (Fig. 1a).

Association with MetS in the cross-sectional case-control study

Having observed the significant associations with persistent central obesity, we further investigated whether these SNPs would show significant associations with MetS in a cross-sectional case-control study involving 816 cases and 1398 controls. Table 4 shows the results of the association analyses of these three SNPs and the combined GRS with MetS. The *GNPDA2* SNP rs10938397 was the only SNP that showed a significant association with MetS ($P_{\text{age, sex-adjusted}}=0.011$; OR (95% CI): 1.20 (1.04, 1.38)). The association of rs10938397 with MetS remained significant even after Bonferroni correction for multiple testing ($P=0.033$). However, this association became insignificant after further adjustment for BMI ($P_{\text{age, sex, BMI-adjusted}}=0.100$; OR (95% CI): 1.14 (0.98, 1.34)). The count GRS showed an OR of 1.10 (95% CI: 1.01, 1.21; $P_{\text{age, sex-adjusted}}=0.036$, $\text{AUC}=0.530$) for each additional risk allele in the combined genetic risk analysis.

Association with persistent MetS in the longitudinal study

Finally, we evaluated the associations of these three SNPs with persistent MetS in the prospective population-based CRISPS cohort involving 225 subjects with persistent MetS and 1221 subjects with persistent absence of MetS (non-MetS). Table 4 shows the results of the association analyses of the three SNPs and the combined GRS with persistent MetS. Figure 1b shows the ORs and 95% CI for association with persistent MetS for these three SNPs. Although significant individual associations of the three SNPs with persistent MetS were not observed, the combined GRS of these SNPs showed an OR of 1.19 (95% CI: 1.03, 1.38; $P_{\text{age, sex-adjusted}}=0.019$, $\text{AUC}=0.547$) for each additional risk allele. However, this association was abolished on adjustment for either fasting insulin level ($P_{\text{age, sex, fasting insulin level-adjusted}}=0.282$; OR (95% CI): 1.10 (0.92, 1.32)) or BMI ($P_{\text{age, sex, BMI-adjusted}}=0.201$; OR (95% CI): 1.12 (0.94, 1.35)), suggesting that the effects of these SNPs are likely to be mediated through obesity-related insulin resistance and adiposity.

Discussion

In this study, we investigated the associations of three obesity-associated SNPs (rs10938397, rs8050136 and rs17782313) identified from recent genome-wide association studies (4, 5) with persisting central obesity and MetS using a longitudinal prospective study. The allele frequencies of these three SNPs observed in this study were similar to those reported in the HapMap Han Chinese population. We have successfully detected significant associations of the *GNPDA2* SNP rs10938397 and the well-known *FTO* SNP rs8050136 with persistent central obesity in the 12-year longitudinal study. We also observed the association of the *GNPDA2* SNP rs10938397 with MetS. The combined genetic risk of all three SNPs showed significant associations with both persistent central obesity and persistent MetS. However, the association of the combined GRS with persistent MetS was abolished following adjustment for fasting insulin level or BMI, suggesting that the increased risk conferred by these SNPs may be secondary to their association with obesity and/or insulin resistance. We failed to detect significant associations of rs17782313 with central obesity or MetS in this study, even though this SNP or another *MC4R* SNP rs12970134 (which is in high LD with rs17782313 – $\text{LD}=0.81$ in Han Chinese according to HapMap) has previously been shown to be associated with insulin resistance, WC, obesity, fat mass, height and weight in Caucasians (30, 31). This could have been due to our small sample size as compared with the larger-scale studies in the European populations and the relatively wide 95% CI.

Table 4 Cross-sectional and longitudinal study of the three SNPs and their combined GRS with MetS and persistent MetS.

CHR	Nearest gene	SNP	Effect allele (1)	Other allele (2)	EAF		Genotype count		OR (95% CI)	P _{age, sex-adjusted} (two-tailed)
					Case	Control	Persistent case (11/12/22)	Persistent control (11/12/22)		
Cross-sectional study for MetS										
4	<i>GNPDA2</i>	rs10938397	G	A	0.309	0.272	(77/350/388)	(105/551/739)	1.20 (1.04, 1.38)	0.011
16	<i>FTO</i>	rs8050136	A	C	0.138	0.128	(17/192/607)	(24/310/1064)	1.09 (0.91, 1.32)	0.351
18	<i>MC4R</i>	rs17782313	C	T	0.158	0.156	(25/206/577)	(27/375/972)	0.99 (0.83, 1.18)	0.906
Combined count GRS of <i>GNPDA2</i> SNP rs10938397, <i>FTO</i> SNP rs8050136 and <i>MC4R</i> SNP rs17782313										
Longitudinal study for persistent MetS										
4	<i>GNPDA2</i>	rs10938397	G	A	0.318	0.275	(24/95/106)	(87/496/636)	1.21 (0.96, 1.52)	0.103
16	<i>FTO</i>	rs8050136	A	C	0.151	0.139	(7/54/164)	(22/273/926)	1.21 (0.91, 1.62)	0.194
18	<i>MC4R</i>	rs17782313	C	T	0.176	0.152	(8/63/154)	(20/325/852)	1.20 (0.90, 1.58)	0.210
Combined count GRS of <i>GNPDA2</i> SNP rs10938397, <i>FTO</i> SNP rs8050136 and <i>MC4R</i> SNP rs17782313										

SNPs ranked by chromosome number. Significant associations are highlighted in bold. CHR, chromosome; EAF, effect allele frequency; MetS, metabolic syndrome.

We observed significant association of the *GNPDA2* and *FTO* SNPs with persistent central obesity in the 12-year longitudinal study. As central obesity represents one of the best predictors for MetS in our population (10), it is therefore not surprising that we also observed a significant association of the combined genetic risk of the three SNPs with persistent MetS although individual association of the three SNPs with persistent MetS was not observed. Indeed, the role of central obesity was considered so significant in the development of MetS that central obesity, as defined by the ethnic-specific WC, was previously proposed by the International Diabetes Federation as a prerequisite for the definition of MetS (13).

Apart from being a good predictor for MetS, central obesity has been suggested to be involved in the development of cardiometabolic disorders, such as T2DM and CVD. In our population, central obesity has been demonstrated to have a greater contribution to the development of cardiovascular risk than general obesity (32) and was also shown to be independently associated with worsening of glucose intolerance (23). There is therefore an urgent need to identify individuals at risk of having persistent central obesity for early interventions such as lifestyle modifications and individualised management strategies, in order to prevent these obesity-related diseases.

The major limitation of this study is our relatively small sample size. Our sample size may not be able to provide sufficient power to detect the significance for some of the associations as the effect sizes and allele frequencies of the SNPs studied were relatively low. At a significance level of 0.05, our sample size for the longitudinal persistent central obesity study provided more than 90% power to detect a significant association of the *FTO* SNP (rs8050135) and *GNPDA2* SNP (rs10938397) with the observed ORs, by assuming a prevalence of 0.323 (average prevalence of central obesity at baseline, CRISPS2 and CRISPS3). However, our sample size for the longitudinal persistent MetS study could only achieve 40–60% power to detect a persistent MetS-susceptible SNP, assuming a disease prevalence of 0.238 (average prevalence of MetS at baseline, CRISPS2 and CRISPS3), likely to be due to the small observed ORs. Larger prospective studies of these genetic variants for predicting central obesity and MetS would be of great interest. We should also acknowledge that as central obesity is the key component of MetS, the significant association with MetS, observed in the persistent central obesity-associated SNP, rs10938397, could be due to the fact that centrally obese subjects are more likely to develop MetS. Moreover, the prospective cases and controls were, in fact, subsets of the cases and controls respectively in the cross-sectional study for MetS. Out of the 816 cases and 1398 controls of the cross-sectional study for MetS, 225 (~28%) cases and 1221 (~87%) controls fulfilled the inclusion criteria as subjects with persistent MetS and persistent absence

of MetS respectively for the longitudinal study for persistent MetS. We have simply identified, among the baseline MetS cases and non-MetS controls, the respective subset that is likely to have a stronger genetic influence because of the apparent persistence of their phenotype. Another large independent population-based prospective cohort would enable us to confirm our current findings.

In conclusion, we have demonstrated in a 12-year longitudinal study that the *FTO* SNP rs8050136 and *GNPDA2* SNP rs10938937 may be useful for predicting persistent central obesity, a key component of MetS, in the Southern Chinese population. However, whether these genetic variants also confer susceptibility to the development of central obesity or MetS in other ethnic groups remains to be confirmed. Further investigations of these genetic variants in other ethnic groups, whether in the form of cross-sectional or longitudinal studies, would be of great interest. With the increasing number of central obesity-susceptible genes being identified, their combined genetic risk might eventually allow us to identify individuals who are at high risk of developing central obesity. Importantly, this information may advance our understanding of the pathogenesis of obesity and MetS and from that may even lead to new therapeutic approaches. The *GNPDA2* gene appeared to be an interesting gene, which might play a role in the development of metabolic disorders, such as obesity and MetS. Further studies to explore the functional relevance of this gene and fine-mapping studies to identify the causative disease-susceptible genetic variants are warranted. Availability of sufficiently large sample size remains one of the issues hindering the progression in genetic studies to detect variants with modest effect sizes. The resolution of this problem would rely on the collaborations of multiple research groups.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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