Obesity Susceptibility Genetic Variants Identified from Recent Genome-Wide Association Studies:
Implications in a Chinese Population


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Context: Recent large-scale genome-wide association studies identified novel genetic variants associated with obesity and body mass index (BMI) in addition to the well-described FTO and MC4R genetic variants.

Objective: This study aimed to examine 13 previously reported obesity and/or BMI-associated loci for associations with obesity in Chinese.

Design and Study Participants: This was a cross-sectional case-control study in 470 obese cases (BMI ≥ 27.5 kg/m²) and 700 normal-weight controls (18.5 ≤ BMI ≤ 23.0 kg/m²).

Results: A significant association with obesity could be replicated (one-tailed \( P < 0.05 \)) in seven of the 13 single-nucleotide polymorphisms (SNPs) in the case-control study. These included GNPDA2 rs10938397 (\( P = 7.3 \times 10^{-6} \)); FTO rs8050136 (\( P = 8 \times 10^{-4} \)); MC4R rs17782313 (\( P = 1.2 \times 10^{-3} \)); KCTD15 rs29941 (\( P = 8 \times 10^{-3} \)); SFRS10-ETV5-DGKG rs7647305 (\( P = 0.023 \)); SEC16B-RASAL2 rs10913469 (\( P = 0.041 \)); and NEGR1 rs3101336 (\( P = 0.046 \)). Combined genetic risk scores were calculated, and we observed ORs ranging from 1.17 to 1.23 for each unit increase in the genetic risk scores. Associations with obesity-related quantitative traits were analyzed separately for cases and controls. KCTD15 SNP rs29941 (\( P = 1 \times 10^{-3} \)) was significantly associated with fasting glucose in the control group, whereas only the FTO SNP rs8050136 was associated with BMI (\( P = 3.5 \times 10^{-3} \)) in the obese group. However, in an extension study of 1938 subjects from the population-based Hong Kong Cardiovascular Risk Factors Prevalence Study, rs8050136, rs10938397, and rs17782313 showed significant associations with BMI.

Conclusion: We have succeeded in replicating, in a Chinese population, the associations with obesity in seven SNPs reported in recent genome-wide association studies. Further functional and fine-mapping studies to elucidate the roles of these putative obesity-related genes and genetic variants are warranted. (J Clin Endocrinol Metab 95: 1395–1403, 2010)

Obesity is a major risk factor for several chronic diseases such as type 2 diabetes mellitus (T2DM) and cardiovascular diseases. The prevalence of obesity is on the rise. According to the World Health Organization, more than 400 million adults were obese in 2005, and it is estimated that more than 700 million adults will be obese by 2015 (1). This phenomenon is largely attributed to the easy access to high-calorie foods and diminished physical activity. A growing body of evidence has linked genetic variations to obesity. The most prominent genetic variants associated with obesity and BMI are FTO and MC4R. However, recent genome-wide association studies have identified additional genetic variants that contribute to obesity susceptibility.

Abbreviations: AUC, Area under the curve; BMI, body mass index; CI, confidence interval; CRISPS, Cardiovascular Risk Factors Prevalence Study; FDR, false discovery rate; GRS, genetic risk score; GWA, genome-wide association; LD, linkage disequilibrium; OGTT, oral glucose tolerance test; OR, odds ratio; ROC, receiver-operating characteristic; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus; WC, waist circumference.
activity in recent decades. This obesity epidemic is affecting both developed and developing countries, such as China. Based on the World Health Organization recommended obesity criteria for Asians (2), the prevalence of obesity [body mass index (BMI) ≥27.5 kg/m²] in men was 10.5% in mainland China (3), whereas that in the Hong Kong Chinese population was higher, being about 16.3% (4), according to the Hong Kong Cardiovascular Risk Factors Prevalence Study (CRISPS).

Obesity is a multifactorial condition resulting from the complex interaction between environmental and genetic factors (1, 5). Twins and adoption studies have demonstrated clear evidence for the genetic predisposition to the development of obesity (6, 7). Recently two large-scale genome-wide association (GWA) studies by Thorleifsson et al. (8) and Willer et al. (9) identified a number of novel genetic variants associated with obesity and/or BMI. These included variants at or close to 13 genetic loci: NEGR1, SEC16B-RASAL2, TMEM18, SFRS10-ETV5-DGKG, GNPD2A, NCR3-AIF1-BAT2, LGR4-LIN7C-BDNF, MTC2A, BCDIN3D-FAIM2, SH2B1-ATP2A1, KCTD15, as well as the well-described FTO (fat mass and obesity associated) (10–12) and MC4R (melanocortin 4 receptor) (13, 14) loci. A recent replication study in the Swedish population reported significant association with obesity in variants at or close to FTO, SH2B1, MTC2A, MC4R, NEGR1, and GNPD2A (15). It should be noted that these studies were conducted mainly on subjects from Caucasian ancestry. Successful replications of the novel association signals in different populations will be important for the validation of these novel findings. Several case-control and population-based studies had shown significant associations of the well-known FTO variants (rs8050136 and rs9939609) with obesity and BMI in Hong Kong, Taiwan, and Singapore Chinese populations (16–18). Contrarily, Li et al. (19) reported no association of the FTO variants with obesity and BMI in a population-based cohort of Shanghai and Beijing Chinese, and a multietnic study also described lack of association of rs9939609 with waist circumference (WC) or severe obesity in a Chinese subgroup (20). However, apart from the FTO variants, little is known about the implications of the other genetic variants discovered in recent GWA studies in Chinese. Our objective was to examine these previously reported obesity and/or BMI-associated loci for associations with obesity in a case-control study of Chinese subjects.

### Subjects and Methods

#### Case-control study

We performed a cross-sectional case-control study involving 1170 Chinese subjects to examine the association with obesity in 13 single-nucleotide polymorphisms (SNPs), each of which would represent one of the genetic loci that were previously reported to have an association with obesity and/or BMI in Caucasians (8, 9). Subjects with BMI of 27.5 kg/m² or greater were considered obese, according to the recommendation for Asians (2). Unrelated obese subjects (n = 470) with BMI of 27.5 kg/m² or greater were either selected, on the basis of their BMI, from the CRISPS cohort, which has been described elsewhere (21–23), or were recruited from the Endocrine Clinic at the Queen Mary Hospital, Hong Kong, whereby secondary causes of obesity had been excluded. Unrelated healthy lean controls (n = 700) were all selected from the CRISPS cohort and had normal BMI defined as 18.5–23 kg/m² (2). In addition, 23.6% of the cases and 3.1% of the normal-weight controls had T2DM. There was no significant difference in age or sex distribution between the two groups (Table 1).

The extension study included a total of 1938 subjects (46.44% male; mean age 45.97 ± 12.21 yr) from the population-based CRISPS cohort with available DNA samples. Of these, 957 (~49%) were already included in the case-control study on the basis of their BMI.

#### Anthropometric and biochemical measurements

The anthropometric (including weight, height, BMI, and WC) and biochemical measurements (including plasma glucose and plasma insulin) were measured as previously described (21–23). Fasting glucose (mmol/liter) 6.2 ± 2.3, 2-h post-OGTT glucose (mmol/liter) 8.4 ± 3.9, HOMA-IR 2.5 (1.5–4.6), Fasting insulin (μU/ml) 9.6 (6.4–16.0).
Genetic analyses
SNPs located in the 13 genetic loci identified through the recent GWA studies showing significant associations with obesity and/or BMI (8, 9) were examined for association with obesity in the present study. For the reported SNPs showing strong linkage disequilibrium (LD) ($r^2 > 0.8$) on the HapMap for Han Chinese (25), only one representative SNP was chosen for genotyping, and for loci with more than one reported association SNPs, the SNP with the strongest association in the previous report was selected to represent the locus. A total of 13 SNPs was thus selected, and these included rs3101336 (NEGR1, $r^2 = 1$ with rs2568958 and rs2815752), rs10913469 (SEC16B-RASAL2), rs4854344 (TMEM, $r^2 = 1$ with rs7561317 and rs6548238), rs7647305 (SFRS10-ETV5-DGKG), rs10938397 (GNPDA2), rs2844479 (NCR3-AIFI-BAT2), rs925946 (LGR4-LIN7C-DBNF), rs10838378 (MTCH2), rs7138803 (BCDIN3D-FAIM2), rs4788102 (SH2B1-ATP2A1, $r^2 = 1$ with rs7498665), rs8050136 (FTO, rs8050136 $r^2 = 1$ with rs9939609), rs17782313 (MC4R, $r^2 = 0.81$ with rs12970134), and rs29941 (KCTD15).

Genomic DNA was extracted from buffy coat by the standard phenol-chloroform extraction procedures. All SNPs were genotyped by the Sequenom iPLEX Gold genotyping assay, except rs10938397, rs2844479, and rs29941. Genotyping for these three SNPs were performed using TaqMan predesigned SNP genotyping assay (rs10938397: assay ID: C_1594245_10; rs2844479: assay ID: C_26778727_10; rs29941: assay ID: C_2843134_10; Applied Biosystems, Foster City, CA). PCRs were performed in the GeneAmp PCR System 9700 thermal cycler according to the manufacturer’s protocols, and assay products were analyzed 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. Hardy-Weinberg equilibrium for each SNP was examined by the exact test using PLINK (26). Hardy-Weinberg equilibrium $P$ values were greater than 0.05 in the case and control subjects for all SNPs. Average successful genotyping call rate in the case-control study was 99.23% and concordant rate was 99.6%, based on 20 duplicate samples. Average successful genotyping call rate and concordant rate in the extension study of the three SNPs were greater than 99.24%.

Statistical analysis
All statistical analyses were performed with either PLINK version 1.05 (available at http://pngu.mgh.harvard.edu/~purcell/plink/) (26) or SPSS (version 16.0; Chicago, IL). All continuous variables were expressed as mean $\pm$ SD or median with inter-quartile range as appropriate. To correct for multiple comparisons, Bonferroni corrections and false discovery rate (FDR) analyses were performed. All variables that did not follow a normal distribution, as shown by a significant $P$ value in the Kolmogorov-Smirnov test, were natural-logarithmically transformed before analysis. $\chi^2$ tests, logistic regressions, and linear regressions under the additive model implemented in PLINK were used to estimate the associations of each SNP with obesity and its related phenotypic parameters. We reported one-tailed $P$ values calculated on the basis of the direction of effects presented in the original GWA studies reports. If an odds ratio (OR) was in the same direction as previously reported, a one-tailed $P$ value was calculated as $P$ divided by 2 ($P/2$), whereas a one-tailed $P$ value for an opposite effect was calculated as 1 minus $P$ divided by 2 ($1-P/2$). A one-tailed $P < 0.05$ was considered as statistically significant.

To compare the effects of SNPs in this study and those in the original GWA reports, a pooled OR was reported in Table 2 for SNPs that were studied in both of the GWA reports. The logged OR from each of the GWA studies were combined and inversely weighted by their variances. This produced a pooled logged OR and its sampling variance, which were then converted into a pooled OR with its 95% confidence interval (CI). The statistical power of the study was calculated using the Genetic Power Calculator (available at http://pngu.mgh.harvard.edu/~purcell/gpc/) (27).

Combined genetic risk scores (GRSs) for the 13 SNPs studied were calculated by four different methods as previously described (28): 1) simple count (count GRS); 2) weighted GRS, based on published ORs; 3) weighted GRS, based on ORs of the current study; and 4) weighted GRS developed by multiple logistic regression analysis of the current data. For comparison with the count GRS, each score derived from methods 2–4 was divided by the corresponding maximum possible score and then multiplied by 26. The GRS derived from each of these methods was analyzed by logistic regression as a continuous predictor variable. Subjects (36 cases and 48 controls) with missing genotypes for any of the 13 SNPs were excluded from analyses of the combined genetic risk. The receiver-operating characteristic (ROC) curves were plotted with the corresponding area under the curve (AUC) calculated in SPSS (version 16.0).

Results
Association with obesity in case-control study
We genotyped 13 SNPs from the 13 loci that showed significant associations with obesity and/or BMI in the recent GWA studies (8, 9) in 470 obese subjects (BMI $\geq 27.5$) and 700 normal-weight individuals (18.5 $\leq$ BMI $\leq 23.0$) of Chinese ancestry. Their clinical characteristics were shown in Table 1. Table 2 shows the results of the association analyses of the 13 SNPs with obesity and the effect allele frequencies. The allele frequencies of SNPs observed in the current study (Table 2) were similar to those reported in the HapMap Han Chinese. In our case-control cohort, seven of the 13 SNPs showed statistically significant associations with obesity. These included the GNPDA2 SNP rs10938397 [one-tailed $P = 7.3 \times 10^{-4}$; OR (95% CI) 1.35 (1.12–1.62)]; FTO SNP rs8050136 [one-tailed $P = 8 \times 10^{-4}$; OR (95% CI) 1.48 (1.16, 1.89)]; MC4R SNP rs17782313 [one-tailed $P = 1.2 \times 10^{-3}$; OR (95% CI) 1.43 (1.14–1.81)]; KCTD15 SNP rs29941 [one-tailed $P = 8 \times 10^{-3}$; OR (95% CI) 1.27 (1.05–1.55)]; SFRS10-ETV5-DGKG SNP rs7647305 [one-tailed $P = 0.023$; OR (95% CI) 1.36 (1.01–1.84)]; SEC16B-RASAL2 SNP rs10913469 [one-tailed $P = 0.041$; OR (95% CI) 1.21 (0.98–1.49)]; and NEGR1 SNP rs3101336 [one-tailed $P = 0.046$; OR (95%
| CHR | Nearest gene(s) | SNP | Reported OR (95% CI) | Effect allele (1) | Other allele (2) | EAF (cases) | EAF (controls) | OR (95% CI) | P
\textsubscript{unadjusted} (one tailed) | P
\textsubscript{adjusted} (one tailed) |
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<td>1.03 (0.98, 1.08)</td>
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<td>G</td>
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SNPs ranked by \( P \text{unadjusted} \) values. SNPs showed statistically significant association with obesity are highlighted in bold. CHR, Chromosome; eAF, Effect allele frequency.

*For effects in the same direction as previously reported OR values were calculated as \( P/2 \); for effects in opposite direction, one-tailed \( P \) values were calculated as \( 1-P/2 \); \( a \) adjusted for age and sex; \( b \) pooled OR (95% CI) of rs8050136 and rs9939609; \( c \) pooled OR (95% CI) of rs2568958 and rs2815752; \( d \) pooled OR (95% CI) of rs7561317 and rs6548238; \( e \) pooled OR (95% CI) of rs7498666.

Table 2. Association analyses of 13 SNPs with obesity
current data set, and ORs derived from multiple logistic regression, respectively. In the ROC analysis, the AUC was 0.582 for the simple count method, and 0.592, 0.614, and 0.617 for the three weighted GRSs, respectively. Supplemental Fig. 1, published as supplemental data on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org, shows the ROC curves and AUCs of each GRS. When the combined genetic risk of the seven SNPs significantly associated with obesity in this study was analyzed, we observed an OR of 1.37 (95% CI 1.25, 1.53; P = 3.34 × 10^{-11}; AUC 0.617) and 1.39 (95% CI 1.26, 1.53; P = 2.97 × 10^{-11}; AUC 0.617) for the weighted GRS based on the ORs of the current study and multiple logistic regression, respectively.

**Association with BMI in the case-control study**

We then further examined the associations of these seven obesity-associated SNPs with the obesity-related quantitative traits including BMI, WC, fasting glucose level, 2-h post-oral glucose tolerance test (OGTT) glucose level, homeostasis model assessment insulin resistance index, and fasting insulin level in case and control groups separately. Supplemental Tables 1 and 2 summarize the results of the association analyses with these quantitative traits in controls and cases, respectively. Only the FTO SNP rs8050136 showed a significant association with BMI [one tailed P = 3.5 × 10^{-3}; β (95% CI) 1.18 (0.32, 2.04)] and only in the obese group, with similar significance level obtained after age and sex adjustment.

**Association with fasting glucose and 2-h post-OGTT glucose level in the case-control study**

The KCTD15 SNP rs29941 was significantly associated with increased fasting glucose level in the control group [one tailed P = 1 × 10^{-3}, β (95% CI) 0.14 (0.05,0.23)] and remained significant after adjustment for age, sex, and BMI [one tailed P_{age,sex,BMI adjusted} = 1 × 10^{-3}, β (95% CI) 0.13 (0.05,0.22)]. The risk allele C of rs29941 was also nominally associated with increased 2-h post-OGTT glucose level in the control group [one tailed P = 0.040, β (95% CI) 0.21 (-0.02, 0.43)], even when adjusted for age, sex, and BMI [one tailed P_{age,sex,BMI adjusted} = 0.045, β (95% CI) 0.19 (-0.03, 0.41)]. None of the other SNPs showed significant association with any other quantitative traits in the case or control group.

**Association with BMI and WC in the extension study**

Because the associations of rs8050136, rs10938397, and rs17782313 with obesity were highly significant and remained significant, even after Bonferroni correction, we suspected that the lack of association of rs10938397 and rs17782313 with BMI or WC in the case or control groups might have been due to the narrow range of BMI and WC in each respective group. We therefore extended the study of these three SNPs to include the rest of the population in the CRISPS cohort with available DNA samples. Supplemental Table S3 summarizes the results of the association analyses with BMI and WC in the extended study. In a total of 1938 subjects of the CRISPS cohort, we observed significant associations of rs10938397 [one tailed P = 0.011, β (95% CI) 0.29 (0.04, 0.54)], rs17782313 [one tailed P = 0.011, β (95% CI) 0.37 (0.05, 0.68)], and rs8050136 [one tailed P = 7 × 10^{-3}; β (95% CI) 0.42 (0.08,0.75)] with BMI. Similar results were obtained after age and sex adjustment. We also observed, in females, significant associations with WC (rs10938397: one tailed P = 1.5 × 10^{-3}; β (95% CI) 1.25 (0.41, 2.09); rs17782313: one tailed P = 2 × 10^{-3}; β (95% CI) 1.59 (0.52,2.65); rs8050136: one tailed P = 0.010; β (95% CI) 1.36 (0.22,2.49)].

**Discussion**

In this study, we investigated the associations of 13 previously reported obesity- and/or BMI-associated SNPs with obesity and obesity-related traits in a case-control study involving 1170 Chinese subjects. We successfully replicated the associations with obesity in 7 SNPs in our population. This demonstrated that some of the published obesity-associated genetic variants based on studies in the
Caucasian population also impact the development of obesity in this Chinese population. For all seven obesity-associated SNPs, we observed even higher ORs than that reported in the original GWA reports (8, 9). However, we also noticed that the \( P \) values observed for the seven obesity-associated SNPs were less significant than those reported in the original studies, likely to be due to our small sample size (supplemental Table S4). Notably, all reported ORs from the GWA studies were contained within the 95% CI in this study (Fig. 1), suggesting that the unsuccessful replication of the other reported SNPs could have been due to the wide 95% CI and small sample size of this study. Alternatively, it might be due to differences in the genetic compositions and LD patterns between Chinese and Caucasian populations. Indeed, these SNPs tend to be less common in the Chinese population than the Caucasian population (supplemental Table S5). Based on the ORs observed in this study, our sample size had a greater than 80% power to detect a significant association of the top three SNPs (98% for rs8050136; 97% for rs10938397 and rs17782313), although the expected power would be 29–62% for these three SNPs if based on the published effect sizes (supplemental Table S5).

We showed that the combination of genetic data from the 13 SNPs might provide some meaningful information for predicting the risk of obesity. Nonetheless, the clinical utility of such information remains to be established. Approximately 17–23% increased risk of obesity was observed for every unit increase in the combined GRSs. However, the discriminatory power of their genetic risk alleles is likely to be limited, as reflected by the modest magnitude of the AUCs in the ROC analyses. In time, with more and more obesity susceptibility genes being identified, their combined genetic information might become useful for clinical applications, such as in the genetic screening of at-risk individuals.

Despite the fact that we observed significant associations between respective SNPs with obesity, we failed to show an association of these SNPs with the common obesity-related phenotypes, BMI and WC, in our case-control study except for the \( FTO \) SNP rs8050136, which was significantly associated with BMI in the case group. This again could have been due to the relatively small sample size and narrow range of the tested quantitative traits in both the case and control groups. In our study, the robust effect of the \( FTO \) variant rs8050136 was clearly evident, being the SNP with the highest OR (1.48) for association with obesity and demonstrating significant association with BMI in the case group despite the relatively small sample size and the narrow range of BMI. It has been shown that the estimated heritability of BMI in Chinese ranged from 0.42 to 0.54 (29–31). However, based on linear regression analysis, only about 4.1% of this could be explained by the seven obesity-associated SNPs reported in the current study.

When the entire population-based CRISPS cohort was included, significant associations with BMI and WC were observed for rs10938397, rs17782313, and rs8050136. However, we should acknowledge that there were overlapping subjects (~49% of the CRISPS cohort) between the case-control and population-based cohort, and observation of significant associations of these three SNPs with BMI and WC in the CRISPS cohort might be just a reflection of an expanded case-control study. Another large independent Chinese population-based cohort would better enable us to validate our current findings and investigate the associations of these obesity-associated SNPs with obesity-related quantitative traits.

Because the identification of \( FTO \) as the important obesity predisposing gene, variants within this gene were extensively studied in different populations (10–12, 16–20, 32–34). rs8050136 and rs9939609, which are in complete LD in the Han Chinese population, are located within a LD block in the first intron of \( FTO \). Various reports described significant associations of the \( FTO \) genetic variants within this well-defined LD block with obesity, BMI, WC, and weight (10–12, 16–18, 32–34). In addition to the well-described \( FTO \) SNP (rs8050136), the \( GNPDA2 \)
(rs10938397) and MC4R (rs17782313) SNPs showed the most promising results in this study. rs10938397 is located about 450 kb upstream of GNPD2A (glucosamine-6-phosphate deaminase 2), which has been proposed to be involved in aminosugar metabolism and carbohydrates metabolisms (35). rs17782313 is located about 190 kb downstream of MC4R: this SNP was previously reported to be associated with obesity, fat mass, weight, and height (13). rs12970134, a SNP in strong LD with rs17782313 in Han Chinese, was also reported to be associated with WC and insulin resistance (14). A search for possible transcription factor binding sites using MatInspector (36) suggested that the risk alleles of rs10938397 (G allele) and rs17782313 (C allele) may abolish binding sites for transcription factors MYT1 (myelin transcription factor 1) and ATF4 (activating transcription factor 4), respectively. MYT1, also known as proteolipid protein binding protein, is a zinc finger transcription factor that is involved in neuronal cells development. Myt1 is expressed in both endocrine progenitor and differentiated endocrine cells in embryonic pancreas (37). Pancreas-specific Myt1 knockout mice showed abnormal endocrine differentiation, glucose intolerance, and attenuated glucose-induced insulin secretion, suggesting a role of Myt1 in regulating differentiation and function of the endocrine pancreas (37). ATF4 is also known as cAMP-response element-binding protein-2, and it may act as a repressor of cAMP-response element-dependent transcription (38). Future works elucidating the roles of these putative obesity-related genes and genetic variants will, no doubt, be of great interest.

Obesity is an important risk factor for hyperglycemia and T2DM, and the relationship of obesity-associated SNPs to glycemia deserves attention. Here we observed a significant association of rs29941 with fasting plasma glucose in the control group and rs29941 located close to KCTD15 with fasting plasma glucose in the control group, even after adjustment for age, sex, and BMI. We showed that the combined genetic risk of SNPs might provide useful information for the prediction of obesity. More positive association signals will continuously emerge through GWA studies in the future, and large-scale independent replication studies from different populations are essential for the verification of these novel association signals. Collaborations between different research groups will be extremely useful in creating a sufficiently large cohort for the detection of variants with modest effect size. Further functional studies to investigate the possible roles of the newly identified obesity-associated genes and fine-mapping studies to identify the causative disease-susceptibility genetic variants will be important to expand our knowledge and understanding of energy homeostasis and the development of obesity.

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