

Associations of Six Single Nucleotide Polymorphisms in Obesity-Related Genes With BMI and Risk of Obesity in Chinese Children

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OBJECTIVE—Childhood obesity strongly predisposes to some adult diseases. Recently, genome-wide association (GWA) studies in Caucasians identified multiple single nucleotide polymorphisms (SNPs) associated with BMI and obesity. The associations of those SNPs with BMI and obesity among other ethnicities are not fully described, especially in children. Among those previously identified SNPs, we selected six (rs7138803, rs1805081, rs6499640, rs17782313, rs6265, and rs10938397, in or near obesity-related genes *FAIM2*, *NPC1*, *FTO*, *MC4R*, *BDNF*, and *GNPDA2*, respectively) because of the relatively high minor allele frequencies in Chinese individuals and tested the associations of the SNPs with BMI and obesity in Chinese children.

RESEARCH DESIGN AND METHODS—We investigated the associations of these SNPs with BMI and obesity in school-aged children. A total of 3,503 children participated in the study, including 1,229 obese, 655 overweight, and 1,619 normal-weight children (diagnosed by the Chinese age- and sex-specific BMI cutoffs).

RESULTS—After age and sex adjustment and correction for multiple testing, the SNPs rs17782313, rs6265, and rs10938397 were associated with BMI ($P = 1.0 \times 10^{-5}$, 0.038, and 0.00093, respectively) and also obesity ($P = 5.0 \times 10^{-6}$, 0.043, and 0.00085, respectively) in the Chinese children. The SNPs rs17782313 and rs10938397 were also significantly associated with waist circumference, waist-to-height ratio, and fat mass percentage.

CONCLUSIONS—Results of this study support obesity-related genes in adults as important genes for BMI variation in children and suggest that some SNPs identified by GWA studies in Caucasians also confer risk for obesity in Chinese children.
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In recent years, the prevalence of adult and childhood obesity has been increasing in most parts of the world, including China (1,2). Overweight children show a higher risk for severe adult obesity (3). Childhood obesity strongly predisposes to some adult diseases such as hypertension, type 2 diabetes, and cardiovascular disease (4–6).

Six single nucleotide polymorphisms (SNPs) (rs7138803, rs1805081, rs6499640, rs17782313, rs6265, and rs10938397, located in or near the fas apoptotic inhibitory molecule 2 [*FAIM2*] gene, the Niemann-Pick disease type C1 [*NPC1*] gene, the fat mass and obesity associated [*FTO*] gene, the melanocortin-4 receptor [*MC4R*] gene, the brain-derived neurotrophic factor [*BDNF*] gene, and the glucosamine-6-phosphate deaminase 2 [*GNPDA2*] gene, respectively) were reported to be associated with obesity by genome-wide association (GWA) studies in Caucasians (7–9). Among these SNPs, rs6265 was associated with BMI in European-American children (10), and rs17782313 and rs10938397 were associated with obesity in Chinese adults (11). However, no independent replication studies of the six SNPs were conducted in Chinese children.

To investigate the associations of these six SNPs with BMI and the risk of overweight and obesity in Chinese children, we genotyped the SNPs in children who participated in the population-based Beijing Child and Adolescent Metabolic Syndrome (BCAMS) study (12). We tested the associations of the six SNPs with BMI, waist circumference, fat mass percentage (FMP), waist-to-height ratio (WHtR), and birth weight as continuous traits. Furthermore, we analyzed the associations of the SNPs with risk of overweight or obesity as dichotomized traits.

RESEARCH DESIGN AND METHODS

Subjects were recruited from a cross-sectional population-based survey termed the BCAMS study (12). The survey included a questionnaire, medical examination, anthropometric measurement, and finger capillary blood tests among a representative sample ($n = 19,593$; boys 50%) of Beijing children aged 6–18 years in 2004. Anthropometric measurement included weight, height, waist circumference, and FMP by bioimpedance analysis. Birth weight was collected from self-report questionnaires that were completed by parents or guardians.

Within this large group of children, 1,229 obese, 655 overweight, and 1,619 normal-weight children were randomly recruited and diagnosed by the Chinese age- and sex-specific BMI cutoffs (supplementary Table 1 available at <http://diabetes.diabetesjournals.org/cgi/content/full/db10-0273/DC1>) (13). Also, venipuncture blood samples were collected. We obtained written informed consent from all participants. The BCAMS study was approved by ethics committees of the Capital Institute of Pediatrics.

Measurement of anthropometric parameters. All instruments were validated following the standard methods of the manufacturers (14). BMI was calculated as weight in kilograms divided by the square of height in meters.

TABLE 1
BMI according to genotypes and per effect allele change in BMI after age and sex adjustment

SNP	Position	Nearest gene	Effect allele (1)	Other allele (2)	BMI			<i>P</i> (additive model)		Per effect allele change in BMI (β)	Lower bound of one-sided 95% CI
					11	12	22	Nominal <i>P</i>	Permuted <i>P</i>		
rs7138803	48533735	<i>FAIM2</i>	A	G	22.4 \pm 0.2	22.0 \pm 0.1	21.7 \pm 0.1	0.0016	0.0097	0.35	0.15
rs1805081	19394430	<i>NPC1</i>	A	G	22.0 \pm 0.1	21.9 \pm 0.1	21.4 \pm 0.3	0.063	0.28	0.21	-0.0047
rs6499640	52327178	<i>FTO</i>	A	G	22.1 \pm 0.4	22.1 \pm 0.1	21.8 \pm 0.1	0.023	0.12	0.29	0.044
rs17782313	56002077	<i>MC4R</i>	C	T	23.1 \pm 0.3	22.2 \pm 0.1	21.6 \pm 0.1	3.6×10^{-7}	1.0×10^{-5}	0.63	0.42
rs6265	27636492	<i>BDNF</i>	G	A	22.2 \pm 0.1	21.9 \pm 0.1	21.6 \pm 0.2	0.0067	0.038	0.27	0.093
rs10938397	45023455	<i>GNPDA2</i>	G	A	22.6 \pm 0.2	22.0 \pm 0.1	21.6 \pm 0.1	0.00016	0.00093	0.45	0.26

Data are means \pm SE. Nominal *P* values were adjusted for age and sex, and permuted *P* values were further corrected for multiple testing. All *P* values were one-sided.

Waist circumference was measured midway between the lowest rib and the superior border of the iliac crest at the end of normal expiration with an inelastic measuring tape to the nearest 0.1 cm. FMP was performed with the use of a body composition analyzer (TBF-300A; TANITA).

Selection of SNPs and genotyping. To achieve a power of not less than 0.75, we selected only SNPs in obesity-related genes with minor allele frequencies >0.14 in Chinese individuals in the HapMap database. With the assumed effect size of 1.2 for an allele frequency of 0.14, the power for detecting positive association was greater than 0.75. We chose the six SNPs (rs7138803 [7], rs1805081 [9], rs6499640 [7], rs17782313 [8], rs6265 [7], and rs10938397 [8]) that have been shown to significantly associate with the risk of obesity.

Genomic DNA was isolated from peripheral blood white cells using the salt fractionation method. SNPs were genotyped by TaqMan (15) Allelic Discrimination Assays with the GeneAmp 7900 Sequence Detection System (Applied Biosystems, Foster City, CA). TaqMan probes were used for genotyping rs7138803 (C_29248155_10), rs1805081 (C_25472673_10), rs6499640 (C_29387696_10), rs17782313 (C_32667060_10), rs6265 (C_11592758_10), and rs10938397 (C_1594245_10). Genotyping call rates for all SNPs were greater than 98%. In order to validate the accuracy of genotyping, we repeated 70 samples randomly for each SNP and observed 100% concordance between the results of the two tests.

Statistical analyses. The allele increasing BMI was defined as the effect allele in our study. Genetic association between the genotypes at each given SNP and a given phenotype was assessed by multiple regression as implemented in the PLINK program (16). For qualitative and quantitative variables, logistic regression and linear regression were carried out, respectively, with age and sex as covariates. Quantitative variables were suitably transformed prior to analysis (log transformation for BMI, waist circumference, and WHtR; square root transformation for FMP). Genotypes were scored as 0, 1, and 2 reflecting the number of susceptibility alleles, where the latter are defined as alleles conferring risk to the phenotype. Empirical significance levels were computed by randomization tests (100,000 permutations) as implemented in the PLINK program. Nominal *P* value was computed in a one-sided manner, i.e., as one half of the two-sided *P* value (all susceptibility alleles were the same as in the published data). False discovery rate, which was computed based on the Benjamini and Hochberg (17) method, was applied for six SNPs, three models (dominant, recessive, and additive), and seven adiposity measures (BMI, waist circumference, WHtR, FMP, birth weight, overweight, and obesity) simultaneously (number of tests: $6 \times 2.21 \times 7$). It has been shown that testing the three models is equivalent to a correction factor of 2.21 (18). Power calculation was performed using Quanto software (<http://hydra.usc.edu/gxe/>). Hardy-Weinberg equilibrium was assessed by χ^2 tests. ANCOVA was applied for comparison of anthropometric indexes between genotypes of SNPs, and linear regression was used to estimate the effect of per allele on anthropometric indexes.

RESULTS

The study included 3,503 children diagnosed by the Chinese age- and sex-specific BMI cutoffs (supplementary Table 1) (13), of whom 1,229 were classified as obese and 655 as overweight. The mean age of subjects was 12.4 ± 3.1 years and 50.8% were boys (see supplementary Table 2 for additional characteristics). We genotyped six SNPs (rs7138803 near *FAIM2*, rs1805081 in exon 6 of *NPC1*, rs6499640 in intron 1 of *FTO*, rs17782313 near *MC4R*, rs6265 near *BDNF*, and rs10938397 near *GNPDA2*) in the

cohort. The genotypes of the SNPs were in Hardy-Weinberg equilibrium in each group ($P > 0.05$) (supplementary Table 3).

After adjusting for multiple testing, statistically significant associations of the SNPs (rs7138803, rs17782313, rs6265, and rs10938397) with BMI (adjusted for age and sex, $P = 0.0097$, 1.0×10^{-5} , 0.038, and 0.00093, respectively) were found under the additive model (Table 1). The data of three models of inheritance (dominant, recessive, and additive) are provided in supplementary Table 4.

We also tested the associations between the six SNPs and anthropometric indexes, including waist circumference, WHtR, FMP, and birth weight (supplementary Table 5). Our results showed that the SNPs rs17782313 and rs10938397 were significantly associated with waist circumference, WHtR, and FMP, and the SNP rs7138803 was significantly associated with waist circumference and WHtR, but none of the six SNPs were associated with birth weight.

All six SNPs, including rs1805081 (borderline significance, $P = 0.048$), were significantly associated with obesity in the Chinese children after age and sex adjustment (Table 2). After adjusting for multiple testing, the significant associations of the SNPs rs17782313, rs6265, and rs10938397 with obesity remained ($P = 5.0 \times 10^{-6}$, 0.043, and 0.00085, respectively). The power for rs1805081 was 0.994, assuming the effect size of 1.33 for the effect allele (9) with the frequency of 0.744. In the analysis of overweight status, the only statistically significant association observed was with rs17782313 after age and sex adjustment and correction for multiple testing (Table 2). The data of three models (dominant, recessive, and additive) with power calculations are provided in supplementary Table 6.

For the 126 (six SNPs, three genetic models, and seven phenotypes) resulting *P* values, associated false discovery rate levels were performed (0.05 as criteria). After multiple testing, the significant associations of the SNPs rs17782313, rs6265, and rs10938397 with BMI and obesity remained (data not shown).

Figure 1 shows the frequency distribution of the number of effect alleles of the six SNPs in normal-weight, overweight, and obese groups. The associations of the number of effect alleles with overweight and obesity are shown in supplementary Table 7. Most subjects of each group carry four to six effect alleles. In the obese group, compared with subjects that carry three or fewer effect alleles, the risk of obesity of the subjects that carry four to six and greater than seven effect alleles was 1.54 (one-sided 95% CI

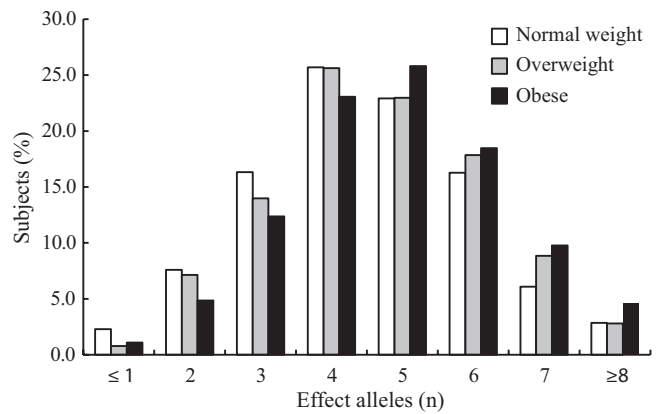


FIG. 1. Frequency distribution of the number of effect alleles in normal-weight, overweight, and obese groups.

>1.31; one-sided $P = 5.9 \times 10^{-6}$) and 2.50 (one-sided 95% CI >1.97; one-sided $P = 1.3 \times 10^{-10}$), respectively. There were significant associations of the number of effect alleles with anthropometric indexes (except birth weight) including BMI, waist circumference, WHtR, and FMP (supplementary Table 8).

DISCUSSION

Recently, GWA studies have discovered several genetic variants in obesity-related genes that modulate body weight in Caucasians (7–9) ([9] was a GWA study for extreme obesity, not BMI in population-based samples as the other GWA studies were). Although the associations of the SNPs rs6265, rs17782313, and rs10938397 with BMI or obesity were investigated in European-American children (10) and subsequently replicated in an adult Chinese population (11), independent replication studies have not been carried out in Chinese children. In the present study, we examined six SNPs in obesity-related genes in Chinese children. There were significant associations of the SNPs rs7138803, rs17782313, rs6265, and rs10938397 with BMI after age and sex adjustment and correction for multiple testing (Table 1). Our results also showed that the SNPs rs17782313, rs6265, and rs10938397 increased the risk of obesity, and the odds ratios (ORs) of these SNPs were higher than those in Europeans (7–9,19) (Table 2). We demonstrated the associations with obesity and BMI as well as other anthropometric indexes including waist circumference, WHtR, and FMP. Our results showed that none of these SNPs were associated with birth weight, suggesting that the genetic influence of body weight occurs after birth.

In our study, no statistically significant association of rs1805081 with BMI and obesity in Chinese children was found (Tables 1 and 2); however, the trend of association is in the same direction as the initial finding, and the A allele is also the risk allele for obesity. Association of rs1805081 with BMI and obesity in our study showed borderline significance after age and sex adjustment. The differences in obesity prevalence between adults and children or the differences in effect size between Caucasians and Chinese might be the reasons why the effect of SNP could not be replicated in our study.

This study is the first to show the associations of SNPs (rs7138803, rs1805081, rs6499640, rs17782313, rs6265, and rs10938397) with BMI and risk of obesity in children with Chinese ancestry. It is important to clarify the impact of

TABLE 2
Associations of SNPs with overweight and obesity in multinomial logistic regression with age and sex adjustment

SNP	Chr.	Nearest gene	Effect allele	Other allele	Overweight ($n = 655$) vs. normal weight ($n = 1,619$)			Obese ($n = 1,229$) vs. normal weight ($n = 1,619$)					
					OR (additive model)	Lower bound of one-sided 95% CI	Nominal P	Permutated P	OR (additive model)	Lower bound of one-sided 95% CI	Nominal P	Permutated P	Reported OR (95% CI)
rs7138803	12	<i>FAIM2</i>	A	G	1.12	0.99	0.056	0.26	1.15	1.04	0.020	0.11	1.14 (1.09–1.19)
rs1805081	18	<i>NPCI</i>	A	G	0.95	0.83	0.20	0.48	1.12	1.01	0.048	0.23	1.33 (1.07–1.75)
rs6499640	16	<i>FTO</i>	A	G	1.03	0.89	0.38	0.50	1.19	1.05	0.016	0.088	1.16 (1.10–1.21)
rs17782313	18	<i>MC4R</i>	C	T	1.26	1.10	0.0021	0.013	1.37	1.23	8.2×10^{-7}	5.0×10^{-6}	1.20 (1.09–1.31)
rs6265	11	<i>BDNF</i>	G	A	1.05	0.94	0.21	0.48	1.16	1.06	0.0075	0.043	1.12 (1.06–1.19)
rs10938397	4	<i>GNPDA2</i>	G	A	1.12	1.00	0.057	0.26	1.24	1.13	0.00014	0.00085	1.20 (1.09–1.31)

Nominal P values were adjusted for age and sex, and permutated P values were further corrected for multiple testing. All P values were one-sided. Obese, overweight, and normal-weight children were diagnosed by the Chinese age- and sex-specific BMI cutoffs (supplementary Table 1) (13). ORs and 95% CIs were calculated using multinomial logistic regression with genotypes, age, and sex as the independent variables. Chr., chromosome.

genetic susceptibility by investigating the association between genetic variants on obesity-related genes and childhood adiposity.

In conclusion, our study showed the associations of six SNPs in obesity-related genes with BMI and risk of obesity in the Chinese children. Results of this study support obesity-related genes in adults as important genes for BMI variation in children. It suggests that some SNPs identified by GWA studies in Caucasians also confer risk for obesity in Chinese children. The functional studies are needed to investigate the roles of these genes in children to prevent adult obesity and other related diseases.

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L.W. wrote the manuscript, researched data, contributed to the discussion, and reviewed/edited the manuscript. B.X. and M.Z. analyzed and interpreted data, and reviewed/edited the manuscript. Y.S. researched data, contributed to the discussion, and reviewed/edited the manuscript. X.Z., H.C., and D.H. reviewed/edited the manuscript. D.S. analyzed data. J.O. analyzed data and reviewed/edited the manuscript. X.W. contributed to the design and discussion and made critical revisions of the manuscript. J.M. designed the study; collected, analyzed, and interpreted data; and made critical revisions of the manuscript.

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