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 FAIIM2, 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.

RESULTS—After age and sex adjustment and correction for multiple testing, the SNPs rs17782313, rs6265, and rs10938397 were associated with BMI (P = 1.0 × 10^{-5}, 0.038, and 0.00093, respectively) and also obesity (P = 5.0 × 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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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 superior border of the iliac crest at the end of normal expiration with an anthropometric instrument.

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. 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 minor allele). In order to validate the accuracy of genotyping, we repeated the genotyping 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 (53237178 FTO), rs17782313 (56002077 MC4R), rs6265 (27636492 BDNF), and rs10938397 (45034553 GPNA2A2) 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 (53237178 FTO), rs17782313 (56002077 MC4R), rs6265 (27636492 BDNF), and rs10938397 (45034553 GPNA2A2) that have been shown to significantly associate with the risk of obesity.

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 GPNA2A2) 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, 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 × 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
DISCUSSION
Recently, GWAS studies have discovered several genetic variants in obesity-related genes that modulate body weight in Caucasians (7–9). It was a GWAS study for extreme obesity, not BMI in population-based samples as the other GWAS studies were (9). Although the associations of the SNPs rs7138803, rs17782313, and rs6265 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 were associated with the number of effect alleles with anthropometric indexes (except birth weight) (supplementary Table 8).

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 genotypes, age, and sex on obesity in Chinese children. It is important to clarify the impact of genotypes, age, and sex on obesity in Chinese children.
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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