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Variations in the *PBEF1* gene are associated with body mass index: A population-based study in northern China

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ABSTRACT

Objective: *PBEF1* and its polymorphisms may be important in the physiopathology of obesity. We hypothesized that polymorphisms in *PBEF1* gene may modify body mass index (BMI).
Methods: Thus, we systematically screened 4 tagging polymorphisms (rs4730153, rs2058540, rs3801267 and rs16872158) in *PBEF1* gene and evaluated the association between the genetic variants and BMI in a population-based study including 442 subjects in northern China.
Results: We found that the SNP rs3801267 was significantly associated with decreased BMI ($P = 0.026$ in additive model), while the other 2 SNPs (rs4730153 and rs16872158) showed a borderline significant association with decreased BMI ($P = 0.068$ and 0.060 in additive models). Combined analysis of these 3 SNPs showed a significant allele–dosage association between the number of variant alleles and decreased BMI ($P_{trend} = 0.007$).
Conclusions: These findings indicate that genetic variants in *PBEF1* gene may modify individual BMI in the Chinese population.

1. Introduction

Obesity is a complex disease associated with a state of chronic low grade inflammation, which may contribute to the development of chronic condition. Many countries have witnessed the epidemic of obesity and overweight caused by economic growth, an increasingly sedentary lifestyle and a nutritional transition to high-calorie diets in the past few decades (Hruby and Hu, 2014; Stevens et al., 2012). Obesity, presents a major challenge to health across the life course around the world, has affected over one-third of the world's population today and emerged as a major public health concern (Visscher and Seidell, 2001; Yang and Colditz, 2015; Sengupta et al., 2015; Medehouenou et al., 2015). As a multifactorial disease with genetic, behavioral, socioeconomic, and environmental origins, obesity along with overweight, raises the risk of morbidity and mortality from cardiovascular disease, diabetes mellitus, cancer, osteoarthritis, and sleep apnea (Speliotes et al., 2010; Prospective Studies, C, et al., 2009; Gallagher and LeRoith, 2015; Berenbaum et al., 2013).

The past several years have witnessed an explosion of the associations between single nucleotide polymorphisms (SNP) and obesity. To date, more than 60 relatively common genetic markers have been implicated in elevated susceptibility to obesity (Speliotes et al., 2010; Hindorff et al., 2009). Recently, there is a growing interest in the potential role of visfatin/*PBEF* (pre-B-cell colony-enhancing factor) as biomarkers of inflammation and metabolic related complications (Moschen et al., 2007; Revollo et al., 2007). Visfatin is a novel protein that is preferentially produced in visceral adipose tissue other than leptin and resistin (Koerner et al., 2005; Samal et al., 1994; Al-Suhaimi and Shehzad, 2013). Its functions mainly serve as both an adipokine and an inflammatory cytokine. Visfatin harbors numerous biological properties, such as proinflammatory (Moschen et al., 2007; Chang et al., 2010) and insulin-mimetic effects, and insulin resistance and many other effects (Sun et al., 2013). Epidemiological evidence indicates that both its tissue expression and secreted plasma levels are increased in parallel with obesity, which indicates that it has a significant role in the pathophysiology of obesity.

The *PBEF1* gene is located on chromosome 7q22.3 and includes 11 exons encompassing 34.7 kb. The *PBEF1* gene may influence the risk of obesity and obesity-related diseases, and this effect is likely mediated by the pro-inflammatory molecules (Romacho et al., 2013). Given the relevance of *PBEF1* to the pathophysiology of obesity, genetic

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predisposition association studies have provided evidence that variants of the *PBEF1* gene are significantly associated with obesity development. To date, several polymorphic markers in the *PBEF1* gene have been reported to be associated with obesity and obesity-related diseases, and also affect the level of visfatin in the serum in obese populations and children (Li et al., 2013; Blakemore et al., 2009; Saddi-Rosa et al., 2013; Wang et al., 2011; Zhang et al., 2006; Agueda et al., 2012). However, these results are inconsistent, probably due to differences in the genetic components, limited information on obesity susceptibility loci, low statistical power or variations in methodological approaches.

The origin of obesity is determined by genetic factors as well as environmental influences. The observed variations in prevalence not only reflect differences in stages of nutrition transition across regions, but also differences in the genetic architecture of various population groups. Additionally, epidemiological studies have suggested that the proportion of overweight among adults is on a steep rise in China, and recently the increase has accelerated (Ng et al., 2014). The genetic variants determining susceptibility and predicting outcome of obesity in Chinese population have not been widely investigated. Therefore, we investigated the distribution of *PBEF1* polymorphisms and evaluated whether *PBEF1* SNPs are associated with BMI in adolescents in a northern Chinese population.

2. Materials and methods

2.1. Study population and study design

A population-based study was carried out in Harbin City in Heilongjiang province, northern China. The study population was drawn from the population aged 40 years and over living in communities using stage stratified sampling methods. Xiangfang district, representing the middle economic level for urban areas of Harbin, was selected from 8 districts of Harbin, and then 4 of 19 communities were randomly selected. Finally, 442 participants aged ≥40 years old were enrolled. All study population underwent a physical examination, and anthropometric measurements were taken. BMI (weight/height^2), the most widely used anthropometric measure of weight status, and is the main outcome measurement. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body weight was measured with a digital scale to the nearest 0.1 kg. Weight status of participants was defined according to the criteria that is recommended by Working Group on Obesity in China (WGOC) based on the analysis of data collected from 239,972 Chinese adults in the 1990s (Zhou and Cooperative Meta-Analysis Group of the Working Group on Obesity in, C, 2002): obese cases were BMI ≥ 28 kg/m^2 and non-obese cases were BMI ≤ 28 kg/m^2. Individuals were defined as smokers if they had smoked at an average of one cigarette or more per day and for at least 1 year in their lifetime; otherwise, individuals were considered as non-smokers. Smokers were considered as former smokers who quit for at least 1 year before recruitment. Individuals that consumed one or more alcohol drinks a week for over 6 months were considered alcohol drinkers; otherwise, individuals were considered as non-drinkers. Drinkers were considered as former drinkers who quit for at least 6 months before recruitment.

The study adhered to the tenets of the Declaration of Helsinki. Participation was voluntary and written informed consent was obtained from each subject. The study was reviewed and approved by the Ethics Committee of Harbin Medical University, China.

2.2. SNPs selection

Based on the NCBI database (http://www.ncbi.nlm.nih.gov/projects/SNP), public HapMap SNP database (phase II + III Feb. 09, on NCBI B36 assembly, dbSNP b126) and the Haploview 4.2 software, common SNPs (Minor allele frequency, MAF ≥ 5% in Chinese Han population) were screened in *PBEF1* gene regions. SNPs with low linkage disequilibrium (LD) analysis (r^2 < 0.8) were retained. As a result, 4 tagging SNPs (rs4730153, rs2058540, rs3801267 and rs16872158) were finally determined to perform genotyping. However, rs2058540 was excluded because of design failure.

2.3. Genotyping

Peripheral blood was collected from each subject only after obtaining signed informed consent, and genomic DNA was extracted from the samples by a DNA extraction Kit (Qiagen, Valencia, CA). A total of 3SNPs were genotyped and analyzed for statistical associations. Genotyping analysis was performed using the iPLEX Sequenom MassARRAY platform (Sequenom, Inc). The following series of methods was used to control the quality of genotyping: (i) two water controls were used in each plate as blank controls; (ii) 5% of the samples were randomly selected for repeat genotyping, as blind duplicates, and the reproducibility was 100%.

2.4. Statistical analysis

Median and 25–75% (quartiles) was used to describe the distribution of BMI. Hardy–Weinberg equilibrium (HWE) for the distribution of each SNP was evaluated using the goodness-of-fit χ^2 test by comparing the observed genotype frequencies with the expected ones among the total subjects. Regression coefficients (β) and their 95% confidence intervals (CI) were calculated by using multiple linear regressions to evaluate the association between SNPs and BMI with an adjustment for age and gender. The regression coefficient (β) means the average change in BMI for per unit change in each SNP (per unit change of each SNP, on average, BMI will change the β unit). To examine the differences between subgroups, the χ^2-based Q-test was used to test the heterogeneity of effect sizes (β and 95% CIs) derived from corresponding subgroups. All of the statistical analyses were performed with Stata Version 10.0 software (Stata, College Station, TX).

3. Results

General characteristics, including age, gender, BMI, smoking status and drinking status of 442 subjects in this study are shown in Table 1. In brief, of all the subjects, the prevalence of overweight (24 ≤ BMI < 28) is 34.84%, while the prevalence of obesity (BMI ≥ 28) is 18.78%.

The basic information of the 3 SNPs were shown in Table 2, the success rates of genotyping for these polymorphisms were all above 99%.

Table 1
General characteristics of the subjects.

Variables	Subjects (n = 442) N (%)
Age, year (mean ± SD)	57.17 ± 9.19
<57[a]	213 (48.19)
≥57[a]	229 (51.81)
Gender	
Male	139 (31.45)
Female	303 (68.55)
BMI (mean ± SD)	24.72 ± 3.63
<24	205 (46.38)
24 ≤ BMI < 28	154 (34.84)
≥28	83 (18.78)
Smoking status	
Current	81 (18.33)
Former	38 (8.60)
Non	318 (71.94)
Unknown	5 (1.13)
Drinking status	
Current	116 (26.25)
Former	18 (4.07)
Non	277 (62.67)
Unknown	31 (7.01)

[a] Median age in all subjects.

Table 2
Associations between genetic variations of *PBEF1* gene and BMI.

Gene	SNPs	Base change[a]	Genotyping rate (%)	MAF[b]	HWE[c]	β (95%CI)[d]	P^d	P^e
PBEF1	rs4730153	G > A	99.37	0.11	0.64	−0.74(−1.53, 0.06)	0.068	0.830
	rs16872158	T > A	99.69	0.05	0.33	−1.05(−2.14, 0.04)	0.060	0.039
	rs3801267	T > A	99.06	0.09	0.47	−0.93(−1.75, −0.11)	0.026	0.227

[a] Major allele > minor allele.
[b] Minor allele frequency.
[c] Hardy–Weinberg equilibrium.
[d] Data were analyzed under an additive genetic model and adjusted for age and gender.
[e] Adjusted for age, gender, rs4730153, rs16872158 and rs3801267 where appropriate in additive model.

The observed genotype frequencies for these SNPs were all in agreement with HWE ($P = 0.64$ for rs4730153, $P = 0.33$ for rs16872158 and $P = 0.47$ for rs3801267). As shown in Table 2, the SNP rs3801267 was significantly associated with decreased BMI ($P = 0.026$ in additive model), while the other 2 SNPs (rs4730153 and rs16872158) showed a borderline significant association with decreased BMI, with *P* values of 0.068 and 0.060, respectively. We then used conditional multiple linear regression analysis to test the independence of the 3 SNPs (Table 2). The effect of rs16872158 on BMI remained significant after being adjusted for age, gender, rs4730153 and rs3801267 ($P = 0.039$). However, the effects of rs4730153 and rs3801267 on BMI were weakened ($P = 0.830$ and $P = 0.227$) after being conditioned on the other two SNPs.

Furthermore, in the stratification analysis, the association between the 3 SNPs and BMI were evaluated in subgroups based on age, gender, smoking status and drinking status. As shown in Table 3, no significant difference between any subgroups was observed for the association of the 3 SNPs with BMI. Notably, as shown in Table 3, for rs4730153, we found the variant genotypes which were associated with a significantly decreased BMI in individuals with age < 57 ($P = 0.037$) and smokers ($P = 0.047$); for rs16872158, we found the variant genotypes which were associated with a significantly decreased BMI in never drinkers ($P = 0.037$); for rs3801267, we found the variant genotypes which were associated with a significantly decreased BMI in individuals with age < 57 ($P = 0.012$), females ($P = 0.049$) and smokers ($P = 0.014$).

In view of the modest or small effect of each individual locus, we further conducted a combined analysis to evaluate the cumulative effect of the 3 SNPs. As shown in Table 4, subjects with "0", "1", "2" or "3–4" variant alleles had a median BMI of 24.47, 23.98, 23.72 or 22.67, respectively. As expected, the more variant alleles the subjects carried, the lower median BMI they have, suggesting an allele-dosage effect ($P_{trend} = 0.007$).

4. Discussion

The prevalence and incidence of obesity have rapidly increased globally and have reached epidemic proportions. Obesity is a consequence resulting from the overall effect of some polymorphisms in several genes and exposure of environmental risks (Hotta, 2009). Visfatin is a novel adipokine produced by the adipose tissue, which simultaneously facilitates adipogenesis and has insulin-mimetic properties (Moschen et al., 2007; Skoczylas, 2009). Epidemiological studies have suggested that vasfatin might be useful as a surrogate marker of pro-inflammatory state, and *PBEF1* gene might be a candidate gene influencing obesity phenotypes (Blakemore et al., 2009; Zhang et al., 2006). The current study was designed to look for SNP variants in *PBEF1* that were associated with individual BMI.

In our present study, we evaluated the association of 3 tagging polymorphisms in the *PBEF1* with BMI in a population-based study including 442 subjects in northern China. The rs3801267 SNPs were identified to be significantly associated with decreased BMI, while the other 2 SNPs (rs4730153 and rs16872158) showed borderline significant association with decreased BMI. That is, these 3 polymorphisms were associated with decreased obesity risk. To the best of our knowledge, this is the first association study of polymorphisms in *PBEF1* (rs4730153, rs16872158 and rs3801267) and BMI. The data presented above suggested strong evidence that SNPs of the *PBEF1* gene are associated with BMI, indicating that *PBEF1* may play a crucial role in the regulation of BMI.

There are several strengths in the present study. First, our study subjects came from a systematic screening of health in a large, population-based study conducted in Heilongjiang Province, China, which may have reduced potential selection bias. Second, we used Sequenom genotyping platform, which have greatly improved the success and accuracy rates of genotyping, and demonstrated for the first time that genetic variants in *PBEF1* (rs3801267, rs4730153 and rs16872158) may influence BMI in Chinese population.

However, several limitations of our study also need to be addressed. First, in view of multiple testing (n = 3), no SNPs were still significantly associated with BMI ($P < 0.017$ for Bonferroni correction); therefore, the results should be treated with caution, and validations are warranted. Second, one SNP rs2058540 was excluded because of design failure, which may limit the success rates of genotyping. Third, exact biological

Table 3
Stratification analysis of the 3 SNPs.

Characteristics	Subjects	rs4730153		P_{het}[b]	rs16872158		P_{het}[b]	rs3801267		P_{het}[b]
		β (95%CI)[a]	*P*		β (95%CI)[a]	*P*		β (95%CI)[a]	*P*	
Age										
<57	213	−1.19(−2.30, −0.08)	**0.037**	0.310	−1.07(−2.57, 0.44)	0.165	0.993	−1.42(−2.51, −0.32)	**0.012**	0.274
≥57	229	−0.37(−1.50, 0.76)	0.515		−1.06(−2.65, 0.53)	0.191		−0.50(−1.73, 0.73)	0.421	
Gender										
Male	139	−0.55(−1.84, 0.73)	0.396	0.701	−0.99(−3.21, 1.24)	0.382	0.945	−0.81(−2.16, 0.55)	0.240	0.791
Female	303	−0.87(−1.88, 0.14)	0.092		−1.08(−2.34, 0.19)	0.094		−1.04(−2.08, −0.01)	**0.049**	
Smoking status										
Ever	119	−1.26(−2.50, −0.02)	**0.047**	0.242	−1.07(−2.99, 0.85)	0.273	0.900	−1.65(−2.96, −0.34)	**0.014**	0.160
Never	318	−0.30(−1.33, 0.72)	0.560		−1.22(−2.57, 0.14)	0.078		−0.45(−1.50, 0.59)	0.396	
Drinking status										
Ever	135	−0.79(−2.12, 0.54)	0.244	0.703	−0.85(−3.05, 1.35)	0.446	0.674	−1.39(−2.81, 0.02)	0.053	0.338
Never	277	−0.45(−1.58, 0.69)	0.441		−1.40(−2.72, −0.08)	**0.037**		−0.50(−1.65, 0.64)	0.390	

[a] Adjusted for age and gender where appropriate in additive model.
[b] *P* for heterogeneity.

Table 4
Joint effect of the 3 SNPs on BMI.

Risk allele number[a]	Subjects N (%)	BMI[b]	β (95%CI)[c]	*P*
0	312 (71.56)	24.47(22.27, 27.46)		
1	46 (10.55)	23.98(22.16, 26.15)	−0.46(−1.59, 0.67)	0.424
2	68 (15.60)	23.72(21.56, 26.38)	−1.01(−1.97, −0.06)	0.038
3–4	10 (2.30)	22.67(19.94, 25.05)	−2.23 (−4.53, 0.07)	0.057
Trend test				0.007

[a] rs4730153-A, rs16872158-A and rs3801267-A alleles were assumed as variant alleles.
[b] Median and 25–75% (quartiles).
[c] Adjusted for age and gender.

mechanism of the promising variants could not be annotated and the real causal variant was unclear. Fourth, smoke and drink status of some subjects is unknown, which may generate information bias, and further follow-up of these subjects are warranted. Nevertheless, there is reason to believe that the findings are of considerable credibility and veracity. Fourth, the study failed to measure the impact of few main components like detailed dietary patterns and regular physical activity due to paucity of information. Together with a relatively small sample size, this study may provide limited statistical power. Last, BMI is the most widely used anthropometric measure of weight status. Indeed, the cut-off value of BMI used to define overweight/obesity in diverse populations have been varied among those populations in Asian and European-American regions, which could generate overweight and obesity misclassifications. The results may differ according to these BMI systems across different regions and diverse populations.

In summary, our study investigated the role of genetic variants in *PBEF1* gene with BMI in a northern Chinese population, and suggested for the first time, that genetic variants in *PBEF1* may modify BMI. This poses a challenge in understanding general pathways underlying obesity susceptibility. Additional studies are required to further specifically focus on the pathophysiological role of the visfatin/*PBEF1* gene in obesity development and to locate the polymorphisms responsible for this genetic effect. Further studies are warranted to validate and extend our findings, and to re-sequence the identified regions and to evaluate the potential functional significance of the loci.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

L.J. and Y.Z.: study design, data collection, interpretation of results, critical revision of manuscript, and writing of the manuscript; M.C., J.R. and B.X. prepared the samples; L.Z., S.W., and T.T. helped with the interpretation of data. All authors read and approved the final manuscript.

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