

SHORT REPORT

Potential association of *INSIG2* rs7566605 polymorphism with body weight in a Chinese subpopulation

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Herbert *et al* reported association with obesity of a common DNA variant rs7566605 at 10 kb upstream of the *INSIG2* gene. We analyzed rs7566605 polymorphism in 3125 Chinese in a cross-sectional study. We found no significant association of rs7566605 polymorphism with body mass index (BMI) and waist circumference among all participants ($P=0.52$). However, if geographic location is considered, the C/C genotype of rs7566605 was marginally associated with increased levels of BMI and risk of obesity among individuals living in Shanghai ($P=0.06$), indicating that the C/C genotype may contribute to obesity in certain subpopulation among Chinese under certain environmental settings.

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Keywords: *INSIG2*; cross-sectional study; obesity; body weight; Chinese population

Introduction

Obesity is becoming a prevalent health problem in both western countries and developing countries such as China. The current prevalence of overweight and obesity in China is 14.7 and 2.6%, respectively, according to WHO criteria.¹ A large-scale genetic study by Herbert *et al*² has revealed a significant association of rs7566605 single-nucleotide polymorphism (SNP) with obesity in a study with a total of 9881 individuals. The rs7566605 locus is located at 10 kb upstream of *INSIG2* gene, the product of which is implicated in the synthesis of fatty acids and cholesterol.³ Since the original report by Herbert *et al*, five independent studies in the United Kingdom, France, Germany and China did not find significant association between

rs7566605 polymorphism and obesity,^{4–8} although a subgroup analysis indicated association of this genotype with obesity in already overweight individuals.⁷ Lately, Lyon *et al*⁹ reported a significant association of the rs7566605 genotype with body mass index (BMI) in five cohorts but saw no association in three other cohorts, suggesting that the effect of rs7566605 genotype on BMI may be heterogeneous across population samples.

Materials and methods

The rs7566605 polymorphism was determined in 3125 Chinese in a cross-sectional study with about half of the participants being recruited from Beijing and the other half from Shanghai, originally designed to analyze the geographic difference in nutrition, lifestyle, genetics and metabolic disorders among middle- to old-aged population (50–70 years old).¹⁰ All participants are Chinese in origin and unrelated. The average BMI is 24.5 ± 3.6 kg/m² (Table 1), considerably lower than the BMI of the

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Table 1 Characteristics of study participants^a

	Total (n = 3125)	Beijing (n = 1574)	Shanghai (n = 1551)	P-values (Beijing vs Shanghai)
Age (year)	58.6 (6.0)	58.4 (5.9)	58.9 (6.1)	0.0242
Female (%)	55.7 (1742)	54.8 (863)	56.7 (879)	0.2993
Rural residents (%)	49.9 (1558)	49.8 (783)	50.0 (775)	0.9013
BMI (kg/m ²)	24.5 (3.6)	25.3 (3.6)	23.7 (3.2)	<0.0001
Waist circumference (cm)	83.8 (10.5)	85.9 (10.3)	81.7 (10.3)	<0.0001
Overweight (25 ≤ BMI < 30)	36.1 (1128)	41.7 (657)	30.4 (471)	<0.0001
Obesity (BMI ≥ 30)	6.7 (210)	9.7 (152)	3.7 (58)	<0.0001
Abdominal obesity ^b	48.3 (1510)	55.5 (873)	41.1 (637)	<0.0001
Diabetes mellitus ^c (%)	13.7 (428)	17.8 (280)	9.5 (148)	<0.0001
<i>Genotype frequency (%)</i>				
GG	40.4 (1263)	39.8 (627)	41.0 (636)	
GC	47.3 (1478)	48.4 (761)	46.2 (717)	0.4539
CC	12.3 (384)	11.8 (186)	12.8 (198)	
C allele	35.9	36.0	35.9	0.9271
P-value for HWE	0.1285	0.0503	0.8535	

BMI, body mass index; HWE, Hardy–Weinberg equilibrium.

^aFigures in parentheses are standard deviation for continuous variables and the number of participants for categorical variables.

^bAbdominal obesity was defined according to the updated NCET/ATPIII criteria for Asian Americans, that is, waist circumference ≥90 cm for men and ≥80 cm for women.

^cDiabetes mellitus was defined as fasting glucose ≥7.0 mmol/l and/or current use of antidiabetic medications and/or diagnosed diabetes by a physician.

Table 2 Associations of rs7566605 genotype with body mass index and waist circumference among 3125 Chinese men and women aged 50–70 years^a

	n	Body mass index			Waist circumference			Overweight or obesity ^b			Abdominal obesity ^c		
		Mean	SE	P-values	Mean	SE	P-values	Case/n	OR	95% CI	Case/n	OR	95% CI
<i>Men</i>													
GG	556	24.5	0.16	0.5678	87.2	0.50	0.5612	195/556	1.0	Reference	201/556	1.0	Reference
CG	656	24.4	0.15		86.6	0.47		224/656	0.89	0.70–1.14	222/656	0.82	0.64–1.05
CC	171	24.6	0.26		87.3	0.80		67/171	1.18	0.82–1.69	67/171	1.12	0.78–1.61
<i>Women</i>													
GG	707	24.8	0.17	0.3972	83.2	0.46	0.6584	254/707	1.0	Reference	404/707	1.0	Reference
CG	822	25.0	0.16		83.4	0.45		301/822	1.02	0.82–1.26	484/822	1.08	0.88–1.33
CC	213	25.2	0.27		83.9	0.74		87/213	1.24	0.90–1.70	132/213	1.26	0.92–1.74
<i>All</i>													
GG	1263	24.7	0.11	0.5156	85.1	0.34	0.6914	449/1263	1.0	Reference	605/1263	1.0	Reference
CG	1478	24.7	0.11		85.1	0.33		525/1478	0.97	0.83–1.14	706/1478	0.97	0.83–1.14
CC	384	24.9	0.19		85.6	0.55		154/384	1.22	0.96–1.55	199/384	1.20	0.95–1.53
<i>Beijing</i>													
GG	627	25.4	0.16	0.8121	87.2	0.46	0.6061	263/627	1.0	Reference	358/627	1.0	Reference
CG	761	25.4	0.15		86.7	0.43		312/761	0.94	0.76–1.17	407/761	0.87	0.69–1.08
CC	186	25.2	0.27		86.7	0.77		82/186	1.08	0.78–1.51	108/186	1.05	0.74–1.48
<i>Shanghai</i>													
GG	636	24.0	0.18	0.0600	83.1	0.52	0.1464	186/636	1.0	Reference	247/636	1.0	Reference
CG	717	24.1	0.17		83.6	0.50		213/717	1.00	0.79–1.26	299/717	1.10	0.87–1.38
CC	198	24.6	0.26		84.6	0.78		72/198	1.39	0.99–1.95	98/198	1.41	1.00–1.97

CI, confidence interval; SE, standard error; OR, odds ratio.

^aAppropriately adjusted for age, sex, region (Beijing/Shanghai), residence (urban/rural) and diabetes mellitus.

^bOverweight or obesity, body mass index ≥25.

^cAbdominal obesity: waist circumference ≥90 cm for men and ≥80 cm for women.

population studies in the United Kingdom, France and Germany.^{4–7} The rs7566605 polymorphism was analyzed by a restriction fragment-length polymorphism via diges-

tion with *MboI* restriction enzyme.⁴ All participants have provided their written informed consents and the protocol was approved by the Institutional Review Board of the

Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences.

Results and discussion

We analyzed rs7566605 polymorphism in 3125 Chinese in a cross-sectional study.¹⁰ The overall C allele frequency was 35.9% and the C/C genotype frequency was 12.3%, similar to the reported studies.^{2,4-7} Participants from Beijing had significantly higher levels of BMI and waist circumference, and higher prevalence of overweight, obesity and abdominal obesity than their counterparts in Shanghai (Table 1). Among all participants, there was no significant association between rs7566605 polymorphism and BMI or waist circumference as analyzed by an additive model (Table 2). This observation appeared to be consistent with recent reports showing a lack of association of rs7566605 alleles with obesity in general population.⁴⁻⁸

However, when the geographic location is stratified, the C/C genotype of rs7566605 polymorphism was marginally associated with an increased level of BMI in Shanghai participants ($P=0.0600$), but not in Beijing participants ($P=0.8121$) as analyzed by an additive model (Table 2). Consistently, a marginally increased risk of overweight or obesity (OR 1.39; 95% CI: 0.99–1.95; $P=0.0412$) and abdominal obesity (OR 1.41; 95% CI: 1.00–1.97; $P=0.0665$) was observed for C/C genotype among Shanghai participants by analysis with an additive model (Table 2). Further analysis with a recessive model revealed that the C/C genotype of rs7566605 polymorphism was significantly associated with elevated BMI (24.6 vs 24.1 kg/m²; $P=0.0263$) and increased risk of overweight and obesity (OR 1.39; 95% CI: 1.01–1.91; $P=0.0411$) among Shanghai participants. Taken together, these findings indicate that the C minor allele of rs7566605 is potentially associated with increased risk of obesity in Shanghai subpopulation in our study.

Assuming that the genetic background is not different among the individuals living at these two geographic locations as supported by our finding that the C allele frequency was equivalent between Beijing and Shanghai subpopulation (36.0% in Beijing, 35.9% in Shanghai, $P=0.9271$), the higher incidence of overweight/obesity in Beijing indicates that environmental factors may contribute more to overweight/obesity in Beijing than in

Shanghai. Under this consideration, the increased contribution of environmental factors to obesity in Beijing may mask the relative weak contribution of genetic factors such as rs7566605 polymorphism. Therefore, we postulate that the rs7566605 SNP may be implicated in the risk of obesity when the contribution of environmental factors is relatively small in population studies. This hypothesis is partly supported by a recent report demonstrating that the effect of rs7566605 polymorphism on BMI may be heterogeneous among different populations.⁹

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