J Hum Genet (2008) 53:857–862
DOI 10.1007/s10038-008-0317-8

SHORT COMMUNICATION

INSIG2 gene rs7566605 polymorphism is associated with severe obesity in Japanese

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Received: 16 April 2008 / Accepted: 18 June 2008 / Published online: 10 July 2008

Abstract The single nucleotide polymorphism (SNP) rs7566605 in the upstream region of the insulin-induced gene 2 (*INSIG2*) is associated with the obesity phenotype in many Caucasian populations. In Japanese, this association with the obesity phenotype is not clear. To investigate the relationship between rs7566605 and obesity in Japanese, we genotyped rs7566605 from severely obese subjects [n = 908, body mass index (BMI) $\geq$ 30 kg/m^2] and normal-weight control subjects (n = 1495, BMI $<$ 25 kg/m^2). A case–control association analysis revealed that rs7566605 was significantly associated with obesity in Japanese. The P value in the minor allele recessive mode was 0.00020, and the odds ratio (OR) adjusted for gender and age was 1.61 [95% confidential interval (CI) = 1.24–2.09]. Obesity-associated phenotypes, which included the level of BMI, plasma glucose, hemoglobin A1c, total cholesterol,

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triglycerides, high-density lipoprotein (HDL) cholesterol, and blood pressure, were not associated with the rs7566605 genotype. Thus, rs7566605 in the upstream region of the *INSIG2* gene was found to be associated with obesity, i.e., severe obesity, in Japanese.

Keywords Insulin-induced gene 2 · Obesity · Japanese population · Association · SNP

Introduction

Obesity has become one of the major issues in public health, medicine, and the economy (Kopelman 2000). Obesity is considered to be important due to its relationship with various complications, such as diabetes mellitus, dyslipidemia, and hypertension. A combination of these dysfunctions is now defined as the metabolic syndrome that significantly increases the risk of cardiovascular disease (Wilson and Grundy 2003). Genetic and environmental factors contribute to the development of obesity (Maes et al. 1997; Barsh et al. 2000; Rankinen et al. 2006). Due to the recent progress in single nucleotide polymorphism (SNP) genotyping techniques, it is possible to conduct genome-wide screens to identify common genetic variants associated with obesity. We conducted a large-scale case–control association study and found that secretogranin III (*SCG3*) (Tanabe et al. 2007) and myotubularin-related protein 9 (*MTMR9*) (Yanagiya et al. 2007) confer susceptibility to the obesity phenotype in the Japanese population. Genome-wide association studies have shown that variations in the upstream region of the insulin-induced gene 2 (*INSIG2*) (Herbert et al. 2006) and in the fat-mass and obesity-associated gene (*FTO*) (Frayling et al. 2007; Scuteri et al. 2007; Hinney et al. 2007) are associated with the obesity phenotype. We recently reported the association between variations in the *FTO* gene and severe obesity in Japanese (Hotta et al. 2008). An association between rs7566605 in the upstream region of the *INSIG2* gene and obesity was also found in several Caucasian and Hispanic American populations (Herbert et al. 2006; Hall et al. 2006; Lyon et al. 2007; Liu et al. 2008). However, results from some reports with respect to these associations could not be reproduced (Lyon et al. 2007; Smith et al. 2007; Boes et al. 2008); further, these associations are not observed in the Indian (Kumar et al. 2007), Chinese (Yang et al. 2008) and Japanese populations (Tabara et al. 2008). Thus, the association between rs7566605 in the *INSIG2* gene and obesity in Japanese remains controversial.

To investigate the relationship between the *INSIG2* gene and obesity in Japanese, we performed a case–control association study involving patients with severe adult obesity (BMI $\geq$ 30 kg/m^2) and normal weight controls (BMI $<$ 25 kg/m^2). We found that rs7566605 was significantly associated with severe adult obesity.

Materials and methods

Study subjects

Severely obese subjects were recruited from among the outpatients of medical institutes. Patients with secondary obesity and obesity-related hereditary disorders were excluded from this study, as were patients with medication-induced obesity. Control subjects were recruited from among subjects who had undergone a medical examination for the screening of common diseases. Each subject provided written informed consent, and the protocol was approved by the ethics committee of each institution and that of RIKEN. The sample size for the severely obese subjects (BMI $\geq$ 30 kg/m^2) was 908 (male:female ratio, 418:590; age, 49.1 $\pm$ 14.2 years; BMI, 34.5 $\pm$ 5.4 kg/m^2), whereas that for the normal weight controls (BMI $<$ 25 kg/m^2) was 1,495 (male:female ratio, 672:823; age, 48.1 $\pm$ 16.5 years; BMI, 21.6 $\pm$ 2.1 kg/m^2). Subjects' clinical features are illustrated in Table 1.

DNA preparation and SNP genotyping

Genomic DNA was prepared from the blood samples of each subject with a Genomix kit (Talent Srl, Trieste, Italy). SNP rs7566605 reported in a previous genome-wide association study (Herbert et al. 2006) was genotyped with TaqMan probe (C_29404113_20; Applied Biosystems; Foster City, CA, USA).

Statistical analysis

Genotype or allele frequencise were compared between cases and controls in three different modes. In the first

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Table 1 Clinical characterization of obese and control subjects

	Obese	Control	*P* value[a]
Sample size	908	1495	–
Gender (M/F)	418/490	672/823	–
Age (year)	49.1 ± 14.2	48.1 ± 16.5	0.050
BMI (kg/m^2)	34.50 ± 5.39	21.65 ± 2.07	<0.000001
Glucose (mg/dl)	129.1 ± 49.7	97.7 ± 23.8	<0.000001
HbA1c (%)	6.5 ± 1.8	5.1 ± 0.6	<0.000001
Total cholesterol (mg/dl)	210.1 ± 38.0	201.2 ± 36.4	<0.000001
Triglycerides (mg/dl)	155.6 ± 111.0	104.0 ± 73.1	<0.000001
HDL cholesterol (mg/dl)	53.1 ± 18.8	65.1 ± 15.6	<0.000001
Systolic blood pressure (mmHg)	136.4 ± 18.2	123.4 ± 17.8	<0.000001
Diastolic blood pressure (mmHg)	83.8 ± 12.0	76.0 ± 11.1	<0.000001

Data are mean ± standard deviation

HbA1c hemoglobin A1c, *HDL* high-density lipoprotein

[a] *P* values were analyzed using Mann–Whitney *U* test

mode, i.e, the allele frequency mode, allele frequencies were compared with a 2 × 2 contingency table. In the second mode, i.e., the minor allele recessive mode, frequencies of the homozygous genotype for the minor allele were compared with a 2 × 2 contingency table. In the third mode, i.e., the minor allele dominant mode, frequencies of the homozygous genotype for the major allele were compared with a 2 × 2 contingency table. A test of independence was performed using Pearson's χ^2 method. Odds ratio (OR) and 95% confidence interval (CI) were calculated by Woolf's method. The rs7566605 genotype was transformed to a multidichotomous variable, i.e., homozygosity with C alleles versus the other genotypes. The OR adjusted for age and gender was calculated by multiple logistic regression analysis, with genotype, age, and gender as independent variables. Hardy–Weinberg equilibrium was assessed using the χ^2 test (Nielsen et al. 1998). A simple comparison of clinical data among the different genotypes was performed by one-way analysis of variance (ANOVA). Statistical analyses were performed with StatView 5.0 (SAS Institute Inc., Cary, NC, USA).

Results

Case–control association study

We successfully genotyped rs7566605 by the TaqMan assay and performed tests of independence between the phenotype and genotype of obesity in severely obese subjects (BMI ≥ 30 kg/m^2) and normal weight controls (BMI < 25 kg/m^2). The minor allele frequency (MAF) of rs7566605 in the control group was 0.31. This was consistent with data obtained from the haplotype map of the human genome (HapMap). As shown in Table 2, rs7566605 demonstrated significant association with the obesity phenotype [recessive mode, $P = 0.00020$, and the OR (95% CI) was 1.62 (1.26–2.10)]. The rs7566605 genotype was transformed to a multidichotomous variable, i.e., CC homozygote versus the other genotypes. Multiple logistic regression analysis was performed, with genotype, age, and gender as independent variables. The *P* values for age, gender, and genotype were 0.21, 0.51, and 0.00030, respectively. OR (95% CI) was 1.61 (1.24–2.09). Our data indicated that rs7566605 in the *INSIG2* gene was associated with severe obesity in Japanese.

A deviation from the Hardy–Weinberg equilibrium was detected in cases ($P = 0.0015$), because this SNP is associated with obesity and cases were selected by phenotype. Cases were selected on the basis of BMI, and the prevalence of subjects with a BMI ≥30 kg/m^2 is only 2–3% in Japan (Yoshiike et al. 2002). Cases may be biased and not representative of the general population. Thus, it is not unexpected that cases were not in accordance with Hardy–Weinberg equilibrium.

Analysis of various quantitative phenotypes with rs7566605

To investigate whether the genotypes of SNP rs7566605 are associated with the phenotypes of metabolic disorders, we compared the following among the different genotypes in cases, controls, and combined groups: ANOVA results; BMI; levels of fasting plasma glucose; hemoglobin A1c (HbA1c); total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol; and blood pressure. Quantitative phenotypes with respect to BMI and levels of fasting plasma glucose; HbA1c; total cholesterol, triglycerides, and HDL cholesterol; and blood pressure were not found to be significantly associated with the rs7566605 genotypes in either cases or controls (Table 3). Systolic and diastolic blood pressures were significantly lower in the GG homozygote in the control group. Blood pressure was higher in GG homozygote in the obese group. Thus, the rs7566605 genotype was not associated with blood pressure.

Table 2 Association of rs7566605 in the *INSIG2* gene with severe obesity

Sample (sample size)	No. of subjects (%)			No. of chromosomes (%)		HWE test[a]	
	CC	CG	GG	C	G	χ^2	*P* value
Case (n = 908)	127 (14)	365 (40)	416 (46)	619 (34)	1,197 (66)	10.1	0.0015
Control (n = 1495)	136 (9)	664 (44)	695 (46)	936 (31)	2,054 (69)	1.6	0.21

Allele frequency mode[b]			Minor allele recessive mode[b]			Minor allele dominant mode[b]		
χ^2	*P* value	OR[c] (95% CI)	χ^2	*P* value	OR[c] (95% CI)	χ^2	*P* value	OR[c] (95% CI)
4.0	0.046	1.13 (1.00–1.28)	13.9	0.00020	1.62 (1.26–2.10)	0.1	0.75	1.03 (0.87–1.21)

[a] Hardy–Weinberg equilibrium test

[b] Association test was performed in three different modes as described in the "Materials and methods", and the results in the three modes are shown

[c] Odds ratio (OR) with 95% confidence interval (CI)

Table 3 Comparison of various quantitative phenotypes among different genotypes at rs7566605 in obese and control subjects

	Obese[a]			Control[a]		
	CC (n = 127)	CG (n = 365)	GG (n = 416)	CC (n = 136)	CG (n = 664)	GG (n = 695)
Age (year)	48.5 ± 15.2	48.0 ± 14.0	50.0 ± 14.2	47.7 ± 17.4	48.1 ± 16.7	48.4 ± 16.4
P value[b]		0.13			0.89	
BMI (kg/m^2)	35.22 ± 6.91	34.28 ± 5.09	34.52 ± 5.21	21.70 ± 2.06	21.68 ± 2.07	21.60 ± 2.10
P value		0.25			0.73	
Glucose (mg/dl)	127.8 ± 44.1	129.3 ± 50.3	129.1 ± 50.8	102.0 ± 40.6	98.0 ± 21.7	97.0 ± 21.9
P value		0.96			0.23	
HbA1c (%)	6.4 ± 1.7	6.5 ± 1.8	6.5 ± 1.8	5.1 ± 0.8	5.1 ± 0.6	5.1 ± 0.6
P value		0.93			0.81	
Total cholesterol (mg/dl)	209.1 ± 39.3	209.3 ± 37.5	210.4 ± 38.1	204.1 ± 35.0	199.4 ± 36.9	202.2 ± 36.3
P value		0.90			0.23	
Triglycerides (mg/dl)	147.1 ± 85.4	160.1 ± 127.3	153.9 ± 102.7	99.6 ± 58.2	103.0 ± 65.5	105.6 ± 82.3
P value		0.51			0.62	
HDL cholesterol (mg/dl)	51.6 ± 14.1	52.7 ± 15.9	53.8 ± 22.2	67.3 ± 14.8	64.9 ± 15.8	65.0 ± 15.6
P value		0.52			0.45	
SBP[c] (mmHg)	134.8 ± 15.3	136.8 ± 18.7	136.6 ± 18.4	122.9 ± 15.8	125.4 ± 17.9	121.9 ± 18.0
P value		0.57			0.0019	
DBP[d] (mmHg)	82.9 ± 11.1	84.6 ± 11.7	83.4 ± 12.4	76.5 ± 11.3	77.0 ± 11.1	75.1 ± 11.1
P value		0.26			0.008	

Data are mean ± standard deviation

BMI body mass index, *HbA1* hemoglobin A1c, *HDL* high-density lipoprotein

[a] Data of each quantitative phenotype were compared among different genotypes at the rs7566605 in obese and control subjects

[b] *P* values were analyzed using analysis of variance in each group of obese and control subjects

[c] Systolic blood pressure

[d] Diastolic blood pressure

Discussion

Recent genome-wide association studies have shown that rs7566605 in the upstream region of the *INSIG2* gene is associated with obesity (Herbert et al. 2006). Associations between rs7566605 and the obesity phenotype have been observed in many Caucasian subjects (Herbert et al. 2006; Hall et al. 2006; Lyon et al. 2007; Liu et al. 2008). However, these associations were controversial with regard to Asian subjects (Yang et al. 2008; Tabara et al. 2008). The association between rs7566605 and BMI may be hard to be replicated in the Asian general population due to the relatively smaller average BMI value and smaller proportion of obesity with BMI >30 kg/m^2 in Asians compared with

those in Caucasians. Indeed, criteria of obesity is BMI >30 kg/m^2 in Caucasians and BMI >25 kg/m^2 in Japanese. We could show the contribution of rs7566605 to obesity in Japanese using severely obese patients with a BMI ≥30 kg/m^2 as cases. SNP rs7566605 could also contribute to the development of severe obesity in Japanese.

Allele frequency was 0.31–0.34 in Japanese, just as observed in European subjects, and the CC genotype was also associated with severe obesity in Japanese, as previously reported (Herbert et al. 2006; Hall et al. 2006; Lyon et al. 2007; Liu et al. 2008). However, CC genotype was not significantly associated with BMI in obese and control groups, although CC homozygotes had higher BMI. Thus, it is possible that our study did not have sufficient power to detect the association between rs7566605 and BMI. The CC genotype would be thrifty variation and have an advantage for survival before modern times. Subjects with CC genotype would be susceptible to obesity in recent years. As a result, the number of CC homozygotes would increase in severely obese group, leading to a deviation from Hardy–Weinberg equilibrium.

Since rs7566605 exists approximately 10 kb upstream from *INSIG2*, SNPs may affect the transcriptional activity of *INSIG2*. INSIG2 is expressed ubiquitously. It was downregulated by insulin in the liver and involved in fatty acid synthesis (Yabe et al. 2003; Takaishi et al. 2004). INSIG2 also mediates feedback control of cholesterol synthesis (Goldstein et al. 2006). Although serum total cholesterol, HDL cholesterol, and triglycerides were not significantly different among genotypes, it is possible that INSIG2 is related to obesity as it affects lipid metabolism.

In summary, our study indicated that rs7566605 in the upstream region of the *INSIG2* gene may influence the risk of severe obesity in Japanese.

Acknowledgments This work was supported by Takeda Science Foundation (KH).

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