Original Article

Interactive effects of main genotype, caloric intakes, and smoking status on risk of obesity

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The aim of this study was to determine the strong candidate genes increasing susceptibility to obesity among previously reported obesity-related genes in Korean subjects and evaluate gene-environmental interactions in susceptibility to obesity. The study population comprised of 163 adolescents (95 boys and 68 girls) and their parents (97 men and 96 women).We used multivariable-adjusted logistic regression analysis, and classification and regression tree (CART) analysis incorporating both the genetic (ADRB2 R16G genotype) and environmental (overeating, smoking status, and parent's obese status) variables. The polymorphisms were genotyped with SNP-ITTM assays using the SNPstream 25KTM System (Orchid Biosciences, New Jersey, USA). Arg16 allele of ADRB2 R16G, smoking and overeating were linked to an increased risk of obesity in adults. CART analysis showed that smoking parents who overate and carried the Arg allele, ADRB2 R16G, had an odds ratio (OR) of 11.7 (95% confidence interval (CI), 2.13-64.04) for obesity compared to non-smoking parents who had none of these factors. Among children, the highest risk group for obesity was the overeater with obese parents (OR, 5.20; 95% CI, 1.86-14.53). The results of the study indicate that beta2-adrenoceptor polymorphism may contribute to the development of obesity through gene-environmental interactions. Further replication studies with larger sample size would be needed to confirm our study results.

Key Words: obesity, adrenergic beta-2 receptors, interaction, nutrition, smoking

INTRODUCTION

Currently, genetic, behavioral, and social-environmental factors are involved in the development of obesity. More than 120 candidate genes have been reported to be associated with obesity-related phenotypes in the 2005 version of the human obesity gene map.[1] There are also differential effects of obese gene variants based on ethnicity.[2] Families may be enhancing the children's susceptibility to obesity, because parents transmit genes and have a powerful influence over their children's environmental conditions.[3] The eating behavior of children may be enhancing their genetic susceptibility to obesity. Some individuals develop obesity while others do not, although they have obesity-related genes. The contribution of obesity-related genes is influenced by an interaction with environmental factors predisposing them to obesity, such as overeating and a sedentary lifestyle.[4] The specific evidence for these interactions is weak, although it seems that obesity is the result of gene-environmental interactions. Gene-environmental interactions of obesity at the individual level are still elusive. Therefore, in this study we identified the strong candidate genes increasing susceptibility to obesity among previously reported obesity-related genes in Korean subjects, and evaluated gene-environmental interactions in susceptibility to obesity using several statistical approaches.

MATERIALS AND METHODS

Participants

The study participants (children or adolescents and their parents) volunteered to participate in this study after seeing an advertisement in the Department of Family Medicine of Asan Medical Center in Seoul, Korea. The study was approved by the Institutional Review Board of Asan Medical Center, and informed consent was obtained from the parents of each participant.

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Subjects were also excluded from participation if they had been treated with any anti-obesity agent, or if they had changed above 5% of their baseline weight during the previous 6 months. The study population comprised of 163 adolescents (95 boys and 68 girls) and their parents (97 men and 96 women).

Anthropometric measurements

Height and weight were measured by an automatic height-weight scale to the nearest 0.1 cm and 0.1 kg, respectively, and body mass index (BMI) was calculated by dividing the weight (kg) by height squared (m^2). Using a non-elastic tape measure, the waist circumference was measured at the end of a normal expiration at the midpoint between the lower border of the rib cage and the iliac crest.

Assessment of lifestyle factors

Unrestricted routine dietary intake by subjects was assessed by a semi-quantitative food frequency questionnaire (FFQ), which includes commonly consumed food items selected from the Korean National Health and Nutrition Survey.[5,6] All subjects were requested to maintain their usual diet before testing. Respondents were instructed to record their usual intake frequency and portion size for all food and beverages consumed over the previous 6 months. Experienced interviewers verified the accuracy of each FFQ by questioning respondents about any modifications of dietary patterns during the previous 6 months. The record for each subject was coded, and standard reference tables were used to convert household portions into grams. Nutrient analyses were quantified using CAN-PRO,[7] a computer-aided nutritional analysis software program developed by the Korean Nutrition Society and the percent intake of carbohydrate, fat, and protein in relation to the total energy consumed was calculated.

The total daily energy expenditure was calculated as the basal metabolic rate (BMR) multiplied by physical activity level (PAL).[8] In the first step, BMR was estimated by the Harris-Benedict equation as a body weight-based equation. In the second step, the WHO PAL values used in this study were 1.55, 1.78, and 2.10 (men), and 1.56, 1.64, and 1.80 (women) for light, moderate, and heavy occupational activities, respectively, to account for individuals engaged in occupational activities of different intensities. Participants were asked about their frequency of physical exercise, including their participation in sports, physically-active hobbies, and fitness exercise, on a weekly basis. Physical exercise was defined as activity causing light perspiration or a slight-to-moderate increase in breathing or heart rates for at least 30 minutes (eg walking, jogging, running, cycling, and swimming).

Measurements of parameters of metabolic syndrome

Blood pressure was measured using a mercury sphygmomanometer with the individual in a sitting position and after 10 minutes of rest. Cuff size was selected according to the arm circumference of each participant. Blood samples were obtained from each subject after a 12-hour overnight fast by evacuation from an antecubital vein into vacutainer tubes. The fasting plasma glucose concentration was measured by the glucose oxidase method, and concentrations of total cholesterol and triglycerides were measured by enzymatic procedures using an autoanalyzer (Hitachi-747; Hitachi Ltd., Tokyo, Japan). The high density lipoprotein-cholesterol (HDL-C) fraction was measured enzymatically after precipitation of apo-B-containing lipoproteins with $MnCl_2$. Low density lipoprotein-cholesterol (LDL-C) was estimated indirectly according to the Friedewald formula for triglyceride concentrations <400 mg/dL. Non-esterified fatty acid (NEFA) levels were determined by enzymatic colorimetry (SICDIA NEFAZYME, Toshiba-200FR; Toshiba, Tokyo, Japan). Fasting insulin concentrations were measured by radioimmunoassay (Dianabott, Tokyo, Japan). The homeostasis model assessment insulin resistance index (HOMA-IR; fasting insulin [μIU/mL]×fasting glucose [mg/dL]/405) was used for estimating insulin sensitivity.[9]

Genotyping of polymorphisms

Five single nucleotide polymorphisms (SNPs) located at the ADRB2 gene and one common SNP at each of the ADRB3, UCP2, UCP3, PPARG and IRS1 genes were explored based on previous studies performed among Koreans.[10-13]The following 10 single nucleotide polymorphisms (SNPs) were genotyped with SNP-ITTM assays using the SNPstream 25KTM System (Orchid Biosciences, New Jersey, USA): ADRB2 A→G rs1042713 (R16G), ADRB2 C→G rs1042714 (E27Q), ADRB2 G→A rs1042717 (L84L), ADRB2 C→A rs1042718 (R175R), ADRB2 G→C rs1042719 (G351G), ADRB3 T→C rs4994 (T64A), UCP2 G→A rs660339 (V55A), UCP3 C→T rs2075577 (Y210Y), PPARG C→T rs3856806 (C161T), and IRS1 G→A rs181278 (G972R). The latter four SNPs were selected for their ability to tag haplotypes of the ADRB2. The genomic DNA region spanning the polymorphic site was PCR-amplified using one phosphothiolated primer and one regular PCR primer, and the amplified PCR products were digested with exonuclease. The 5' phosphothioates protected one strand of the PCR product from exonuclease digestion, resulting in the generation of a single-stranded PCR template. The single-stranded PCR template was overlaid onto a 384-well plate containing a covalently-attached SNP-ITTM primer extension primer, designed to hybridize immediately adjacent to the polymorphic site. The SNP-ITTM primer was extended for a single base with DNA polymerase and a mixture of appropriate acycloterminators, which were labeled with fluorescein-isothiocyanate (FITC) or biotin, and were complementary to the polymorphic nucleotide. The identity of the incorporated nucleotide was determined using serial colorimetric reactions with antialkaline phosphatase (AP)-conjugated FITC and streptavidin-horseradish peroxidase, respectively. The yellow and/or blue colors were analyzed with an ELISA reader and the final genotype determinations were made using the QCReviewTM program.

Statistical analysis

All values are shown as the means ± SDs or as frequencies using percentages. Obesity in parents was defined as a BMI ≥25 kg/m^2, according to the proposed obesity criteria of the Asia-Pacific region.[14] Obese children were classified according to the international cut-off points for BMI for overweight by gender between 2 and 18 years of age defined to pass through a BMI of 25 kg/m^2 at age 18.[14] Chi-square tests were used to determine whether individual variants were in equilibrium at each locus in the population (Hardy-Weinberg equilibrium) and also were used to test differences between the control and obesity groups for categorical variables and each of the SNP genotypes and alleles. Differences in the continuous clinical variables between the two groups were analyzed by using a two sample *t*-test. To determine the gene-environmental interaction, we used multivariable-adjusted logistic regression analysis, and classification and regression tree (CART) analysis incorporating all genetic, caloric intakes, and smoking status variables as indicators for the parents and all genetic, parental phenotype, and caloric intake variables as indicators for the children. Indicator variables for terminal nodes in the final tree were used in logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs). CART is an approach designed to produce a decision tree for identifying subgroups of subjects at higher risk.[15] Splitting rules are used to stratify data into subsets of individuals, which are represented in the CART decision tree as nodes. The CART model selects the variable used to split each branch and the split point. Each 'child node' is selected considering only a subset of the population within a 'parent node' to explain class, thus, the results are conditioned on the first splitting variable. CART was implemented the Gini index to set the splitting criterion. To keep the tree structure simple and to discover combinations of predisposing factors affecting relatively large groups of individuals, we set the minimum root node size at 10 and the minimum end node size at 5. Maximum branch level in the trees was limited to five. A random 10-fold cross-validation was performed to determine the balance between the discrimination of the two classes of individuals and the risk of over fitting the trees. CART analysis was carried out using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). A *p*-value <0.05 was deemed statistically significant. All statistical tests were two-sided.

RESULTS

Characteristics of the subjects

The proportion of obesity was 40.4% and 45.4% in parents 30-57 years of age (mean age, 42 years) and their children, 6-19 years of age (mean age, 13 years), respectively. Both obese parents and children had higher blood pressures, worse lipid and glycemic profiles, as well as higher BMI, body fat percentages, and waist circumferences compared with their controls (Table 1). Compared with control parents, obese parents were more likely to smoke and ate significantly more than their total daily energy expenditure. Obese children reported significantly higher daily caloric intake (p<0.001), but did not eat significantly more than their total daily energy expenditure compared with control children (p=0.116).

Table 1. Clinical characteristic of the subjects

Variables	Parents		Children	
	Control (n = 115)	Obesity (n = 78)	Control (n = 89)	Obesity (n = 74)
Age	42.0 ± 4.2	42.6 ± 4.7	13.5 ± 3.4	12.8 ± 3.2
Male (%)	52 (45.2)	45 (57.7)	47 (52.8)	48 (64.9)
Body mass index (kg/m^2)	22.5 ± 1.6	27.3 ± 2.2*	18.8 ± 2.7	26.1 ± 4.5*
Waist circumference (cm)	77.7 ± 6.4	89.0 ± 6.1*	66.9 ± 8.2	84.7 ± 12.1*
Systolic BP (mmHg)	115 ± 13.3	122 ± 12.6*	109 ± 11.9	116 ± 13.0**
Diastolic BP (mmHg)	70.3 ± 11.6	77.6 ± 11.5*	64.1 ± 10.0	66.8 ± 12.4*
Fasting plasma glucose (mg/dL)	87.6 ± 9.9	93.4 ± 15.3**	84.6 ± 6.1	84.4 ± 6.8**
Total cholesterol (mg/dL)	187 ± 32.4	198 ± 30.6***	165 ± 29.2	177 ± 36.2***
Triglyceride (mg/dL)	103 ± 74.0	159 ± 99.8*	72.4 ± 34.7	122 ± 68.9*
HDL cholesterol (mg/dL)	54.3 ± 12.2	48.0 ± 10.8*	57.2 ± 11.7	50.1 ± 12.9*
LDL cholesterol (mg/dL)	113 ± 28.3	117 ± 26.4	93.8 ± 23.1	103 ± 29.2***
Insulin (uIU/mL)	7.6 ± 4.4	11.0 ± 6.1*	10.9 ± 5.7	18.1 ± 14.4*
HOMA-IR	1.68 ± 1.06	2.44 ± 1.21*	2.29 ± 1.26	3.82 ± 3.30*
NEFA (uEq/mL)	454 ± 190	540 ± 177**	543 ± 222	596 ± 289**
Daily caloric intake (kcal/day)	1786 ± 402	2061 ± 500*	1775 ± 344	2149 ± 623*
Overeating (%)	33 (28.7)	36 (46.2)***	29 (32.6)	33 (44.6)
Smoker (%)	18 (15.7)	25 (32.1)**	3 (3.4)	3 (4.1)
Regular exercise (>3/wk)	45 (39.1)	31 (39.7)	27 (30.3)	35 (47.3)***
High education (%)	42 (36.5)	25 (32.1)	-	-
Medication (%)				
Antihypertensives	5 (4.3)	6 (7.7)	-	-
Antidiabteics	2 (1.7)	1 (1.3)	-	-

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment insulin resistance index; NEFA, non-esterified fatty acid

Data values are the means±SDs and numbers (%). Over eating indicates a greater intake of calories than expended daily (daily caloric intake > daily caloric requirement). High education ranges beyond college.

The *p*-value was estimated by a two sample *t*-test, except a chi-square test for non-parametric variables (overeating, smoker, regular exercise, high education, and medication history).

*p<0.001, **p<0.01, ***p<0.05

Table 2. The association between obesity-related gene and obesity among parents

Genes (SNP ID)	Genotypes				Alleles			
		Control (n = 115)	Obese (n = 78)	*p*-value		Control (n = 115)	Obese (n = 78)	*p*-value
ADRB2 R16G (rs1042713)	AA	31 (27.0)	34 (43.6)	0.021	A	92 (80.0)	71 (91.0)	0.038
	AG	61 (53.0)	37 (47.4)					
	GG	23 (20.0)	7 (9.0)		G	84 (73.0)	44 (56.4)	0.016
ADRB2 E27Q (rs1042714)	CC	93 (80.9)	66 (84.6)	0.461	C	113 (98.3)	78 (100)	0.242
	CG	20 (17.4)	12 (15.4)					
	GG	2 (1.7)	0 (0.0)		G	22 (19.1)	12 (15.4)	0.503
ADRB2 L84L (rs1042717)	GG	49 (42.6)	44 (56.4)	0.107	G	102 (88.7)	74 (94.9)	0.137
	GA	53 (46.1)	30 (38.5)					
	AA	13 (11.3)	4 (5.1)		A	66 (57.4)	34 (43.6)	0.060
ADRB2 R175R (rs1042718)	CC	49 (42.6)	45 (57.7)	0.080	C	102 (88.7)	74 (94.9)	0.050
	CA	53 (46.1)	29 (37.2)					
	AA	13 (11.3)	4 (5.1)		A	66 (57.4)	33 (41.6)	0.040
ADRB2 G351G (rs1042719)	GG	34 (29.6)	31 (39.7)	0.175	G	90 (78.3)	68 (87.2)	0.115
	GC	56 (48.7)	37 (47.4)					
	CC	25 (21.7)	10 (12.8)		C	81 (70.4)	47 (60.3)	0.142
ADRB3 T64A (rs4994)	TT	86 (74.8)	54 (69.2)	0.482	T	112(97.4)	77 (98.7)	0.467
	CT	26 (22.6)	23 (29.5)					
	CC	3 (2.6)	1 (1.3)		C	29 (25.2)	24 (30.8)	0.396
UCP2 V55A (rs660339)	GG	29 (25.2)	20 (25.6)	0.608	G	92 (80.0)	58 (74.4)	0.355
	GA	63 (54.8)	38 (48.7)					
	AA	23 (20.0)	20 (25.6)		A	86 (74.8)	58 (74.4)	0.947
UCP3 Y210Y (rs2075577)	CC	29 (25.2)	19 (24.4)	0.973	C	86 (74.8)	58 (75.3)	0.892
	CT	57 (49.6)	40 (51.3)					
	TT	29 (25.2)	19 (24.4)		T	86 (74.8)	59 (75.5)	0.892
PPARG C161T (rs3856806)	CC	76 (66.1)	55 (70.5)	0.330	C	112 (97.4)	78 (100)	0.209
	CT	36 (31.3)	23 (29.5)					
	TT	3 (2.6)	0 (0.0)		T	39 (33.6)	23 (29.5)	0.518
IRS1 G972R (rs181278)	GG	111 (96.5)	77 (98.7)	0.346	G	115 (100)	77 (100)	1.000
	GA	4 (3.5)	1 (1.3)					
	AA	0 (0.0)	0 (0.0)		A	4 (3.5)	1 (1.3)	0.327

Chi-square test, except for Fisher's exact test, for the T allele for ADRB3 T64A, the C allele for PPARG C161T, and the G and A allele for IRS1 G972R.

SNPs associated with obese risk

The distribution of all evaluated SNPs in the control subjects were in agreement with the Hardy-Weinberg equilibrium ($p>0.05$). After evaluating the most associated SNP with obesity using chi-square or Fisher's exact tests (Table 2), multivariable-adjusted logistic regression analysis showed that the presence of the Arg allele, ADRB2 R16G (AA+AG), was most strongly linked to an increased risk of obesity (OR 3.08, 95% CI 1.19-8.01) in parents. The other significant variables were smoking, and overeating. Besides, only parent's obesity was positively associated with risk of child obesity after adjusting for age and gender (Table 3).

Table 3. Effects of main genotype and environmental factors on risk of obesity

Variables	*p*-value	Odds ratio	95% CI
Parents			
Arg16 allele			
No		1	
Yes	0.021	3.08	1.19-8.01
Smoking			
No		1	
Yes	0.045	2.34	1.02-5.38
Overeating			
No		1	
Yes	0.012	2.24	1.19-4.21
Children			
Parent's obesity			
No		1	
Yes	0.004	2.81	1.40-5.64
Overeating			
No		1	
Yes	0.135	1.70	0.85-3.39

After adjusting for age and gender

Predictive clinicogenomic model (Figure 1)

To further determine the gene-environmental interaction, we did CART analysis incorporating both the genetic (ADRB2 R16G genotype) and environmental (overeating, smoking status, and parent's obese status) variables. CART uses the Gini index for determining the best split. Figure 1A and 1B showed the final CART models selected for parents and their children, respectively after pruning. In the model for parents (Figure 1A), the first split was according to over-intakes, indicating a dominant effect. The next split nodes were according to ADRB2

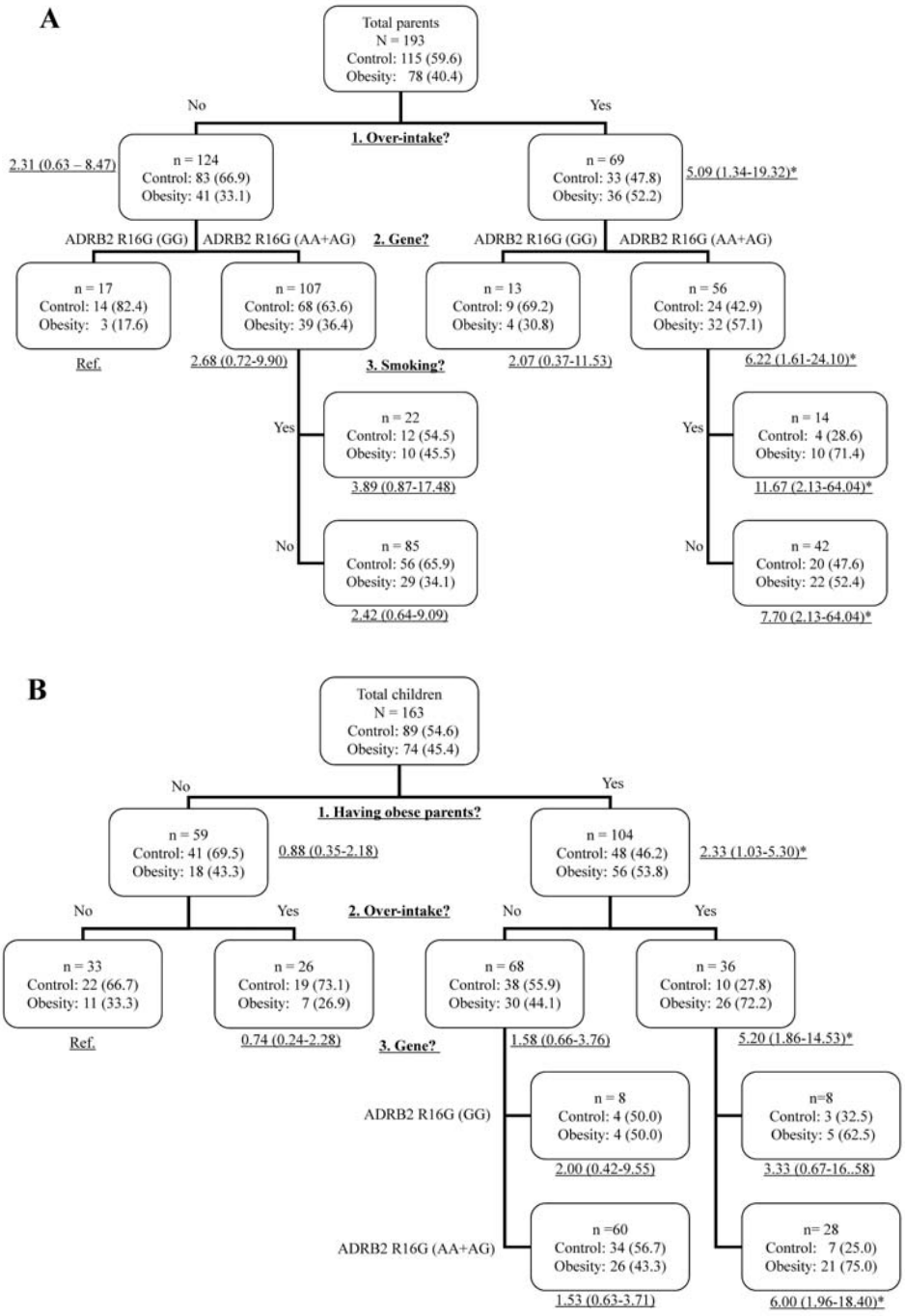

Figure 1. Predictive clinico-genomic model of adults (A) and their children (B). *p<0.05

R16G genotype and smoking. With those overeating with ADRB2 R16G (GG) serving as the reference group, Figure 1A also presents naive ORs for other terminal nodes. The CART model for parents indicated some potential interactions among caloric intakes, ADRB2 R16G genotype and smoking status. The interaction of overeating, ADRB2 R16G (AA+AG) and smoking significantly increased the risk of obesity (Figure 1A, OR 11.67, 95% CI 2.13-64.04). However, some decreased risk of obesity was found among the subjects overeating with the Arg allele, ADRB2 R16G, but who do not smoke. In the model for children (Figure 1B), the first split was according to the parent's obese status, indicating a dominant effect. The next split nodes were according to caloric intakes and the ADRB2 R16G genotype. With those who do not overeat and are without obese parents as the reference group, Figure 1B also presents naive ORs for other terminal nodes. The interaction of the parent's obesity, ADRB2 R16G (AA+AG) and overeating significantly increased the risk of obesity among children (Figure 1B, OR 6.00, 95% CI 1.96-18.40).

DISCUSSION

We first examined the relationship between obesity and 10 SNPs, including ADRB2, ADRB3, UCP2, UCP3, PPARG, and IRS1, before evaluation of gene-environmental interactions in obesity. All of the selected SNPs satisfied the Hardy-Weinberg equilibrium and the DNA sequence variation in ADRB2 R16G and R175R were associated with obesity in the parents (Table 2). Notably, the ADRB2 Arg16Gly polymorphism (the Arg16 allele) was the strongest candidate gene increasing susceptibility

to obesity among the subjects of the present study (Table 3). Parents with the Arg16 allele had a more than three-fold increased risk of obesity than parents with the Gly16 homozygote. An association between variation in the ADRB2 gene and obesity has been reported in many, but not all studies.[1,17-20]A study reported that the Arg16Gly and Gln27Glu variants of the ADRB2 gene have shown associations with obesity-related phenotypes.[1] However, no correlations were observed between the ADRB2 gene and obesity in some studies performed in Caucasians,[17,20] as well as Asians[18,19] inciting considerable debate on these associations.

Furthermore, the estimated frequency of the Gly16 allele was 15.5% in the present study. It was much lower than in Caucasians and Blacks,[21] while similar to the Japanese.[18] In addition, some studies performed in the Western population have shown an association between the Gly16 allele and a higher risk of obesity,[21,22] while contrary to this, our results demonstrated an association between the Gly16 allele and a lower risk of obesity, which is consistent with a previous study from Brazil[23] and Japan.[24] Pereira *et al.* showed that the Arg16 allele was significantly associated with increased BMI and a higher risk of obesity in the general population.[23] Ishiyama-Shigemoto *et al.* reported that the frequency of Gly16 homozygotes was lower in obese women when compared with non-obese women.[24] Some studies also show contradictory results regarding the association between the Gly16 allele and the change in body weight over time.[25,26] The genetic pathway of the ADRB2 polymorphisms underlying obesity has so far yielded inconclusive results in the aforementioned studies, although some researchers have suggested that individuals with the Gly16 allele may be more likely to become obese than Arg16 homozygotes because the beta 2 receptor in the Gly16 allele was found to lead to less efficient stimulation of lipolysis in adipose tissue and excess fat accumulation over time compared with the Arg16 allele.[22] Ethnicity is maybe the most important reason for these differences, although some of these discrepancies may be a reflection of differences in obesity criteria, gender, comorbidities, sample size, and the ethnic background of the subjects. Studies have reported an association between obesity-related phenotypes and ADRB3 T64A, UCP2 V55A, UCP3 Y210Y, PPARG C161T, and IRS1 G972R.[1] There was however no association between these candidate genes and obesity in the present study. We therefore selected the Arg16Gly polymorphism of ADRB2 as a genetic factor for the development of a prediction model of obesity.

In our study, the proportion of obesity demonstrated in the present study was higher than estimates from other studies based on a national survey because our study selected volunteers who wanted to participate in this study after they saw an advertisement.[27,28] Both obese parents and children had a significantly worse metabolic profile than their controls (Table 1). This finding is compatible with the recent observations based on investigations of a nationwide representative sample of Koreans as well as Caucasians.[27,28] We found a higher proportion of smokers and overeaters in the obese parents than in the controls. However, there were no differences in smokers and overeaters between the obese children and controls. Furthermore, contrary to expectations, obese children had a higher frequency of regular exercise habits than the controls. These findings in children may be explained partly by school food service programs, a very small proportion of smokers among children, and recent school health policies to promote physical activity among obese children.[29]

Results from twin, family, and adoption studies suggest that genetic factors explain 20 to 90% of the variance in BMI, leaving only a small part to be accounted for by environmental factors. As observational evidence on both environmental exposures (lifestyle and dietary intake) and genotyping, several studies mainly examined the interactions between energy intake and genes involved in the regulation of energy balance and adipose tissue metabolism. Previous genetic studies on obesity have mainly focused on the association between gene SNPs and the obesity phenotype.[1] However, more studies on the proportion of total genetic variation explained by candidate genes and analyses of interactions between gene and several environmental factors are still needed and is a relatively new field.[30,31] Thus, in this study we finally evaluated the gene-environmental interactions underlying susceptibility to obesity using the Arg16 allele of the ADRB2 gene as a genetic factor and the obesity status of parents and overeating for children, as well as overeating and smoking status for parents as environmental factors. The CART model indicated some potential interactions among caloric intakes, ADRB2 R16G genotype and smoking status in parents and presented some potential interactions among caloric intakes, ADRB2 R16G genotype and smoking status in children. These findings suggest that obese-related gene expression is provoked by environmental and behavioral factors and therefore provide evidence that obesity results from gene-environmental interactions. A study has shown that the relationship between the Arg16Gly polymorphism and obesity becomes stronger with age, which is in accordance with our study.[16] These results suggest that children might need time to manifest obesity, even though they have the obesity candidate genes.[24] The subgroup with the highest obesity risk was the smokers who overate and carried the Arg allele, ADRB2 R16G (OR, 11.67), among parents (Figure 1A). Among children, the subgroups with the highest obesity risk were those overeating with obese parents and the Arg allele, ADRB2 R16G (OR, 6.00, Figure 1B).

Our results support previous twin and adoption studies that have shown a genetic contribution to obesity.[32] Park *et al*.[10] reported that SNPs in the ADRB genes could explain only 18% of the variation in adolescent obesity, which suggests that obesity is a complex problem compounded by multiple factors, including other genes and environmental factors. Differences in genetic susceptibility to obesity may partly explain why some individuals develop obesity while others do not. In our predictive model, the overall correct prediction rates of the model were 62.7% and 64.4% in parents and their children, respectively (data not shown). These results suggest that environmental factors, and gene-gene and gene-environ-

mental interactions during the entire lifespan of an individual might be important to develop or prevent obesity.

Our study has some limitations, including the cross-sectional design. The generalizabilty of our study to non-Korean populations is also uncertain, because all of the participants were Korean. In addition, the sample size of our study may be relatively small for a predictive clinico-genomic model. Nevertheless, this is a significant study to evaluate gene-environmental interactions in the susceptibility to obesity using logistic regression analysis in both parents and their children. We provided some examples of models to explain the gene-environmental interaction for the development of obesity. In conclusion, our results indicate that beta2-adrenoceptor polymorphism may contribute to the development of obesity through gene-environmental interactions. The current practice in the field is to have a 1st stage study followed by a replication study. Replication studies with larger sample size would be needed to confirm our study results. In addition, further research considering the simultaneous effects of multiple genes and gene-environment interactions is needed to extend our findings.

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AUTHOR DISCLOSURES

Sangyeoup Lee, Cheol Min Kim, Hyun Jun Kim, Hye Soon Park, no conflicts of interest.

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Original Article

Interactive effects of main genotype, caloric intakes, and smoking status on risk of obesity

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基因、熱量和抽菸對於肥胖風險的交互作用

這篇研究的主要目的是確認之前發表過的韓國人與肥胖有關的候選基因對於肥胖的易感受性，以及評估與環境間的交互作用。此篇研究族群是 163 名青少年(95 名男性和 68 名女性)以及他們的雙親(97 名男性和 96 名女性)。利用多變量羅吉斯迴歸分析和迴歸分類樹(CART)分析基因(ADRB2 R16G genotype)和環境因子(飲食過量、抽菸、雙親肥胖)。使用 SNPstream 25KTM 系統分析基因多型性。ADRB2 R16G、抽菸和飲食過量被認為會增加成人肥胖風險。迴歸分類樹分析結果顯示帶有 ADRB2 R16G 基因型、飲食過量且抽菸的雙親者比起雙親不抽菸且無任何一項因子者，其肥胖的 OR 值為 11.7 (95% CI: 2.13-64.04)。對孩童而言，肥胖高風險群為雙親肥胖且飲食過量(OR, 5.20; 95% CI, 1.86-14.5)。此篇研究指出 β_2 腎上腺素受體基因多型性或許對於肥胖相關基因和環境間的交互作用有貢獻。未來需要較大樣本的研究來確認本篇研究結果。

關鍵字：肥胖、β_2 腎上腺素受體、交互作用、營養、抽菸