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SHORT COMMUNICATION

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Single nucleotide variants in the β_2-adrenergic and β_3-adrenergic receptor genes explained 18.3% of adolescent obesity variation

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Abstract Associations of obesity with its candidate genes, β-adrenergic receptor genes (*ADRBs*), peroxisome proliferator-activated receptor-γ (*PPARγ*), and uncoupling proteins (*UCPs*) were studied in Korean adolescents. We analyzed the obesity-related phenotypes body mass index (BMI), percentage of body fat, plasma leptin and insulin levels, fasting glucose concentration, and plasma lipid profile in 329 teenagers to investigate the effects of seven single nucleotide variants 252G/A, 523C/A and 1053G/C in *ADRB2*; Trp64Arg in *ADRB3*; 161C/T in *PPARγ*; Ala55Val in *UCP2*; and 210C/T in *UCP3*. The 1053G/C polymorphism ($P < 0.05$) in the *ADRB2* gene and the Trp64Arg polymorphism ($P < 0.01$) in the *ADRB3* gene were associated with BMI after adjustment for dietary energy intake. Trp64Arg polymorphism also influenced percentage of body fat ($P < 0.01$) and plasma leptin level ($P < 0.05$). Furthermore, significant interaction effects between the 1053G/C and Trp64Arg polymorphisms were observed on BMI ($P < 0.01$). The polymorphisms of the *ADRB2* and *ADRB3* genes explained 4.3% and 10.1% of the variation on BMI, and the two loci effect, including their epistasis, explained 18.3%. We concluded that 1053G/C and Trp64Arg polymorphisms of the *ADRB* genes additively and interactively contributed to the variation of complex adolescent obesity.

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Introduction

Since the epidemic of childhood and adolescent obesity will contribute to a large increase of adult obesity and metabolic complication (Sorensen and Sonne-Holm 1988), there has been a great concern to study the early metabolic alterations characterizing juvenile and adolescent obesity and the associated genetic factors. In general, obesity is a complex phenotype resulting from the combined effects of genetic, environmental, and behavioral factors. In recent years, much has been learned about specific genes that influence human obesity. Candidate genes for obesity include β-adrenergic receptors (*ADRBs*), peroxisome proliferator-activated receptor-γ (*PPARγ*), and uncoupling proteins (*UCPs*) (Chagnon et al. 2000). It has been speculated that the β_2-adrenergic receptor (*ADRB2*) and β_3-adrenergic receptor (*ADRB3*) may influence accumulation in body fat. These receptors, which are expressed in adipose tissue, regulate energy balance through the mediation of the rate of both lipolysis and thermogenesis. The *PPARγ* is a member of the nuclear hormone receptor superfamily that is expressed predominantly in adipocytes and is thought to have a role in energy homeostasis, adipogenesis, and insulin sensitivity by regulating the expression of genes involved in lipid and glucose metabolism. The *UCP* genes are also known for various effects on metabolism and obesity (Dalgaard and Pedersen 2001).

We investigated the influence of single nucleotide variants in these candidate genes for childhood obesity on obesity-related traits in Korean adolescents. Three single nucleotide polymorphisms (SNPs) located at the *ADRB2* gene and one common SNP at each of the *ADRB3*, *PPARγ*, *UCP2*, and *UCP3* genes were explored.

Subjects and methods

The study enrolled 329 unrelated adolescents (199 males; 130 females) aged 11–19 who were recruited to the Asan Medical Center between July 2002 and February 2004. The study protocol was approved by the Ethics Committee of the Asan Medical Center. Informed consents were obtained from parents of all subjects before drawing blood. Patients with hypothyroidism, Cushing's disease, cancer, severe debilitating diseases, or intentional weight reduction during the preceding 6 months were excluded. Subjects were also excluded if they had been treated with any antiobesity agent or insulin. Anthropometric measurements were conducted with subjects wearing light clothing and without shoes. An automatic height–weight scale was used to measure height to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Body fat was determined using bioimpedance analysis (In body 3.0; Biospace, Korea). Waist circumference was measured at a point midway between the lower border of the rib cage and the iliac crest at the end of normal expiration, hip circumference was measured at the widest part of the hip, and waist-to-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. Dietary energy intake was assessed by the semiquantitative food frequency questionnaire (FFQ), which includes commonly consumed food items selected from the Korean National Health and Nutrition Survey. Biochemical measurements were determined in blood samples collected after an overnight fast. The samples were characterized with the use of standard laboratory automated techniques for fasting glucose, insulin, leptin, free fatty acid, triglyceride, total cholesterol, and high-density lipoprotein (HDL) cholesterol concentrations.

Three synonymous SNPs located at the *ADRB2* coding region, 252G/A, 523C/A, and 1053G/C, were genotyped. The Trp64Arg polymorphism of *ADRB3*, the 161C/T polymorphism in exon 6 of *PPARγ*, the Ala55Val polymorphism of *UCP2*, and the 210C/T polymorphism in exon 5 of *UCP3* were genotyped. Genomic DNA was amplified by standard polymerase chain reaction (PCR) methods using the corresponding primers (http://ilsongls.hallym.ac.kr/obesity.htm). The PCR product was sequenced using the ABI PRISM 3700 DNA analyzer (Applied Biosystems, Foster City, CA, USA).

The anthropometric and laboratory data were analyzed by ANOVA to test single nucleotide variant effects and their interaction effects on BMI, percentage body fat, triglyceride, HDL cholesterol, free fatty acid, leptin, insulin, and glucose. The analytical model included dietary energy intake as a covariate. Interaction effects were assessed with markers selected based on their significant associations with the traits. Backward selection was utilized to include the interaction terms in the analytical models. Statistical analyses were performed using SAS/STAT software Version 8.01 for Windows (SAS Institute Inc., Cary, NC, USA). In order to get the heritability of the single nucleotide variants, variance and covariance components were estimated using the mixed model, as shown below:

$$y = X\beta + Z\theta + e,$$

where y represents a vector of observations for traits adjusted for dietary energy intake effect, β is a vector of gender fixed effects, and θ is a vector of single nucleotide variants and their interaction random effects with the assumption of $\theta \sim N(0,R)$. R is a variance and covariance matrix for single nucleotide variants. For example, if we have only two single nucleotide variants, then $R = \begin{bmatrix} I\sigma_a^2 & I\sigma_{ab} \\ I\sigma_{ab} & I\sigma_b^2 \end{bmatrix}$, where I is identity matrix, σ^2_a and σ^2_b are variances for single nucleotide variants a and b, and σ_{ab} is their covariance. The e is a random vector of residuals with the assumption of $e \sim N(0, I\sigma^2_e)$, where σ^2_e is the residual variance component. The X and Z are known incidence matrices relating the fixed and random effects, respectively, to their corresponding observations. Inferences about unknown variance components for nucleotide variants and their interaction effects in the Bayesian approach were based on their marginal posterior distribution, and the marginalization of the joint posterior distribution was attained through Gibbs sampling as a Markov chain Monte Carlo. The posterior mean estimate for the variance and covariance components was calculated as the mean of the conditional expected values of the parameters in post-warming-up rounds from Gibbs sampling.

Results and discussion

Phenotypic characteristics of the subjects are presented in Table 1. The range of BMI for the subjects was 12.9–38.0 (male, 14.3–38.0; female, 12.9–37.4). Based on the

Table 1 Phenotypic characteristics of the subjects[a]. *HDL* high-density lipoprotein cholesterol

	Male ($n=199$)	Female ($n=130$)	*P*
Age (years)	13.3 ± 0.31	13.2 ± 0.37	0.724
Body weight (kg)	60.9 ± 2.00	51.1 ± 1.59	< 0.001
Body height (cm)	161.7 ± 1.51	153.6 ± 1.40	< 0.001
Body mass index (kg/m^2)	22.6 ± 0.47	21.2 ± 0.48	0.046
Waist circumference (cm)	77.8 ± 1.28	71.4 ± 1.17	< 0.001
Hip circumference (cm)	92.3 ± 1.20	89.6 ± 1.18	0.118
Waist-to-hip ratio	0.84 ± 0.066	0.80 ± 0.093	< 0.001
Body fat (%)	22.9 ± 0.79	28.4 ± 0.79	< 0.001
Fasting glucose (mg/dl)	85.1 ± 0.62	83.8 ± 0.63	0.125
Plasma insulin (uIU/l)	14.5 ± 1.14	12.3 ± 0.80	0.137
Plasma leptin (ng/ml)	6.93 ± 0.59	10.4 ± 0.73	< 0.001
Total cholesterol (mg/dl)	170.5 ± 3.08	173.6 ± 3.22	0.499
HDL cholesterol (mg/dl)	53.5 ± 1.21	55.5 ± 1.30	0.258
Triglyceride (mg/dl)	97.6 ± 5.71	91.3 ± 4.87	0.424
Free fatty acid (μEq/l)	550.2 ± 23.0	582.7 ± 26.1	0.353

[a]Data are presented as mean ± SEM

international age-specific and gender-specific cut-off points for children (Cole et al. 2000), the prevalence of overweight was 27.8% (male = 30.3% and female = 24.4%) and the prevalence of obesity was 17.2% (male = 21.0% and female = 12.2%). There were no significant differences ($P > 0.05$) by gender in age, hip circumference, fasting glucose, plasma insulin, total cholesterol, triglyceride, or free fatty acid. The other phenotypic measurements showed statistical difference ($P < 0.05$) by gender. They were mostly larger in males than in females. Only percentage of body fat and plasma leptin were larger in females.

Initial examination for SNP effects was to look at the differences in their allele frequencies of each locus among normal, overweight, and obesity groups (Table 2). In this analysis, dietary energy intake effects were not adjusted. Statistical significances were not observed when both male and female data were analyzed simultaneously ($P > 0.05$). However, when the data were partitioned by gender, we found that the *UCP2*-210C/T Ala55Val and the *UCP3*-210C/T polymorphisms were statistically associated ($P < 0.05$) with adolescent obesity in the female subgroup but not ($P > 0.05$) in males. In female obese subjects, frequencies of the C allele of *UCP2*-210C/T Ala55Val and the C allele of *UCP3*-210C/T were significantly smaller ($P < 0.05$) than those of normal and overweight females. This suggested heterogeneity by gender, and agreed with the San Luis Valley Diabetes Study, which presented a significant gender-specific effect of *UCP3*-210C/T on fat composition (Damcott et al. 2004). The significance test for this allele frequency difference had the disadvantage of losing information on BMI by categorizing the continuous variable into three groups. Hence, the significance test results from analysis of variance (ANOVA) that overcome such problems might be preferable.

In the ANOVA with the seven variants in *ADRB2*, *ADRB3*, *UCP2*, *UCP3*, and *PPARγ* genes (Table 3), statistically significant associations with BMI ($P < 0.05$) were demonstrated in the *ADRB2*-1053G/C and *ADRB3*-Trp64Arg polymorphisms, respectively and interactively. Associations of SNPs at codons 16 and 27 of the *ADRB2* gene with obesity have been reported (Ukkola et al. 2000), yet the significance of *ADRB2*-1053G/C in our study was novel. The significance of a common *ADRB3* variant replacing tryptophan with arginine (Trp64Arg) on BMI has been shown in both adult (Hao et al. 2004) and children (Endo et al. 2000; Arashiro et al. 2003) populations. *ADRB3*-Trp64Arg also influenced percentage of body fat ($P < 0.01$) and plasma leptin level ($P < 0.05$). Since the gender effects were observed in both percentage body fat and plasma leptin level ($P < 0.01$), the traits were further analyzed with the data partitioned by gender to determine the heterogeneity of the *ADRB3*-Trp64Arg effects. The *ADRB3*-Trp64Arg still significantly influenced percentage of body fat ($P < 0.01$) in both male and female data but not plasma leptin level ($P > 0.05$). This was probably due to reduced sample size of the partitioned data. A significant interaction was observed between the *ADRB2*-1053G/C and *ADRB3*-Trp64Arg variants not only for BMI ($P < 0.01$) but also for percentage of body fat ($P < 0.05$) and HDL cholesterol ($P < 0.05$). In addition, there was significant interaction between these genetic variants and gender affecting free fatty acid levels ($P < 0.05$), implying another gender-specific effect. This finding concurred with the study of Corella et al. (2001) where there was heterogeneity of *ADRB3*-Trp64Arg effect for obesity when the data of a Mediterranean population were partitioned by gender.

The ADRBs mediate the action of catecholamines on multiple human tissues. Activation of ADRBs leads to increased lipolysis in white adipocytes and thermogenesis in brown adipocytes (Walston et al. 1995). Defective expression at the cell surface or impaired signaling of ADRBs may lead to decreased lipolysis and thermogenesis in fat tissue that may contribute to obesity. Trp64Arg mutation appears at the beginning of the first

Table 2 Allele frequencies for the *ADRB2, ADRB3, PPARγ, UCP2*, and *UCP3* polymorphisms

	ADRB2			*ADRB3*(Trp64Arg)	*PPARγ*(161C/T)	*UCP2*(Ala55Val)	*UCP3*(210C/T)
	252G/A	523C/A	1053G/C				
Allele	A	A	C	C	T	C	C
Total							
Normal	0.30	0.30	0.44	0.13	0.17	0.54	0.51
Overweight	0.34	0.32	0.40	0.16	0.17	0.53	0.51
Obesity	0.28	0.28	0.46	0.15	0.17	0.49	0.47
Male							
Normal	0.31	0.31	0.43	0.11	0.16	0.59	0.56
Overweight	0.31	0.29	0.39	0.13	0.13	0.53	0.54
Obesity	0.26	0.26	0.48	0.16	0.16	0.56	0.52
Female							
Normal	0.30	0.30	0.45	0.14	0.18	0.49[a]	0.45[a]
Overweight	0.36	0.36	0.41	0.21	0.23	0.52[a]	0.48[a]
Obesity	0.32	0.32	0.41	0.14	0.18	0.32[b]	0.32[b]

[a,b] The figures with different superscripts mean statistical significances ($P < 0.05$) by Duncan multiple range tests among the normal, overweight, and obesity groups

Table 3 *P* values of *F* statistics for genetic variants and their interaction for obesity-related phenotypes in Korean adolescent samples. *BMI* body mass index, *BFAT* percentage body fat, *Tchol* total cholesterol, *HDL* high-density lipoprotein cholesterol, *FFA* free fatty acid

	BMI	BFAT	TG	Tchol	HDL	FFA	Leptin	Insulin	Glucose
ADRB2									
252G/A	0.426	0.868	0.171	0.944	0.521	0.442	0.779	0.215	0.076
523C/A	0.321	0.681	0.179	0.864	0.593	0.578	0.608	0.081	0.122
1053G/C	**0.012**[b]	0.053	0.328	0.449	0.644	0.664	0.535	0.338	0.905
ADRB3 (Trp64Arg)	**0.007**	**0.003**	0.585	0.285	0.098	0.815	**0.032**	0.737	0.370
PPARγ (161C/T)	0.609	0.581	0.221	0.992	0.697	0.696	0.749	0.390	0.660
UCP2 (Ala55Val)	0.065	0.340	0.778	0.937	0.588	0.814	0.245	0.299	0.754
UCP3 (210C/T)	0.149	0.766	0.904	0.752	0.873	0.843	0.875	0.620	0.772
Gender	0.313	**0.000**	0.417	0.428	0.466	0.481	**0.001**	0.782	0.212
1053G/C·Trp64Arg	**0.001**	**0.034**	0.210	0.251	**0.012**	0.889	0.103	0.215	0.360
1053G/C·Gender	0.837	0.650	1.000	0.759	0.870	0.520	0.723	0.971	0.690
Trp64Arg·Gender	0.325	0.158	0.333	0.799	0.388	0.158	0.577	0.551	0.784
1053G/C·Trp64Arg·Gender	0.628	0.823	0.740	0.492	0.513	**0.036**	0.872	0.785	0.886
Dietary energy intake[a]	**0.000**	**0.000**	**0.008**	0.906	**0.000**	0.996	**0.000**	**0.000**	0.514

[a]Dietary energy intake was included as a covariate in the analytical model
[b]Figures in bold indicate the statistical significance ($P < 0.05$) after Bonferroni correction

intracellular loop of the *ADRB3*. This domain is thought to function in trafficking of the receptor to the cell surface and its coupling to G proteins. The presence of the mutant allele may reduce the receptor synthesis, binding, and/or signaling (Lowell and Spiegelman 2000).

While the initial examination for *UCP2* and *UCP3* SNP effects showed the differences in their allele frequencies among normal, overweight, and obesity females (Table 2), their effects were not observed in the main ANOVA (Table 3). This discrepancy was mainly due to the following: First, the latter used the original continuous variable, but the former used the classified variable leading to loss of information. Second, dietary energy intake effects were explained in the former analyses but not in the latter analyses. Although *UCP2* and *UCP3* genes did not show strong evidence for association with adolescent obesity, they have been known as a candidate gene for obesity. The exon 8 ins/del polymorphism of *UCP2* was associated ($P < 0.05$) with childhood-onset obesity (Jaberi 2004). The 3'UTR insertion in the heterozygous state appeared to be associated ($P < 0.05$) with increased values of serum leptin in American children of different ethnic origin (Yanovski et al. 2000). The common −866 G/A polymorphism in the promoter of *UCP2* was associated ($P < 0.05$) with obesity in Mediterranean and Central European children (Le et al. 2004), but not ($P > 0.05$) and in German adolescents (Schauble et al. 2003). Some articles dealt with the loci examined in our study. Association studies of Ala55Val variant in exon 4 of *UCP2* with obesity are also conflicting. Wang et al. (2004) reported significant differences ($P < 0.05$) in genotype frequencies of the Ala55Val polymorphism between obese and control subjects. On the other hand, such differences were not found ($P > 0.05$) in the study of Maestrini et al. (2003). Regarding the *UCP3* gene, Lanouette et al. (2001) reported suggestive linkage ($P < 0.05$) between its common variant in codon 210 in exon 5 (210C/T) and BMI (additionally, fat mass and leptin level) in black and white populations.

Our study revealed that the 161C/T variant at exon 6 of the *PPARγ* gene had no prominent effect on obesity risk. Yet the SNP has been reported to be associated with lipoprotein profiles (Wang et al. 1999). The interaction effect between the 161C/T variant and apoE-ϵ4 genotype on serum cholesterol level has been suggested (Peng et al. 2003).

Variance and covariance components were estimated to see how much variation of the BMI were explained by the candidate genes. The variance estimates of *ADRB2*-1053G/C, *ADRB3*-Trp64Arg, and residuals were 0.91, 2.17, and 17.45, respectively, and the covariance estimate between the *ADRB2*-1053G/C and the *ADRB3*-Trp64Arg effects was 0.42. Therefore, the polymorphisms of the *ADRB2* and *ADRB3* genes explained 4.3% [$=0.91/(0.91+2.17+2\times0.42+17.45)$] and 10.1% [$=2.17/(0.91+2.17+2\times0.42+17.45)$] of the variation on BMI. Effect of two loci, i.e., their additive genetic effects and epistasis, explained 18.3% [$=(0.91+2.17+2\times0.42)/(0.91+2.17+2\times0.42+17.45)$]. This finding is useful to explain genetic effects in adolescent obesity. Further studies on other candidate genes are continuously required to see genetic architecture of complex adolescent obesity. Such endeavors would eventually lead to a promising remedy against adolescent obesity.

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