Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 1570–1575
Metabolism
Clinical and Experimental
www.metabolismjournal.com

No effect of the Trp64Arg variant of the β_3-adrenergic receptor gene on weight loss by diet and exercise intervention among Japanese adults

Shinichi Kuriyama[a,*], Taichi Shimazu[a,b], Atsushi Hozawa[a,c], Shigeo Kure[d], Naoyuki Kurokawa[e], Masako Kakizaki[a], Toshimasa Sone[a], Kaori Matsuda-Ohmori[a], Naoki Nakaya[a], Hiroshi Satoh[e], Ichiro Tsuji[a]

[a]*Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi 980-8575, Japan*
[b]*Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo 104-0045, Japan*
[c]*Department of Health Science, Shiga University of Medical Science, Shiga 520-2192, Japan*
[d]*Department of Medical Genetics, Tohoku University Graduate School of Medicine, Sendai 980-8574, Japan*
[e]*Department of Environmental Health Sciences, Tohoku University Graduate School of Medicine, Sendai 980-8575, Japan*

Received 29 February 2008; accepted 24 June 2008

Abstract

Controversy remains as to whether the presence of the tryptophan-to-arginine (Trp64Arg) variant of the β_3-adrenergic receptor gene impedes the magnitude of body weight loss by diet and exercise intervention. The objectives of the present study were to compare the changes in body weight between carriers and noncarriers of the Trp64Arg variant before and after 6 months of diet and exercise interventions for weight loss. A total of 37 middle-aged Japanese individuals (12 carriers and 25 noncarriers of the Trp64Arg variant) participated in the study. There were no significant differences in body weight between the 2 groups at the baseline. There were significant reductions in body weight both in carriers and noncarriers, but no significant differences between the 2 groups with respect to changes in these variables. The weight changes were −2.52 kg (95% confidence interval [CI], −3.56 to −1.48) among carriers and −1.89 kg (95% CI, −2.65 to −1.13) among noncarriers, and the change in the variant carrier group minus the change in the variant noncarrier group was −0.47 (95% CI, −1.97 to 1.02). These results suggest that the presence of the Trp64Arg variant of the β_3-adrenergic receptor gene may not play a major role as a hindrance to weight reduction.

1. Introduction

The magnitude of weight loss in lifestyle intervention programs varies substantially among participants [1]. For instance, the Diabetes Prevention Program, a successful weight loss intervention, has demonstrated that 50% of participants achieve a weight loss goal of 7% or more through diet and exercise intervention by the end of the curriculum (at 24 weeks), whereas the remaining participants fail to do so [2]. If persons with obesity who will not respond to the diet and exercise intervention program could be predicted by objective markers, they could be provided more intensive protocols or treated by medication or surgery [3,4].

Genetic factors have been shown to influence a predisposition to obesity by being associated with body fat mobilization and energy balance [5]. One such gene is involved in formation of the β_3-adrenergic receptor, which is the main receptor associated with the regulation of thermogenesis and lipolysis in brown and white adipose tissue [6]. The tryptophan-to-arginine (Trp64Arg) variant of the β_3-adrenergic receptor gene has therefore been suggested to be associated with low rates of energy expenditure [7-9]. On the basis of these findings, it has been hypothesized that the presence of the Trp64Arg gene variant influences the magnitude of weight loss of persons with obesity receiving diet and exercise intervention. To date, 8 studies have examined the association between the Trp64Arg variant of the β_3-adrenergic receptor gene and the magnitude of weight

* Corresponding author. Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi 980-8575, Japan. Tel.: +81 22 717 8123; fax: +81 22 717 8125.
E-mail address: kuriyama-thk@umin.ac.jp (S. Kuriyama).

0026-0495/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2008.06.013

loss; but the results were inconsistent [10-17]. Half of the studies showed that persons with the Trp64Arg variant had difficulty losing body weight [10,12,13,16], whereas the other half did not [11,14,15,17]. All of the positive results were reported from Japan [10,12,13,16]; and the null results were from France [11], the United States [14,15], and Korea [17], suggesting that the inconsistent results were due to ethnic differences.

We therefore tested the hypothesis that middle-aged Japanese adults with the Trp64Arg variant of the β_3-adrenergic receptor gene will lose less body weight during a diet and exercise intervention program than those without the variant.

2. Methods

2.1. Study population

The persons included in the present study were those who participated in a diet and exercise intervention program in 2004 or 2005 for prevention of obesity-related diseases, such as type 2 diabetes mellitus, living in Nishiaizu town, Fukushima prefecture, Japan [18,19]. The inclusion criteria for the intervention program were body mass index (BMI) of 23.0 or higher [2,20], fasting plasma glucose concentration of 125 mg/dL or lower, and postload plasma glucose concentration (2 hours) of 199 mg/dL or lower [2]. The criteria also included no history of cancer, myocardial infarction, stroke, or kidney disease. A total of 53 persons participated in the intervention program, of whom 37 gave written informed consent to participate in the present study. The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine.

2.2. Genotyping

Genetic testing was carried out in company X. The Trp64Arg variant of the β_3-adrenergic receptor gene was detected by the polymerase chain reaction–restriction fragment length polymorphism method [21]. Briefly, DNA was extracted from 7 mL of whole blood treated with the anticoagulant ethylenediaminetetraacetic acid (EDTA) after digestion with proteinase K and purification with phenol-chloroform. The polymerase chain reaction was carried out using 100 ng DNA and the following primers: sense 5′-CGC CCA ATA CCG CCA ACA C-3′ and antisense 5′-CCA CCA GGA GTC CCA TCA CC-3′. The amplification product was digested with *Bst*NI.

The fragments were resolved on a 2.5% agarose gel and detected. According to the fragment size revealed by electrophoresis, the genotype was judged as follows. The fragment size was judged as the Arg/Arg type if 158 and 31 base pairs (bp); the Trp/Trp type if 97, 61, and 31 bp; and the Trp/Arg type if 158, 97, 61, and 31 bp.

Genetic testing was conducted after the postintervention examination.

2.3. Intervention program

Nishiaizu town consists of 5 districts. The intervention program was conducted in 2004 in districts A and B, and in 2005 in districts C and D. The participants underwent a diet and exercise weight loss program for 6 months including diet, exercise, and supportive group therapy [19]. The objectives of the intervention were to lose 7% of body weight [2]. A 10-lesson and 1-letter curriculum in district A, a 5-lesson and 1-letter curriculum in district B, and a 7-lesson and 1-letter curriculum in districts C and D covering diet, exercise, and behavior modification were designed to help the participants achieve their goals. The curriculum, taught by trained nurses and nutritionists on a one-to-two basis during the 6 months after enrollment, was flexible, culturally sensitive, and individualized.

The behavioral program for obesity was based on learning principles such as recognizing a participant's health risks related to obesity, studying healthy life skills, setting specific behavioral goals, modifying behavior determinants, and reinforcing desired behavior. The approach began with a health check to recognize their situation regarding obesity and obesity-associated diseases. The second step offered intensive, professional individual information to improve the participants' unhealthy lifestyle, that is, overeating and insufficient physical activity, and self-monitoring ability, that is, daily checking of weight, daily estimation of caloric intake, and monitoring of the number of steps walked. Participants were committed to achieve their specific behavioral and anthropometric goals, as related to their individual lifestyles and measured physiologic data.

2.4. Outcome measures

The primary outcome measure was the change in body weight. The secondary measurements included the changes in BMI, body fat distribution, glycemic control, insulin resistance, plasma lipid concentration, plasma adiponectin concentration, and plasma 8-*iso*-prostaglandin (PG) F2α concentration. 8-*iso*-PGF2α is a lipid peroxidation biomarker, which is suggested to be able to quantify the status of oxidative stress in vivo [22-24]. The outcome measurements were performed before and after the intervention.

After an overnight fast, body weight and height were measured. Body weight was measured with the subject dressed only in light clothing. Body mass index was calculated as weight (in kilograms) divided by squared height (in square meters). One cross-sectional computed tomographic scan was obtained at the umbilicus level using a General Electric Yokogawa Medical Systems (Tokyo, Japan) high-speed DX/I. Abdominal adipose tissue areas, including intraabdominal and subcutaneous, were analyzed using computed tomographic scanning and the abdominal adipose tissue analysis software package Fat Scan Ver.2.0 (N2 System, Ibaraki, Japan) [25].

Venous blood was collected from the antecubital vein after a 12-hour overnight fast. Blood samples were collected into

2 tubes containing EDTA-2Na, and plasma was separated by a 10-minute centrifugation at 3000 rpm. Serum samples were separated by a 5-minute centrifugation at 3000 rpm and then stored at −80°C until assay within 3 months.

The participants underwent a 75-g glucose tolerance test after a 12-hour overnight fast. Blood was taken at 0, 60, and 120 minutes; and plasma glucose and serum insulin were evaluated. Blood glucose concentrations were measured by an enzymatic method (Shi-no-Test, Tokyo, Japan). Concentrations of insulin were measured by enzyme-linked immunosorbent assay (insulin enzyme immunoassay test; Wako, Osaka, Japan). Homoeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting serum insulin (in microunits per milliliter) × fasting plasma glucose (in milligrams per deciliter)/405. Hemoglobin A_{1c} (HbA_{1c}) was measured by high-performance liquid chromatography with a reference range of 3.8% to 5.5%, which was standardized by the standard substance provided by the Japan Diabetes Association.

Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL-C), and triglyceride (TG) concentrations were measured by enzymatic methods (Kyowa Chemical, Kagawa, Japan, for TC and TG; Daiichi Chemical, Osaka, Japan, for LDL-C and HDL-C).

Serum adiponectin concentrations were measured by a commercial radioimmunoassay (Linco Research, St Louis, MO). The intraassay coefficient of variation was less than 6.2%, and the interassay coefficient of variation was less than 9.2%. Assay sensitivity was 1 μg/mL. All plasma samples were diluted 1:250 to yield an effective range of 0.2 to 50 μg/mL.

Total (esterified plus free) 8-*iso*-PGF2α concentrations were assayed in plasma by a specific enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI) [26-29]. For total 8-*iso*-PGF2α measurement, peripheral venous blood was collected in EDTA-2Na– and EDTA-4Na–coated cold polyethylene tubes containing indomethacin, an inhibitor of cyclooxygenase, and aprotinin, an inhibitor of kallikrein, to prevent any in vitro formation of 8-*iso*-PGF2α. After collection, blood samples were immediately cooled at 4°C; and the samples were centrifuged at 3000 rpm at 4°C for 10 minutes. The plasma fraction was removed and stored at −80°C for later 8-isoprostane assay.

2.5. Statistical analysis

Participants were divided into 2 groups: Trp64Arg variant carriers (Trp/Arg or Arg/Arg) and noncarriers (Trp/Trp). Comparison of frequencies among categories was performed by χ^2 or Fisher exact test, where appropriate. Comparisons between the 2 groups were performed by Student *t* test to assess the differences in anthropometric and metabolic parameters. Effects of the diet and exercise intervention on weight loss or other secondary outcomes were tested using a paired *t* test in each group before and after the intervention. Analysis of covariance was used to investigate the significances of differences in the initial values as well as those of net changes after the intervention among the 2 groups. The net change in each variable was calculated as (the variable after intervention − the variable before intervention) in the variant carrier group − (the variable after intervention − the variable before intervention) in the variant noncarrier group. We considered the following variables to be potential confounders a priori: age at the baseline in years (continuous variable), sex, participants' district of residence, and individual baseline variables. All statistical analyses were performed with SAS version 9.1 (SAS, Cary, NC). We used approximate variance formulas to calculate the 95% confidence intervals (CIs). Differences were accepted as statistically significant at *P* less than .05.

3. Results

The present intervention for 6 months yielded an average weight loss of 2.1 kg, and 89% of the participants reduced their body weight.

Comparison of baseline variables between Trp64Arg variant carriers and noncarriers is shown in Table 1. Among the 37 participants, 1 person was an Arg64Arg variant carrier, 11 were Trp64Arg variant carriers, and 25 were noncarriers. The participants showed no statistically significant difference with respect to sex ratio and mean age, although the ratio of men was small among Trp64Arg variant carriers.

There were significant reductions in body weight and BMI among both Trp64Arg variant carriers and noncarriers, indicating that the present intervention program was effective. The changes in weight were −2.52 kg (95% CI, −3.56 to −1.48) among carriers and −1.89 kg (95% CI, −2.65 to −1.13) among noncarriers (Table 2). The reductions of body weight and BMI were larger among carriers than among noncarriers, although there were no significant differences between carriers and noncarriers with respect to changes in these variables. In addition, there were no effects of the variant on the number of participants who reached a goal of 7% weight reduction. Three of the 12 participants among

Table 1
Characteristics of participants according to the Trp64Arg β_3-adrenergic receptor gene variant

	Trp64Arg β_3-adrenergic receptor gene variant		*P* value
	Carriers (Trp/Arg or Arg/Arg)	Noncarriers (Trp/Trp)	
No. of participants	12 (11 Trp/Arg, 1 Arg/Arg)	25	
Men/women	1/11	8/17	.22
Age (y) (SD)	59.5 (6.7)	60.1 (6.2)	.78
Districts participants lived			
A area	2	6	.73
B area	4	10	
C or D area	6	9	

P value with Fisher exact test for men to women ratio and for districts participants lived; otherwise, with Student *t* test.

Table 2
Changes in body weight and other variables according to the Trp64Arg β_3-adrenergic receptor gene variant

Variables	Trp64Arg β_3-adrenergic receptor gene variant	Preintervention (SE)	Postintervention (SE)	Post − pre change (SE)	P value[a]	Net change[b] (95% CI)	P value[b]
Body weight (kg)	Carriers (Trp/Arg or Arg/Arg)	59.1 (1.88)	56.6 (1.72)	−2.52 (0.53)	.0006	−0.47 (−1.97 to 1.02)	.52
	Noncarriers (Trp/Trp)	60.6 (2.21)	58.7 (2.22)	−1.89 (0.39)	<.0001		
BMI (kg/m^2)	Carriers (Trp/Arg or Arg/Arg)	25.6 (0.72)	24.5 (0.67)	−1.08 (0.23)	.0007	−0.17 (−0.78 to 0.44)	.57
	Noncarriers (Trp/Trp)	24.8 (0.75)	24.0 (0.75)	−0.80 (0.15)	<.0001		
Abdominal adipose tissue areas (cm^2)							
Intraabdominal	Carriers (Trp/Arg or Arg/Arg)	100.1 (12.0)	94.3 (6.22)	−5.78 (7.40)	.45	−7.77 (−27.27 to 11.69)	.42
	Noncarriers (Trp/Trp)	106.2 (7.96)	109.9 (9.17)	3.71 (6.02)	.54		
Subcutaneous	Carriers (Trp/Arg or Arg/Arg)	222.4 (16.6)	205.5 (16.5)	−16.88 (10.1)	.12	1.06 (−20.29 to 22.41)	.92
	Noncarriers (Trp/Trp)	189.2 (15.0)	176.4 (13.9)	−12.77 (5.91)	.04		
Fasting plasma glucose concentration (mg/dL)	Carriers (Trp/Arg or Arg/Arg)	100.4 (3.06)	95.9 (2.10)	−4.50 (1.55)	.01	−2.97 (−7.39 to 1.44)	.18
	Noncarriers (Trp/Trp)	100.1 (2.02)	100.2 (1.89)	0.08 (1.78)	.96		
Postload plasma glucose concentration (2 h) (mg/dL)	Carriers (Trp/Arg or Arg/Arg)	140.8 (8.76)	138.1 (8.60)	−2.75 (7.76)	.73	6.99 (−13.06 to 27.03)	.48
	Noncarriers (Trp/Trp)	141.8 (7.36)	130.0 (6.88)	−11.84 (6.71)	.09		
HbA_{1c} (%)	Carriers (Trp/Arg or Arg/Arg)	5.33 (0.10)	5.14 (0.06)	−0.18 (0.07)	.02	−0.09 (−0.20 to 0.02)	.09
	Noncarriers (Trp/Trp)	5.32 (0.08)	5.22 (0.06)	−0.10 (0.04)	.02		
Fasting plasma insulin concentration (μU/mL)	Carriers (Trp/Arg or Arg/Arg)	6.77 (1.61)	5.13 (0.65)	−1.64 (1.38)	.26	−1.06 (−2.48 to 0.36)	.14
	Noncarriers (Trp/Trp)	6.21 (1.09)	5.37 (0.82)	−0.83 (0.57)	.16		
HOMA-IR	Carriers (Trp/Arg or Arg/Arg)	1.75 (0.47)	1.22 (0.16)	−0.53 (0.39)	.21	−0.33 (−0.71 to 0.06)	.10
	Noncarriers (Trp/Trp)	1.54 (0.27)	1.33 (0.21)	−0.21 (0.14)	.15		
Plasma TC concentration (mg/dL)	Carriers (Trp/Arg or Arg/Arg)	209.3 (4.99)	216.2 (7.22)	6.92 (5.92)	.27	10.31 (−8.49 to 29.11)	.27
	Noncarriers (Trp/Trp)	219.4 (6.50)	216.3 (7.72)	−3.08 (5.11)	.55		
Plasma HDL-C concentration (mg/dL)	Carriers (Trp/Arg or Arg/Arg)	62.3 (3.78)	63.4 (2.04)	1.08 (2.54)	.68	−0.11 (−6.54 to 6.32)	.97
	Noncarriers (Trp/Trp)	58.7 (2.98)	62.7 (3.14)	4.04 (2.06)	.06		
Plasma LDL-C concentration (mg/dL)	Carriers (Trp/Arg or Arg/Arg)	132.6 (4.46)	133.3 (6.03)	0.67 (5.35)	.90	7.46 (−6.47 to 21.38)	.28
	Noncarriers (Trp/Trp)	138.0 (6.11)	131.2 (6.38)	−6.76 (3.85)	.09		
Plasma TG concentration (mg/dL)[c]	Carriers (Trp/Arg or Arg/Arg)	4.40 (0.10)	4.45 (0.11)	0.05 (0.08)	.56	0.02 (−0.30 to 0.34)	.89
	Noncarriers (Trp/Trp)	4.53 (0.13)	4.48 (0.12)	−0.05 (0.11)	.63		
Plasma adiponectin concentration (μg/mL)	Carriers (Trp/Arg or Arg/Arg)	10.9 (1.80)	12.9 (1.66)	1.93 (0.55)	.005	−0.50 (−1.96 to 0.96)	.49
	Noncarriers (Trp/Trp)	9.5 (0.91)	12.1 (0.99)	2.61 (0.37)	<.0001		
Plasma 8-*iso*-PGF2α concentration (pg/mL)	Carriers (Trp/Arg or Arg/Arg)	10.3 (0.64)	8.63 (1.04)	−1.68 (1.29)	.22	−0.38 (−1.73 to 0.96)	.56
	Noncarriers (Trp/Trp)	11.7 (0.69)	9.84 (0.53)	−1.85 (0.96)	.07		

[a] Paired t test.
[b] The change in the variant carrier group (Trp/Arg or Arg/Arg) minus the change in the variant noncarrier group (Trp/Trp). The net differences were calculated by analysis of covariance.
[c] Log-transformed.

carriers and 3 of the 25 participants among noncarriers reached their goal ($P = .37$). The changes in body weight and BMI in the variant carrier group minus the changes in the variant noncarrier group were −0.47 (95% CI, −1.97 to 1.02) and −0.17 (95% CI, −0.78 to 0.44), respectively.

There also were significant reductions in plasma HbA_{1c} levels and significant increases in plasma adiponectin levels, but no significant differences were observed between carriers and noncarriers with respect to change in these variables.

Significant reduction in subcutaneous adipose tissue area was observed only among noncarriers; but the magnitude of the reduction was larger among carriers than among noncarriers, and there was no significant difference between carriers and noncarriers with respect to changes in this variable. Significant reduction in fasting plasma glucose concentration was observed only among carriers, and there was no significant difference between carriers and noncarriers with respect to changes in this variable.

There were no apparent changes in the area of intraabdominal adipose tissue, postload plasma glucose concentration (2 hours), fasting plasma insulin concentration, HOMA-IR, plasma TC concentration, plasma HDL-C concentration, plasma LDL-C concentration, plasma TG concentration, or plasma 8-*iso*-PGF2α concentration.

4. Discussion

We tested a hypothesis that middle-aged Japanese individuals with the Trp64Arg variant of the β_3-adrenergic receptor gene would lose less body weight during a weight reduction program involving diet and exercise intervention than individuals without the variant. Contrary to our hypothesis, although the present intervention for 6 months yielded an average weight loss of 2.1 kg, we found no difference between carriers and noncarriers in loss of body weight after the weight loss intervention.

Previous studies that have examined the association between the Trp64Arg variant of the β_3-adrenergic receptor gene and the magnitude of weight loss achieved by diet and

exercise intervention have yielded inconsistent results [10-17]. All of the positive results have been reported from Japan [10,12,13,16]); and null results were reported from France [11], the United States [14,15], and Korea [17], suggesting that the inconsistent results were due to ethnic differences. However, of the 4 studies reporting positive results, 3 were conducted by the same research group [10,12,13]; and the remaining one [16] showed a small difference in weight loss of −0.01 and −0.74 kg ($P = .035$) for women with and without the Trp64Arg variant, respectively. The consistency of our data for Japanese subjects with data from France [11], the United States [14,15], and Korea [17] indicates that the discrepancy cannot be fully explained by ethnic differences.

We also found no difference between carriers and noncarriers in the loss of abdominal adipose tissue area, fasting plasma glucose concentration, postload plasma glucose concentration (2 hours), HbA_{1c}, fasting plasma insulin concentration, HOMA-IR, plasma TC concentration, plasma HDL-C concentration, plasma LDL-C concentration, plasma TG concentration, plasma adiponectin concentration, or plasma 8-*iso*-*PG*F2α concentration. Among previous studies demonstrating that persons with the Trp64Arg variant of the β_3-adrenergic receptor gene have had no difficulty in losing body weight [11,14,15,17], 2 studies [14,17] have reported that persons with the Trp64Arg variant had difficulty in improving their body fat distribution [14,17], TC/HDL-C ratio [14], and glycemic control [17] than persons without the variant. Further studies are needed to examine the effects of the variant on these variables, giving careful consideration to multiple comparisons.

Our results indicating an absence of any effect of the Trp64Arg variant of the β_3-adrenergic receptor gene on body weight loss may be partly explained by the aggressive weight loss program, which may have masked the modest effects of the gene variant. That is, the environmental challenge may have overwhelmed any modest gene effects of the Trp64Arg variant on body weight. Meta-analyses of cross-sectional studies have demonstrated that, across the population, persons with the Trp64Arg variant of the β_3-adrenergic receptor gene show only a slight increase in average BMI of 0.19 (95% CI, −0.03 to 0.41) kg/m^2 [30], 0.26 (95% CI, 0.18 to 0.42) kg/m^2 [31], and 0.30 (95% CI, 0.13 to 0.47) kg/m^2 [32] compared with persons without the variant, suggesting that the effects of the Trp64Arg variant on body weight may be small. However, the possibility that the discrepancy among the results of the studies could have been due to the difference in the degree of intervention and the amount of weight loss seems unlikely because the average weight loss values were widely distributed in these studies. The average weight loss in carriers and noncarriers was 5.2 kg (homozygotes)/5.5 kg (heterozygotes) vs 8.3 kg [10], 4.6 kg vs 8.3 kg [12], 4.8 kg vs 7.4 kg [13], and 0.01 kg vs 0.74 kg [16] among the studies that showed positive effects of the Trp64Arg variant, whereas it was 7.6 kg vs 6.4 kg [11], 16.4 kg vs 14.1 kg [14], about 15 kg vs about 15 kg [15], 3.5 kg vs 3.4 kg [17], and 2.5 kg vs 1.9 kg (present study) among the studies that showed no effects of the variant.

Our study had some limitations. First, our prospective interventional study design yielded a relatively small number of participants. Thus, we may not have had adequate power to detect modest gene effects on the phenotypes. However, we do not believe that the null findings of the present study were due to a type 2 error because the point estimate of the weight loss was larger in carriers than in noncarriers. Second, the participants of the present study had a relatively mild average BMI of 25.6 kg/m^2 in carriers and 24.8 kg/m^2 in noncarriers. Therefore, the effects of the Trp64Arg variant on body weight loss among persons with much higher BMI were unclear. Third, we could not obtain details of the participants' lifestyles including diet and exercise after intervention because of the nature of the intervention program. Thus, there was a possibility that intervention intensities differed between carriers and noncarriers. However, genetic testing was conducted after the postintervention examination; and therefore, this possibility seems unlikely. Finally, because 76% of our study population included women, it is uncertain whether our results could be applied to men.

In conclusion, we have found that persons who carry the Trp64Arg variant of the β_3-adrenergic receptor gene show a response to diet and exercise intervention similar to that of noncarriers of the variant. These results suggest that the presence of the Trp64Arg variant of the β_3-adrenergic receptor gene should not be a hindrance to weight reduction by diet and exercise intervention.

Acknowledgment

This study was supported by a Grant-in-Aid for Scientific Research (C) (term of project, 2005-2006; project number, 17590532) from the Japan Society for the Promotion of Science, Japan.

References

[1] Dansinger ML, Tatsioni A, Wong JB, et al. Meta-analysis: the effect of dietary counseling for weight loss. Ann Intern Med 2007;147:41-50.
[2] Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
[3] Adamo KB, Tesson F. Genotype-specific weight loss treatment advice: how close are we? Appl Physiol Nutr Metab 2007;32:351-66.
[4] Ioannides-Demos LL, Proietto J, McNeil JJ. Pharmacotherapy for obesity. Drugs 2005;65:1391-418.
[5] Bouchard C. Genetics of obesity: an update on molecular markers. Int J Obes Relat Metab Disord 1995;19(Suppl 3):S10-3.
[6] Emorine LJ, Feve B, Pairault J, et al. The human β_3-adrenergic receptor: relationship with atypical receptors. Am J Clin Nutr 1992;55 (1 Suppl):S215-8.
[7] Walston J, Silver K, Bogardus C, et al. Time of onset of non–insulin-dependent diabetes mellitus and genetic variation in the β_3-adrenergic-receptor gene. N Engl J Med 1995;333:343-7.
[8] Valve R, Heikkinen S, Rissanen A, et al. Synergistic effect of polymorphisms in uncoupling protein 1 and β_3-adrenergic receptor

genes on basal metabolic rate in obese Finns. Diabetologia 1998;41: 357-61.

[9] Sipiläinen R, Uusitupa M, Heikkinen S, et al. Polymorphism of the β_3-adrenergic receptor gene affects basal metabolic rate in obese Finns. Diabetes 1997;46:77-80.

[10] Yoshida T, Sakane N, Umekawa T, et al. Mutation of β_3-adrenergic–receptor gene and response to treatment of obesity. Lancet 1995;346: 1433-4.

[11] Fumeron F, Durack-Bown I, Betoulle D, et al. Polymorphisms of uncoupling protein (UCP) and β_3 adrenoreceptor genes in obese people submitted to a low calorie diet. Int J Obes Relat Metab Disord 1996;20: 1051-4.

[12] Sakane N, Yoshida T, Umekawa T, et al. Effects of Trp64Arg mutation in the β_3-adrenergic receptor gene on weight loss, body fat distribution, glycemic control, and insulin resistance in obese type 2 diabetic patients. Diabetes Care 1997;20:1887-90.

[13] Kogure A, Yoshida T, Sakane N, et al. Synergic effect of polymorphisms in uncoupling protein 1 and β_3-adrenergic receptor genes on weight loss in obese Japanese. Diabetologia 1998;41:1399.

[14] Tchernof A, Starling RD, Turner A, et al. Impaired capacity to lose visceral adipose tissue during weight reduction in obese postmenopausal women with the Trp64Arg β_3-adrenoceptor gene variant. Diabetes 2000;49:1709-13.

[15] Rawson ES, Nolan A, Silver K, et al. No effect of the Trp64Arg β_3-adrenoceptor gene variant on weight loss, body composition, or energy expenditure in obese, caucasian postmenopausal women. Metabolism 2002;51:801-5.

[16] Shiwaku K, Nogi A, Anuurad E, et al. Difficulty in losing weight by behavioral intervention for women with Trp64Arg polymorphism of the β_3-adrenergic receptor gene. Int J Obes Relat Metab Disord 2003; 27:1028-36.

[17] Kim OY, Cho EY, Park HY, et al. Additive effect of the mutations in the β_3-adrenoceptor gene and UCP3 gene promoter on body fat distribution and glycemic control after weight reduction in overweight subjects with CAD or metabolic syndrome. Int J Obes Relat Metab Disord 2004;28:434-41.

[18] Hozawa A, Shimazu T, Kuriyama S, et al. Benefit of home blood pressure measurement after a finding of high blood pressure at a community screening. J Hypertens 2006;24:1265-71.

[19] Kuriyama S, Shimazu T, Hozawa A, et al. Comparison of intensive and moderate individual life-style intervention programs for overweight or obese persons with fasting glucose levels of 95-125 mg/dl in Japan. Nippon Koshu Eisei Zasshi 2006;53:122-32 [in Japanese].

[20] WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63 [Erratum in: Lancet 2004;363:902].

[21] Widen E, Lehto M, Kanninen T, et al. Association of a polymorphism in the β_3-adrenergic–receptor gene with features of the insulin resistance syndrome in Finns. N Engl J Med 1995;333:348-51.

[22] Morrow JD, Roberts II LJ. The isoprostanes. Current knowledge and directions for future research. Biochem Pharmacol 1996;51:1-9.

[23] Lawson JA, Rokach J, FitzGerald GA. Isoprostanes: formation, analysis and use as indices of lipid peroxidation in vivo. J Biol Chem 1999;274:24441-4.

[24] Kuriyama S, Ebihara S, Hozawa A, et al. Dietary intakes and plasma 8-*iso*-prostaglandin F2alpha concentrations in community-dwelling elderly Japanese: the Tsurugaya project. Int J Vitam Nutr Res 2006;76: 87-94.

[25] Yoshizumi T, Nakamura T, Yamane M, et al. Abdominal fat: standardized technique for measurement at CT. Radiology 1999;211: 283-6.

[26] Collins CE, Quaggiotto P, Wood L, et al. Elevated plasma levels of F2alpha isoprostane in cystic fibrosis. Lipids 1999;34:551-6.

[27] Dillon SA, Lowe GM, Billington D, et al. Dietary supplementation with aged garlic extract reduces plasma and urine concentrations of 8-isoprostaglandin F2*a* in smoking and nonsmoking men and women. J Nutr 2002;132:168-71.

[28] Wood LG, Fitzgerald DA, Lee AK, et al. Improved antioxidant and fatty acid status of patients with cystic fibrosis after antioxidant supplementation is linked to improved lung function. Am J Clin Nutr 2003;77:150-9.

[29] Desideri G, Ferri C. Effects of obesity and weight loss on soluble CD40L levels. JAMA 2003;289:1781-2.

[30] Allison DB, Heo M, Faith MS, et al. Meta-analysis of the association of the Trp64Arg polymorphism in the beta3 adrenergic receptor with body mass index. Int J Obes Relat Metab Disord 1998;22:559-66.

[31] Kurokawa N, Nakai K, Kameo S, et al. Association of BMI with the beta3-adrenergic receptor gene polymorphism in Japanese: meta-analysis. Obes Res 2001;9:741-5.

[32] Fujisawa T, Ikegami H, Kawaguchi Y, et al. Meta-analysis of the association of Trp64Arg polymorphism of beta 3-adrenergic receptor gene with body mass index. J Clin Endocrinol Metab 1998;83:2441-4.