Effects of genetic polymorphism of uncoupling protein 2 on body fat and calorie restriction-induced changes

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The purpose of this study is to estimate the effects of *Ala55Val* genetic polymorphism of uncoupling protein 2 on computed tomography-measured body fat area and calorie restriction-induced changes. Among 386 Korean female subjects, the *AlaAla* type was seen in 30.3%, the *AlaVal* type was seen in 47.2%, and the *ValVal* type was seen in 22.5%. This finding was in agreement with Hardy-Weinberg equilibrium. The frequency of the major *Ala* allele was 0.54, and that of the minor *Val* allele was 0.46, which were similar to those seen in Caucasian populations. When cross-sectional areas of fat tissues in the subjects were measured by computed tomography, it was shown that the total abdominal fat area and abdominal subcutaneous fat area were significantly smaller in the *ValVal* type compared with the *AlaVal* or *AlaAla* type (p =0.043 and p =0.044, respectively). The *Ala55Val* polymorphism had no effects on visceral fat area and thigh subcutaneous fat area. Among the 386 subjects, 236 subjects finished the 1-month calorie restriction program. The results showed that the body fat was reduced significantly less in the *ValVal* type compared with the other types (p =0.016), whereas the changes in lean body mass, protein, mineral, and water contents were not significantly different according to the *Ala55Val* polymorphism.

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A number of studies have indicated that 40–70% of the variation in body mass index (BMI) and body fat mass is genetically determined (COMUZZIE and ALLISON 1998). Although several single gene mutations cause obesity in animal models, the situation in the common form of human obesity is much more complex. Human obesity is determined by the interaction of multiple genes, as well as environmental factors, behaviors, and dietary patterns (RICE et al. 1996).

As one of the risk factors for obesity, low energy expenditure can increase obesity and related metabolic disorders when accumulated over decades (RAVUSSIN et al. 1998). Uncoupling proteins (UCPs), which are located in the mitochondrial inner membrane, are well-known to regulate energy expenditure and fat oxidation (GURA 1998). *UCPs* dissipate the proton electrochemical gradient, so that the energy is converted to heat without the synthesis of ATP (GARLID et al. 1996). Among the *UCP* family members, the human *UCP-1* gene was cloned and shown to be located on chromosome 4 by Cassard et al. in 1990

(CASSARD et al. 1990; OPPERT et al. 1994). In 1997, Fleury et al. found that the human *UCP-2* gene is located on chromosome 11, notably, on a region that has been linked to obesity and hyperinsulinemia (FLEURY et al. 1997). Unlike *UCP-1*, which is exclusively expressed in brown adipose tissue (BAT), *UCP-2* is expressed in a variety of different tissues, including white adipose tissue, skeletal muscle, heart, liver and kidney tissue (FLEURY et al. 1997). SURWIT et al. reported that *UCP-2* mRNA expression was more than two-fold higher in the white adipose tissue of obesity-resistant mice compared to that of obesity-prone mice (SURWIT et al. 1998). It was also reported that the expression of *UCP-2* is increased by high fat diet and leptin treatment (RIPPE et al. 2000; SANIGORSKI et al. 2000; ZHANG et al. 2004).

In genetic polymorphism studies of *UCP-2*, five polymorphisms in the promoter region and a 45 bp insertion/deletion were found in the 3′-untranslated region (ESTERBAUER et al. 2001). In the coding region, a polymorphism of alanine to valine at the 55th codon, *Ala55Val*, was also found in exon 4 (UHAMMER et al.

Abbreviations: BAT, brown adipose tissue; BMI, body mass index; CT, computed tomography; DBP, diastolic blood pressure: GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HDL, high density lipoprotein; LDH, lactate dehydrogenase; LDL, low density lipoprotein; SBP, systolic blood pressure: *UCP*, uncoupling protein: V/S ratio, visceral fat to subcutaneous fat ratio

1997). Several studies were conducted to elucidate the relationships between the *Ala55Val* polymorphism of *UCP-2* and obesity phenotypes (ASTRUP et al. 1999; KLANNEMARK et al. 1998; ROSMOND et al. 2002).

However, few studies were conducted to elucidate the effects of the *Ala55Val* polymorphism on computed tomography (CT)-measured body fat characteristics and calorie restriction-induced changes in East Asian populations. In this study, we analyzed the association of this polymorphism with body fat area and calorie restriction-induced changes of body components in Korean female subjects.

MATERIAL AND METHODS

Subjects

In this study, 386 Korean female subjects were recruited from Kirin Oriental Medical Hospital (Seoul, Republic of Korea). The general characteristics of the subjects were: age, 27.08 ± 0.40 (mean $\pm$ SE); weight, 68.62 ± 0.65 kg; BMI, 26.44 ± 0.22 kg m^{-2}; waist-to-hip ratio (WHR), 0.889 ± 0.004; systolic blood pressure, 115.61 ± 0.70 mm Hg; diastolic blood pressure, 72.05 ± 0.56 mm Hg. Genomic DNA was obtained with informed consent, and the protocol of this study was approved by the Institutional Review Board of the Korea Institute of Oriental Medicine. Body compositions were measured by bio-impedance analysis using a commercial device (Inbody 2.0, Biospace Co., Republic of Korea). The areas of abdominal subcutaneous and visceral fat of all subjects were measured from CT cross-sectional images of the abdominal region, as described previously (MATSUZAWA 1995). The subcutaneous fat areas at the thigh were also measured using CT (Hispeed CT/e, GE, USA). Among all 386 subjects, 236 subjects finished the 1-month weight loss program, which consisted of a 700 kcal day^{-1} calorie restriction, with 130 g carbohydrate and 70 g protein per day. Changes in body weight, BMI, and body compositions before and after the program were assessed.

Genotyping assay

Genomic DNA from each subject was extracted from blood using a Qiagen DNA blood kit according to the instructions of the manufacturer. The genotyping of the *Ala55Val* polymorphism was based on the analysis of primer extension products generated from previously amplified genomic DNA using a chip-based matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry platform (SEQUENOM, Inc., CA). The general procedures were performed according to standard protocol of the manufacturer. Primers for PCR and primer extension

analysis were designed using the Primer3 program (http://primer3.sourceforge.net). Each allele-specific primer extension product was analyzed in the fully automated mode with the MALDI-TOF MassARRAY system (Bruker-SEQUENOM, CA).

The primer sequences used for genotyping are listed below:

> forward primer: ACGTTGGATGGCATCGAGA-TGACTGGAGGT
> reverse primer: ACGTTGGATGGTCAGAATG-GTGCCCATCAC
> PCR product size: 149 bp
> extension primer: GGGCCAGTGCGCGCTA-CAG

Serum biochemical profile analysis

Blood samples were obtained from each subject after fasting overnight for more than 12 h, and were centrifuged at 2000 rpm for 10 min. Serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, glucose, LDH, albumin, GOT, and GPT were measured by auto-biochemical analyzer (SP-4410, ARKRAY, Japan).

Statistical analysis

All values were presented as mean $\pm$ SE. Age-adjusted univariate analysis of variance was performed by a general linear model procedure to examine the independent effect of the *Ala55Val* polymorphism on dependent variables. To compare the outcomes of the calorie-restriction program, general linear model analyses were conducted after the adjustment of the initial value of body weight, BMI, or body compositions, as well as age. Statistical significance was established at the level of $p < 0.05$. All analyses were performed using SPSS ver. 10.0 (SPSS Inc., IL).

RESULTS

The frequencies of the genotypes in the *UCP-2 Ala55Val* polymorphism were measured among 386 Korean female subjects. It was shown that the *AlaAla* type was present in 30.3% (n =117) of the population, while the *AlaVal* type was present in 47.2% (n =182), and *ValVal* type in 22.5% (n =87) of the population. This was in agreement with Hardy-Weinberg equilibrium (p =0.314). The frequency of the major *Ala* allele was 0.54, and that of the minor *Val* allele was 0.46. The allelic frequencies were similar to the findings of previous studies conducted in Caucasian populations (ASTRUP et al. 1999; KLANNEMARK et al. 1998; ROSMOND et al. 2002). Table 1 shows the comparison of the physical characteristics and body

Table 1. *Comparisons of physical characteristics and body compositions by Ala55Val polymorphism.*

Genotype		*AlaAla* type (n = 117)	*AlaVal* type (n = 182)	*ValVal* type (n = 87)	p-value
Physical characteristics					
Weight	(kg)	68.14 ± 1.23[1]	69.94 ± 0.97	66.01 ± 1.21	0.055[2]
BMI	(kg m^{-2})	26.44 ± 0.43	26.78 ± 0.34	25.71 ± 0.44	0.146
SBP	(mm Hg)	115.27 ± 1.39	115.87 ± 1.03	114.81 ± 1.39	0.552
DBP	(mm Hg)	71.15 ± 0.97	71.29 ± 0.84	73.21 ± 1.24	0.690
Body composition					
Fat	(kg)	24.50 ± 0.82	25.43 ± 0.67	22.50 ± 0.81	**0.044**
Percent body fat	(%)	35.07 ± 0.61	35.48 ± 0.48	33.38 ± 0.64	0.053
Lean body mass	(kg)	43.64 ± 0.55	44.50 ± 0.41	43.51 ± 0.55	0.189
Protein	(kg)	10.63 ± 0.16	10.76 ± 0.12	10.64 ± 0.17	0.656
Mineral	(kg)	2.56 ± 0.03	2.61 ± 0.02	2.54 ± 0.03	0.125
Water	(kg)	30.47 ± 0.40	31.13 ± 0.29	30.32 ± 0.39	0.139

[1] mean ± SE
[2] p-values were obtained by general linear model analysis adjusted for age.

compositions of the subjects by *Ala55Val* polymorphism. The mean body weight and BMI were lower in the *ValVal* type compared with the *AlaAla* or *AlaVal* type, although these differences were not statistically significant. When body composition was measured by bio-impedance analysis, body fat mass was significantly lower in subjects with the *ValVal* type compared with those with the *AlaAla* or *AlaVal* type (p = 0.044), and the body fat percentage also tended to be decreased in the *ValVal* type (p = 0.053). In contrast, lean body mass, protein mass, mineral mass, and water content showed no differences according to the *Ala55Val* polymorphism.

For the accurate evaluation of the effects of the *Ala55Val* polymorphism on body fat, the subjects were tested using CT to measure the cross-sectional fat tissue areas at the abdominal and distal portions of the body. An example of CT-measured body fat area is shown in Fig. 1. The abdominal subcutaneous fat area and total abdominal fat area were about 11% smaller in subjects with the *ValVal* type compared to those with the *AlaAla* or *AlaVal* type (p = 0.044 and p = 0.043, respectively) (Table 2). However, the visceral fat area, visceral fat to subcutaneous fat ratio, and thigh subcutaneous fat area did not differ significantly according to the *Ala55Val* polymorphism.

Among all subjects, 236 females finished the 1-month calorie restriction program. The changes in weight and body compositions during the program were compared according to *Ala55Val* polymorphism (Table 3). The reduction of body weight tended to be smaller in the *ValVal* type (p = 0.073) than in the other types, and this tendency remained after adjustment for initial body weight (p = 0.082). Among the changes in body composition, only the fat change was shown to

differ significantly according to *Ala55Val* genotype (p = 0.016). The reduction of body fat was about 21% smaller in the *ValVal* type compared with the other types. After adjustment for initial fat mass, subjects with the *ValVal* type still tended to show a lower degree of body fat reduction (p = 0.085). The changes in other components of the body, such as protein, mineral, and water, showed no significant differences according to the *Ala55Val* polymorphism. The comparison of serum biochemical characteristics of the subjects by *Ala55Val* polymorphism showed no significant differences (Table 4).

DISCUSSION

Many studies have recently been performed to determine the genetic risk factors of obesity and related metabolic disorders (COMUZZIE and ALLISON 1998). *UCP-2*, which is expressed in various tissue types, is among the candidate factors. Until now, seven genetic polymorphisms were reported in the *UCP-2* gene. In the promoter region, *T-2723A, G-1957A, G-866A, G-371C* and 13 bp deletion/insertion polymorphisms have been found (ESTERBAUER et al. 2001). *Ala55Val* in exon 4 and the 45 bp deletion/insertion in the 3′-untranslatied region have also been reported (UHAMMER et al. 1997). Several previous studies were conducted to determine the relationships between *UCP-2* polymorphisms and weight gain, BMI, and energy expenditure (UHAMMER et al. 1997; KLANNEMARK et al. 1998; ASTRUP et al. 1999; BUEMANN et al. 2001; ESTERBAUER et al. 2001; ROSMOND et al. 2002; MAESTRINI et al. 2003).

In this paper, we elucidated the association between *Ala55Val* polymorphism and body fat in 386 Korean
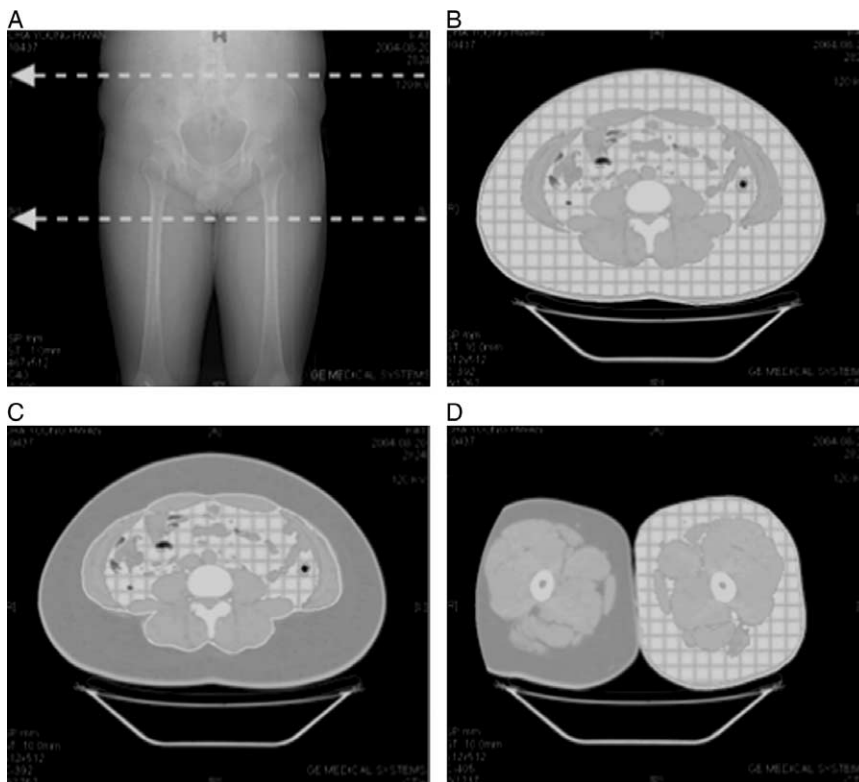
Fig. 1A–D. Measurement of cross-sectional fat tissue area using CT. (**A**) Abdominal and thigh positions for the measurement of the cross-sectional fat area. (**B**) An example of total abdominal fat area. (**C**) An example of visceral fat area. (**D**) An example of thigh subcutaneous fat area.

female subjects. The frequency of the Val allele was 0.46, a finding that is similar to those of previous studies conducted in Caucasian populations (ASTRUP et al. 1999; KLANNEMARK et al. 1998; ROSMOND et al. 2002). The average BMI was 26.4, 26.8, and 25.7 for the *AlaAla, AlaVal*, and *ValVal* type (Table 1), respectively, which was very similar to the report by ROSMOND et al., which reported BMI of 26.5, 26.1, and 25.7 for the *AlaAla, AlaVal* and *ValVal* types, respectively, in the Swedish population

(ROSMOND et al. 2002). In a study among Italian subjects, the frequency of the *Val* allele was lower in obese subjects compared with control subjects (MAESTRINI et al. 2003).

Until now, only a few reports have been found about the effects of the *Ala55Val* polymorphism on CT-measured fat tissue area in East Asian populations. In this paper, we elucidated the association between the *Ala55Val* polymorphism and cross-sectional areas of abdominal subcutaneous fat, visceral fat, and thigh

Table 2. *Comparison of CT-measured fat areas by Ala55Val polymorphism.*

Genotype		*AlaAla* type (n =112)	*AlaVal* type (n =176)	*ValVal* type (n =86)	p-value
Abdominal subcutaneous fat	(mm²)	29825 ± 1262[1]	30199 ± 995	26504 ± 1017	**0.044**[2]
Abdominal visceral fat	(mm²)	6293 ± 346	5852 ± 236	5577 ± 338	0.102
Total sbdominal fat[3]	(mm²)	36118 ± 1528	36052 ± 1168	32082 ± 1300	**0.043**
V/S ratio[4]	(mm²)	0.211 ± 0.007	0.197 ± 0.005	0.205 ± 0.007	0.576
Thigh subcutaneous fat	(mm²)	15106 ± 400	15639 ± 295	14381 ± 368	0.125

[1] mean ± SE
[2] p-values were obtained by general linear model analysis adjusted for age.
[3] total abdominal fat is the sum of abdominal subcutaneous fat and abdominal visceral fat.
[4] V/S ratio is the ratio of abdominal visceral fat to abdominal subcutaneous fat.

Table 3. *Changes in body weight and body composition during a 1-month calorie restriction program.*

Genotype		*AlaAla* type (n = 76)	*AlaVal* type (n = 110)	*ValVal* type (n = 50)	p-value[2]	Adjusted p-value
Weight	(kg)	-7.24 ± 0.31[1]	-7.03 ± 0.24	-6.19 ± 0.31	0.073	0.082[3]
BMI	(kg m^{-2})	-2.79 ± 0.11	-2.70 ± 0.09	-2.43 ± 0.12	0.104	0.108[4]
Fat	(kg)	-4.99 ± 0.23	-5.06 ± 0.27	-3.92 ± 0.27	**0.016**	0.085[5]
Lean body mass	(kg)	-2.34 ± 0.22	-2.12 ± 0.21	-2.27 ± 0.22	0.571	0.142[6]
Protein	(kg)	-0.58 ± 0.08	-0.55 ± 0.05	-0.57 ± 0.06	0.780	0.257[7]
Mineral	(kg)	-0.10 ± 0.01	-0.10 ± 0.01	-0.08 ± 0.02	0.577	0.650[8]
Water	(kg)	-1.64 ± 0.16	-1.49 ± 0.15	-1.51 ± 0.17	0.662	0.253[9]

[1] mean $\pm$ SE.
[2] p-values were obtained by general linear model analysis adjusted for age.
[3] p-values were obtained by general linear model analysis adjusted for age and initial body weight.
[4] p-values were obtained by general linear model analysis adjusted for age and initial BMI.
[5] p-values were obtained by general linear model analysis adjusted for age and initial fat mass.
[6] p-values were obtained by general linear model analysis adjusted for age and initial lean body mass.
[7] p-values were obtained by general linear model analysis adjusted for age and initial protein mass.
[8] p-values were obtained by general linear model analysis adjusted for age and initial mineral mass.
[9] p-values were obtained by general linear model analysis adjusted for age and initial water mass.

subcutaneous fat (Table 2). Results of this study showed that the *ValVal* type of the *UCP-2* gene was significantly associated with smaller abdominal subcutaneous fat and abdominal total fat areas (p = 0.044 and p = 0.043, respectively).

In this study, the effects of calorie restriction on the body compositions of the subjects were also compared according to the *Ala55Val* polymorphism. There was no difference in the calorie restriction-induced changes of protein, mineral, or water content related to the *Ala55Val* polymorphism. However, calorie restriction-induced reduction of body fat was significantly lower in the *ValVal* type compared with the *AlaAla* and *AlaVal* types (p = 0.016) (Table 3). ASTRUP et al. reported that energy expenditure during 24 h was lower in the *ValVal* type, by 311 and 299 kj day^{-1}, compared with the *AlaAla* and *AlaVal* type, respectively; fat oxidation was also found to be significantly decreased in the *ValVal* type (ASTRUP et al. 1999).

BUEMANN et al. (2001) also reported that, when the same work was performed, energy expenditure was lower in *ValVal* type subjects than in subjects of other types. These previous studies showed that the *ValVal* type was associated with lower energy expenditure, and may provide some explanation for the results of our study.

Table 4 shows that the *Ala55Val* polymorphism was not associated with biochemical parameters in this study, even though it had significant effects on body fat. It is well known that visceral fat is related to aberrant metabolic profiles (BJÖRNTORP 1991), but the relationship between subcutaneous fat and metabolic syndrome has not yet been identified. MATSUZAWA et al. (1995) suggested that the visceral fat to subcutaneous fat ratio (V/S ratio) is a better indicator of metabolic syndrome than most other parameters. In this study, the *Ala55Val* polymorphism was not found to be significantly associated with the

Table 4. *Comparison of serum biochemical profiles by Ala55Val polymorphism.*

Genotype		*AlaAla* type (n = 117)	*AlaVal* type (n = 182)	*ValVal* type (n = 87)	p-value
Total cholesterol	(mg dl^{-1})	221.64 ± 6.62[1]	221.82 ± 5.81	228.77 ± 8.33	0.835[2]
LDL cholesterol	(mg dl^{-1})	169.62 ± 7.35	164.73 ± 5.25	162.82 ± 7.55	0.747
HDL cholesterol	(mg dl^{-1})	50.04 ± 1.59	48.87 ± 1.21	49.38 ± 4.52	0.909
Triglyceride	(mg dl^{-1})	77.87 ± 3.63	79.62 ± 3.11	84.00 ± 5.08	0.610
Glucose	(mg dl^{-1})	100.53 ± 3.11	101.08 ± 2.10	99.26 ± 2.75	0.610
LDH	(U/L)	196.34 ± 20.47	181.81 ± 12.69	173.35 ± 18.12	0.658
Albumin	(g dl^{-1})	5.52 ± 0.16	5.85 ± 0.26	5.79 ± 0.20	0.568
GOT	(IU/L)	14.12 ± 1.48	14.17 ± 1.71	12.15 ± 1.41	0.712
GPT	(IU/L)	23.98 ± 2.83	21.75 ± 1.25	26.25 ± 2.32	0.339

[1] mean $\pm$ SE.
[2] p-values were obtained by general linear model analysis adjusted for age.

visceral fat area or V/S ratio, thus providing some explanation for the similar metabolic profiles among the *Ala55Val* genotypes.

In summary, the *Ala55Val* polymorphism of the *UCP-2* gene was associated with abdominal subcutaneous fat area and calorie restriction-induced body fat reduction in Korean female subjects.

REFERENCES

Astrup, A., Toubro, S., Dalgaard, L. T. et al. 1999. Impact of the v/v 55 polymorphism of the uncoupling protein 2 gene on 24-h energy expenditure and substrate oxidation. – Int. J. Obes. Relat. Metab. Disord. 10: 1030–1034.

Björntorp, P. 1991. Metabolic implications of body fat distribution. – Diabetes Care 14: 1132–1143.

Buemann, B., Schierning, B., Toubro, S. et al. 2001. The association between the val/ala-55 polymorphism of the uncoupling protein 2 gene and exercise efficiency. – Int. J. Obes. Relat. Metab. Disord. 25: 467–471.

Cassard, A. M., Bouillaud, F., Mattei, M. G. et al. 1990. Human uncoupling protein gene: structure, comparison with rat gene, and assignment to the long arm of chromosome 4. – J. Cell Biochem. 43: 255–264.

Comuzzie, A. G. and Allison, D. B. 1998. The search for human obesity genes. – Science 280: 1374–1377.

Esterbauer, H., Schneitler, C., Oberkofler, H. et al. 2001. A common polymorphism in the promoter of UCP2 is associated with decreased risk of obesity in middle-aged humans. – Nat. Genet. 28: 178–183.

Fleury, C., Neverova, M., Collins, S. et al. 1997. Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia. – Nat. Genet. 15: 269–272.

Garlid, K. D., Orosz, D. E., Modriansky, M. et al. 1996. On the mechanism of fatty acid-induced proton transport by mitochondrial uncoupling protein. – J. Biol. Chem. 271: 2615–2620.

Gura, T. 1998. Uncoupling proteins provide new clue to obesity causes. – Science 280: 1369–1370.

Klannemark, M., Orho, M. and Groop, L. 1998. No relationship between identified variants in the uncoupling protein 2 gene and energy expenditure. – Eur. J. Endocrinol. 139: 217–223.

Maestrini, S., Podesta, F., Di Blasio, A. M. et al. 2003. Lack of association between UCP2 gene polymorphisms and obesity phenotype in Italian Caucasians. – J. Endocrinol. Invest. 26: 985–990.

Matsuzawa, Y., Nakamura, T., Shimomura, I. et al. 1995. Visceral fat accumulation and cardiovascular disease. – Obes. Res. 5: 645S–647S.

Oppert, J. M., Vohl, M. C., Chagnon, M. et al. 1994. DNA polymorphism in the uncoupling protein (UCP) gene and human body fat. – Int. J. Obes. Relat. Metab. Disord. 18: 526–531.

Ravussin, E., Lillioja, S., Knowler, W. C. et al. 1998. Reduced rate of energy expenditure as a risk factor for body-weight gain. – N. Engl. J. Med. 318: 467–472.

Rice, T., Tremblay, A., Deriaz, O. et al. 1996. A major gene for resting metabolic rate unassociated with body composition: results from the Quebec family study. – Obes. Res. 4: 441–449.

Rippe, C., Berger, K., Boiers, C. et al. 2000. Effect of high-fat diet, surrounding temperature, and enterostatin on uncoupling protein gene expression. – Am. J. Physiol. Endocrinol. Metab. 279: E293–300.

Rosmond, R., Bouchard, C. and Bjorntorp, P. 2002. Lack of association between the uncoupling protein-2 Ala55Val gene polymorphism and phenotypic features of the Metabolic syndrome. – Biochim. Biophys. Acta 1588: 103–105.

Sanigorski, A., Cameron-Smith, D., Lewandowski, P. et al. 2000. Impact of obesity and leptin treatment on adipocyte gene expression in *Psammomys obesus*. – J. Endocrinol. 164: 45–50.

Surwit, R. S., Wang, S., Petro, A. E. et al. 1998. Diet-induced changes in uncoupling proteins in obesity-prone and obesity-resistant strains of mice. – Proc. Natl Acad. Sci. USA 95: 4061–4065.

Uhammer, S. A., Dalgaard, L. T., Sorensen, T. I. A. et al. 1997. Mutational analysis of the coding region of the uncoupling protein 2 gene in obese NIDDM patients: impact of a common amino acid polymorphism on juvenile and maturity onset forms of obesity insulin resistance. – Diabetologia 40: 1227–1230.

Zhang, J., Phillips, D. I., Wang, C. et al. 2004. Human skeletal muscle PPARalpha expression correlates with fat metabolism gene expression but not BMI or insulin sensitivity. – Am. J. Physiol. Endocrinol. Metab. 286: E168–175.