Relation of weight maintenance and dietary restraint to peroxisome proliferator–activated receptor γ2, glucocorticoid receptor, and ciliary neurotrophic factor polymorphisms

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ABSTRACT
Background: Genetic variation in the peroxisome proliferator–activated receptor γ2 (PPARγ2), glucocorticoid receptor (GRL), and ciliary neurotrophic factor (CNTF) genes may play a role in the etiology of obesity.

Objective: We examined biological, psychological, and genetic determinants associated with weight maintenance (WM) after weight loss.

Design: Subjects (n = 120) followed a 6-wk diet and then a 1-y period of WM. Body weight (BW), body composition, leptin concentration, attitude toward eating (measured with the Three-Factor Eating Questionnaire), physical activity, and the polymorphisms of the PPARγ2, GRL, and CNTF genes were measured.

Results: BW loss was 7.0 ± 3.1 kg. After 1 y, 21 subjects showed successful WM (<10% regain); 99 were unsuccessful (≥10% regain). Compared with unsuccessful subjects, successful subjects had a higher increase in dietary restraint over time (4.8 ± 5.0 and 1.8 ± 3.9, respectively; P < 0.01) but significantly less sensation of general hunger (−4.0 ± 4.9 and −1.2 ± 2.7, respectively; P < 0.05). Successful subjects had a significantly different frequency distribution for the PPARγ2 (P = 0.05) and GRL (P < 0.05) genes than did unsuccessful subjects. The more successful genotypes showed a higher baseline body mass index and waist circumference (PPARγ2), a greater decrease in disinhibition of dietary restraint (GRL), and less sensation of hunger (GRL). The G/G genotype (GRL) was an independent predictor of successful WM.

Conclusion: The different genotypes of the PPARγ2 and GRL genes contribute to WM, either directly (GRL) or indirectly (PPARγ2 and GRL) via baseline body mass index and waist circumference, and to changes in Three-Factor Eating Questionnaire scores.


KEY WORDS Obesity, body weight loss, weight maintenance, dietary restraint, peroxisome proliferator–activated receptor γ2, PPARγ2, glucocorticoid receptor, GRL

INTRODUCTION

Overweight and obesity are emerging as major health problems. Weight-control methods often produce short-term success, but sustained weight maintenance (WM) is difficult to achieve (1–3). Strategies to improve the maintenance of weight loss have resulted in behavior modifications, such as changes in diet and increased physical activity (4–6). With respect to strategies to maintain weight loss, we observed that the subjects with greater dietary restraint (control over food intake to influence body weight and shape) during weight loss were most successful at WM (7). Furthermore, WM was predicted by high initial body mass index (BMI; in kg/m²), waist circumference, and fat mass and by preserved fat-free mass (7). Obesity or the failure to maintain weight loss may also be explained by genetic factors or an interaction between genetic and environmental factors (8). Peroxisome proliferator–activated receptors (PPARs) are members of the nuclear hormone receptor subfamily of ligand-dependent transcription factors. The isoform PPARγ2, is mainly expressed in adipose tissue, where it modulates the expression of target genes involved in adipocyte differentiation. The Pro12Ala PPARγ2 gene missense mutation has been associated with higher BMIs and greater weight regain (9, 10). We therefore hypothesize that subjects who are homozygous for the Pro allele would have better WM. The glucocorticoid receptor (GRL) gene has an important role in the metabolism of adipose tissue and in the regulation of abdominal fat distribution (11). Variation in the GRL gene shown by a BstII RFLP is present in intron 2, which is 646 nucleotides downstream from exon 2. Two restriction fragments of 2.3 (C allele) and 4.5 (G allele) kb can be distinguished (12). The G allele was found to be associated with an elevated BMI, a greater amount of abdominal visceral fat, and a higher waist-to-hip ratio (13, 14). However, contradictory results have also been reported (12). The ciliary neurotrophic factor (CNTF) exerts its multiple effects through a receptor complex whose sequence, localization, and mode of signal transduction share remarkable similarities with the receptor for leptin (15). In the human CNTF gene, a mutation in the first intron creates a new splice acceptor site, and the resulting mRNA codes for an aberrant protein (16). O’Dell et al (17) found that males who were homozygous for this naturally occurring null mutation had significantly higher body weight (BW) and BMI than did those who...
were not homozygous. Others have reported no association (15, 18). Therefore, in the current study, we assessed the possible relations between the GRL, CNTF, and PPARγ2 genotypes and WM after a period of weight loss.

SUBJECTS AND METHODS

Subjects

Subjects were recruited by advertisements in local newspapers. One hundred fifty subjects complied with the selection criteria of BMI > 25 and age between 20 and 65 y. The exclusion criteria were the consumption of other research medication or diet up to 30 d before the study or participation in another scientific study up to 30 d before this study. One hundred thirty-three subjects first consumed a very-low-calorie diet (VLCD) for 6 wk. Before the start of the VLCD, 17 subjects had withdrawn for various reasons (eg, lack of motivation). The 133 subjects (x ± SD age: 48.1 ± 9.5 y; BMI: 31.1 ± 3.7) who completed the VLCD were measured before and after weight loss and at 3 mo and 1 y after the weight-loss period. At the 3-mo measurement, 13 subjects dropped out for various reasons (eg, moving). The dropouts did not significantly change the baseline characteristics of the subjects. Data have been analyzed for the 120 subjects (age: 49.0 ± 9.8 y; BMI: 31.0 ± 3.8) who completed the study.

Subjects gave written informed consent for participation in the study. The study was approved by the Medical Ethics Committee of Maastricht University.

Study design

Part of the study design—ie, the weight-loss and WM protocol—was described previously (7). In short, the study consisted of a 6-wk dietary weight-loss intervention under free-living circumstances and a 1-y WM period. The VLCD (Modifast; Novartis Nutrition, Brussels, Belgium) consisted of 2.1 MJ/d (500 kcal/d) given in 3 sachets per day. It provided 50 g carbohydrates, 52 g protein, 7 g fat, and a vitamin and mineral content that met the Dutch recommended daily allowance. The VLCD was dissolved in water to make a soup, milkshake, or dessert. In addition to the VLCD, subjects were allowed to consume 2 pieces of fruit and an unrestricted amount of vegetables, without sauces or vinaigrettes, every day.

Measurements of BW, body composition, and leptin concentration, attitude toward eating, and physical activity took place before the VLCD (time zero; t0), immediately after the VLCD (t1), 3 mo after t0 (t2), and 1 y after t0 (t3). A blood sample was taken at t0 and stored for DNA analysis.

Measurements

Anthropometric measurements

Height was measured by using a wall-mounted stadiometer (model 220; Seca, Hamburg, Germany), and BW was measured by using a digital balance that was accurate to 0.1 kg (D7470; Sauter, Ebingen, Germany). Measurements were taken while the subjects were wearing their underwear, after an overnight fast, and after voiding the bladder. While the subjects were standing, the waist circumference was measured at the narrowest level between the rib cage and the iliac crest.

Body composition

Body composition was measured by using the deuterium (H2O) dilution technique. The H2O dilution was used to measure total body water (TBW). Subjects were asked to collect a urine sample in the evening just before drinking the H2O-enriched water solution. After ingestion of this solution, no further consumption was allowed. Ten hours after drinking the water solution, another urine sample was collected. The dilution of the H2O is a measure of the TBW of the subject. The H2O was measured in the urine samples by using an isotope ratio mass spectrometer (VG-Isogas Aqua Sira; VG Isogas, Middlewich, United Kingdom). TBW was obtained by dividing the measured H2O dilution space by 1.04. Fat-free mass (FFM) was calculated by dividing TBW by the hydration factor 0.73 (19–21).

Attitude toward eating

The Three-Factor Eating Questionnaire (TFEQ) is a self-reported measure of eating behaviors that are believed to be particularly relevant to the development and maintenance of obesity. The TFEQ has been widely used in obesity treatment and includes 3 subscales: cognitive dietary restraint (factor 1), disinhibition of dietary restraint and emotional eating (factor 2), and hunger (factor 3) (22, 23). Factor 1 is regarded as the best available tool for the psychometric assessment of restrained eating (24). It measures control over food intake to influence BW and body shape (eg, “I consciously hold back at meals to keep from gaining weight”) (25). It was observed, for example, that restrained eaters consumed less energy, took fewer meals, and showed higher preferences for low-energy foods than did unrestrained eaters (26, 27). Correspondingly, the adjusted energy expenditure was found to be significantly lower in restrained eaters, which may indicate that they have an energy balance below the biologically given level (27). For factor 2, the subscale for disinhibition of dietary restraint measures the tendency to lose control over eating when feeling hungry or when exposed to external stimuli (eg, “Sometimes when I start eating, I just can’t seem to stop”), and the subscale for emotional eating measures the propensity to overeat in relation to negative mood states (eg, when feeling lonely, anxious, or depressed) (25). Factor 3 measures a person’s general subjective feeling of hunger. Because a subset of the subjects from this study (n = 40) participated in earlier studies in our lab, we were able to correlate baseline TFEQ data from the earlier studies and from the current study. All 3 factors were significantly correlated (factor 1: r = 0.4, P < 0.01; factor 2: r = 0.7, P < 0.001; factor 3: r = 0.4, P < 0.05), which indicates the reliability of this questionnaire. For the current study, we used a validated Dutch translation of the TFEQ (23).

Physical activity

An estimation of the physical activity level was determined by using the Baecke questionnaire validated by the doubly labeled water method (28). The Baecke questionnaire consists of work, sports, leisure-time, and total indexes (29).

Leptin

Blood samples were taken after a 12-h overnight fast. Serum leptin concentrations were measured with a double-antibody, sandwich-type enzyme-linked immunosorbent assay that used a monoclonal antibody specific for human leptin. The lower and
upper limits of detection are 0.5 and 50 µg/L, respectively. The intraassay and interassay CVs were 9% and 12%, respectively. The leptin concentrations in normal-weight subjects ranged from 2 to 12 µg/L.

**Determination of the genotypes**

The genomic DNAs of 119 subjects were isolated from peripheral blood leukocytes by using a QIAamp kit (Qiagen, Hilden, Germany).

**Peroxisome proliferator-activated receptor γ2 genotyping**

A 270-bp fragment of the PPARγ2 gene was generated from genomic DNA by using polymerase chain reaction (PCR) with forward primer 5′-GCCAATTCAAGCCAGTC-3′ and mutagenic reverse primer 5′-GATATGGTTGCCAGACAGTGTAT-CAGTGAAGGAAATCGCTTTCCG-3′, the latter of which introduces a BsrU-I restriction site only when the C→G substitution at nucleotide 34 is present in relation to the Pro12Ala polymorphism (30). The PCR products were digested with BsrU-I at 60 °C for 60 min, electrophoresed on a 2.5% agarose gel, and stained with ethidium bromide. The expected products after digestion with BsrU-I are 270 bp for P/P homozygotes, 227 and 43 bp for P/A heterozygotes, and 134 bp for null mutation homozygotes (A/A), and 134, 94, and 40 bp for A/A homozygotes.

**Glucocorticoid receptor genotyping**

An 87-bp fragment of the GRL gene was generated from genomic DNA by using PCR with forward primer 5′-GCTCAGAGGGTCTGCCCATA-3′ and reverse primer 5′-TTGCACCATGTTGACACCAAT-3′, the latter of which includes a C/G polymorphism in intron 2, which is 646 nucleotides downstream from exon 2 (12). The PCR products were digested with BclI at 50 °C for 60 min, electrophoresed on a 3% agarose gel, and stained with ethidium bromide. The expected products after digestion with BclI are 87 bp for G/G homozygotes, and 40 bp for G/C heterozygotes.

**Ciliary neurotrophic factor genotyping**

A 134-bp fragment encompassing the null mutation at position −6 before the second exon of the CNTF gene was generated from genomic DNA by using PCR with forward primer 5′-CCAGAGAGATGAGTGATTTTTG-3′ and reverse primer 5′-CAGGTTGATGTTGCTTTGACC-3′ (16). The PCR products were digested with HaeIII at 37 °C for 60 min, electrophoresed on a 2.5% agarose gel, and stained with ethidium bromide. The expected products after digestion with HaeIII are 94 and 40 bp for normal homozygotes (G/G), 134 bp for null mutation homozygotes (A/A), and 134, 94, and 40 bp for heterozygotes (G/A).

**Statistical analysis**

We used repeated-measures analysis of variance to test for differences between groups over time and 2-sample t tests to assess the differences in single variables between groups (STATVIEW SE GRAPHICS for MACINTOSH, version 1.03; Abacus Concepts, Berkeley, CA). Relations between variables were evaluated as Pearson correlations, and chi-square tests were used for the Hardy-Weinberg equilibrium. Associations between genotype and the outcome variable (un)successful WM were tested with Fisher’s exact test. The relation of the outcome variable of successful or unsuccessful WM to genotype was analyzed with correction for possible confounder variables by using logistic regression (SPSS for WINDOWS, version 11.5; SPSS, Chicago, IL). All statistical tests were 2-sided, and differences were considered significant at P < 0.05. Values are expressed as mean ± SD.

**RESULTS**

To identify factors that distinguish successful subjects from unsuccessful subjects, subjects were categorized into 2 distinct groups according to either high or low rates of weight change over the follow-up period. On the basis of the analysis by Weinsier et al (31), we assessed success in WM by using the criterion of 10% weight regain in the unsuccessful group. In our study, 8.2% of the subjects met this criterion. The differences in changes in the subjects’ characteristics over time between the successful and unsuccessful groups and the baseline differences between the successful and unsuccessful subjects with respect to BMI, waist circumference, and fat mass are shown in Table 1 (7). There was a significant (P < 0.001) overall group × time interaction based on a 2-factor repeated-measures analysis of variance for BW, BMI, waist circumference, percentage body fat, fat mass, dietary restraint, and hunger feelings. The subjects in the successful WM group maintained their lower post-weight-loss BW, BMI, waist circumference, body fat, and fat mass and their dietary restraint values for a period of 1 year, but the unsuccessful group showed a regain.

The observations on WM were related to the genotype frequency distribution in the successful and unsuccessful groups, as follows. The frequency distribution of the PPARγ2, GRL, and CNTF genotypes in 119 subjects are shown in Table 2; the overall frequencies were in Hardy-Weinberg equilibrium (data not shown). The genotype frequency distribution of the GRL gene differed significantly between the successful and unsuccessful groups (P < 0.05); that of the PPARγ2 gene tended to be significantly different (P = 0.05), but that of the CNTF gene did not differ significantly between the 2 groups (Table 2).

For the PPARγ2 genotype, the successful group had fewer heterozygous (P/A) subjects (9.5% and 23.5%, respectively) and more subjects with the homozygous Pro allele (P/P) (85.7% and 76.5%, respectively) than did the unsuccessful group. In addition, all subjects with the P/P genotype had a significantly higher baseline BW (91.9 ± 15.9 and 83.9 ± 11.5 kg, respectively; P = 0.02), BMI (31.3 ± 3.9 and 29.7 ± 3.0, respectively; P = 0.05), and waist circumference (102.9 ± 12.2 and 96.8 ± 10.0 cm, respectively; P = 0.02) than did those with the P/A genotype. In general, a higher baseline BMI and waist circumference were associated with better WM (Table 1). Binary logistic regression analysis shows that, after correction for baseline BW, BMI, and waist circumference, the more successful P/P genotype had no direct association with better WM (P > 0.05).

For the GRL genotype, it appeared that the successful group had more homozygous carriers of the G allele than did the unsuccessful group (28.6% and 8.2%, respectively). Compared with the C/C and C/G genotypes, the G/G genotype had a significantly higher baseline BMI (30.2 ± 3.1, 31.2 ± 4.1, and 32.9 ± 4.3, respectively; P = 0.05), showed a greater decrease in disinhibition of dietary restraint or emotional eating during the first 3 mo of the study (−0.4 ± 1.8, −0.2 ± 2.1, and −1.9 ± 1.9,
Indeed, subjects with the higher BMI (kg/m²) had significantly less weight regain than did subjects with the C/C and the G/G genotypes (61.3 ± 52.0%, 60.8 ± 56.7%, and 23.3 ± 51.8%, respectively; P = 0.05).

For the CNTF gene, the frequency distribution of the genotype did not differ significantly between the successful and unsuccessful groups. Nevertheless, the successful group seemed to show more G/A genotypes than did the unsuccessful group (38.1% and 24.5%, respectively), a difference that did not reach statistical significance. However, compared with subjects with the G/G genotype, subjects with the G/A genotype had a significantly lower serum leptin concentration at baseline (28.5 ± 17.5 μg/L, 1.2 ± 12.5 μg/L, respectively; P < 0.05) and a lower delta leptin concentration during weight loss (−19.3 ± 14.5 and −13.4 ± 9.6 μg/L, respectively; P < 0.05). Moreover, during the

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Characteristics of successful and unsuccessful subjects at baseline, after a very-low-calorie diet (VLCD), after 3 mo, and after 1 y</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (t0)</td>
</tr>
<tr>
<td>BW (kg)²</td>
<td>Successful</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
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<tr>
<td></td>
<td>BMI (kg/m²)²</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>Waist circumference (cm)²</td>
<td>Successful</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>Body fat (%)²</td>
<td>Successful</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>Fat mass (kg)²</td>
<td>Successful</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>Successful</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>TFEQ factors¹⁰</td>
<td>Diet restraint (factor 1)²</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
</tr>
<tr>
<td></td>
<td>Disinhibition (factor 2)²</td>
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<td></td>
<td>Unsuccessful</td>
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<tr>
<td></td>
<td>Hunger (factor 3)²</td>
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<td></td>
<td>Unsuccessful</td>
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<tr>
<td>Physical activity (Bauecke)</td>
<td>Successful</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
</tr>
<tr>
<td>Leptin (μg/mL)</td>
<td>Successful</td>
</tr>
<tr>
<td></td>
<td>Unsuccessful</td>
</tr>
</tbody>
</table>

¹⁰ Values represent the number of relevant questions.

³ Overall group × time interaction was significant, P < 0.001 (2-factor repeated-measures ANOVA).
⁴ P < 0.05 (2-factor repeated-measures ANOVA with group × time interaction from t0 to t2).
⁵ P < 0.001 (2-factor repeated-measures ANOVA with group × time interaction from t0 to t3), significantly different from unsuccessful subjects at baseline, P < 0.05 (t test).
⁶ P = 0.06 (t test, successful group versus unsuccessful group at baseline).

respectively; P < 0.05), and had significantly less feelings of hunger during weight loss (−0.5 ± 2.6, −1.9 ± 2.9, and −2.6 ± 5.8, respectively; P < 0.05). Binary logistic regression analysis shows that, after correction for the influence of baseline BMI, disinhibition of dietary restraint or emotional eating, and hunger, the more successful G/G genotype appeared to be an independent predictor for successful WM (odds ratio: 5.032; P < 0.05) (Table 3). In addition, a change in the dietary restraint (factor 1) score during weight loss was inversely correlated with a change in the disinhibition of dietary restraint or emotional eating (factor 2) score (r = −0.4, P < 0.001) and with changes in the hunger (factor 3) score during the whole study period (r = −0.36, P < 0.001) and during the WM period (r = −0.25, P < 0.01) (7). Indeed, subjects with the G/G genotype had significantly less weight gain than did subjects with the C/C and the G/G genotypes (61.3 ± 52.0%, 60.8 ± 56.7%, and 23.3 ± 51.8%, respectively; P = 0.05).
TABLE 2
Frequency distribution of the genotypes in all subjects, those with successful weight maintenance, and those with unsuccessful weight maintenance

<table>
<thead>
<tr>
<th>Gene and genotypes</th>
<th>All (n = 119)</th>
<th>Successful (n = 21)</th>
<th>Unsuccessful (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARγ2&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P/P</td>
<td>93 (78.2)</td>
<td>18 (85.7)</td>
<td>75 (76.5)</td>
</tr>
<tr>
<td>P/A</td>
<td>25 (21.0)</td>
<td>2 (9.5)</td>
<td>23 (23.5)</td>
</tr>
<tr>
<td>A/A</td>
<td>1 (0.8)</td>
<td>1 (4.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>GRL&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>49 (41.2)</td>
<td>6 (28.6)</td>
<td>43 (43.9)</td>
</tr>
<tr>
<td>C/G</td>
<td>56 (47.0)</td>
<td>9 (42.9)</td>
<td>47 (48.0)</td>
</tr>
<tr>
<td>G/G</td>
<td>14 (11.8)</td>
<td>6 (28.6)</td>
<td>8 (8.2)</td>
</tr>
<tr>
<td>CNTF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>85 (71.4)</td>
<td>13 (61.9)</td>
<td>72 (73.5)</td>
</tr>
<tr>
<td>G/A</td>
<td>32 (26.9)</td>
<td>8 (38.1)</td>
<td>24 (24.5)</td>
</tr>
<tr>
<td>A/A</td>
<td>2 (1.7)</td>
<td>0 (0)</td>
<td>2 (2.0)</td>
</tr>
</tbody>
</table>

1 Successful weight maintenance = <10% regain within 1 y; unsuccessful weight maintenance = ≥10% regain within 1 y.
2 P = 0.05, successful vs unsuccessful (Fisher’s exact test).
3 P < 0.05, successful vs unsuccessful (Fisher’s exact test).

1-y WM period, the successful subjects had a significantly smaller change in leptin concentrations than did the unsuccessful subjects (3.4 ± 4.6 and 8.8 ± 5.7 μg/L, respectively; P < 0.005) (7). In general, in the whole group, leptin was correlated positively with fat mass at all measured time points (at baseline, after VLCD, and after 1 y: r = 0.6, P < 0.001; after 3 mo: r = 0.7, P < 0.001), and the change in leptin concentrations during the WM period was positively correlated with the percentage BW regain at 1 y (r = 0.2, P = 0.01) and with the change in fat mass during the WM period (r = 0.3, P < 0.01) (7).

DISCUSSION

Subjects were categorized into 2 distinct groups (successful and unsuccessful WM) according to either high or low rates of weight change during the follow-up period. There was a break below and above 10% weight regain. Subjects with the homozygous P/P genotype for the PPARγ2 gene and those with the homozygous G/G genotype for the GRL gene (the genotype frequencies that were more frequent in the successful group) appeared to have a higher baseline BMI than did subjects with the other genotypes for both genes. Moreover, subjects with the P/P genotype had a significantly larger waist circumference than did those with the other 2 genotypes for the PPARγ2 gene. Subjects with a high baseline BMI, waist circumference, and fat mass (FM) appeared to lose more weight and body fat, while at the same time they showed better WM, related to effective changes in body composition (7); these characteristics occurred more frequently in subjects with the homozygous P/P genotype for the PPARγ2 gene and in subjects with the homozygous G/G genotype for the GRL gene. Each of those genes plays an important role in the metabolism of adipose tissue—ie, the PPARγ2 gene modulates the expression of target genes involved in adipocyte differentiation (9), and the GRL gene is involved in the regulation of abdominal fat distribution (11)—and therefore, each may be related to WM. After correction for baseline BW, BMI, and waist circumference, the PPARγ2 gene was not an independent predictor of better WM.

As previously shown (32–35), leptin was strongly dependent on FM in obese subjects (both successful and unsuccessful). Variation in the CNTF genotype had no influence on better WM, but the different genotypes were in fact related to leptin concentration. Compared with subjects with the CNTF G/G genotype, subjects with the G/A genotype appeared to have a smaller decrease in leptin concentration during weight loss. A smaller decrease in leptin concentration may contribute to better WM; both animal and human studies indicate that low baseline or reduced (as observed during fasting) leptin concentrations act as a peripheral signal of starvation, which subsequently may be a trigger to increase weight, thereby ensuring survival of the species (36).

As in previously reported observations (2, 37), subjects who were able to increase their dietary restraint throughout the study period were better able to control or maintain their weight (Table 3). McGuire et al (38) found that increases in dietary restraint in the WM period were significantly related to decreases in BW. An increase in dietary restraint is often related to a decrease in disinhibition (39–41). In the current study, we found this inverse correlation as well (7). Moreover, weight gainers appear to be low in dietary restraint and high in disinhibition (39, 42, 43). This implies that WM may be sustained only with high dietary restraint scores in combination with low disinhibition scores. Furthermore, in the current study, we found that successful subjects appeared to increase dietary restraint and at the same time to reduce their general hunger feelings over time. Thus, subjects who do not experience hunger may not be susceptible to an inhibition of dietary restraint, and therefore they sustain or even increase their dietary restraint and, consequently, maintain their BW. In addition, compared with the other 2 genotypes, the homozygous carriers of the G allele of the GRL gene had significant decreases over time in their disinhibition of dietary restraint or emotional eating scores and their hunger scores, which may result in decreased food intake. Moreover, independently of these variables, the GRL gene had a direct influence on WM, in that the G/G genotype was an independent predictor for successful WM, so that the subjects with the G/G genotype had a chance of success 5 times that of the subjects with other genotypes. In summary, we speculate that, because of environmental changes, any person may become overweight. But having the “right” genetic background may contribute to successful WM, a more favorable body composition (which allows more BW flexibility), and less sensation of hunger, less disinhibition, and less emotional eating. Therefore, persons with these particular genotypes may be more sensitive to certain treatments, because the treatment is more rewarded and the lower BW is maintained (and vice...
versa). In fact, these are the very persons who are not necessarily prone to overweight.

For both the PPARγ2 and GRL genes, we have found that the successful subjects had a genotype frequency distribution that differed significantly from that of the unsuccessful subjects. For the PPARγ2 genotype, the successful group had proportionally fewer heterozygous (P/A) subjects than did the unsuccessful group. Similar results were reported by Nicklas et al (10), who found that mean weight regain during follow-up was greater in women with the Ala allele than in women who were homozygous for the Pro allele (5.4 ± 0.9 and 2.8 ± 0.4 kg, respectively; P < 0.01). Other studies also found that greater weight gain was associated with the Ala allele (44, 45). For the GRL genotype, we found that the successful group had proportionally more homozgyous carriers of the G allele than did the unsuccessful group. In addition, these homozygous G allele carriers had a significantly higher initial BMI than did the C allele carriers. The latter result was in accordance with the findings of Rosmond et al (13) and Buemann et al (14). Little research investigated the association of the CNTF genotype and obesity. O’Dell et al (17) found that males who were homozygous for the null mutation had a significantly higher BW and BMI than did males with the other genotypes, whereas other studies, including the current study, reported no or very little association with obesity.

A strength of the current study is that, after weight loss, there were 2 measurement periods, one after 3 mo and one after 1 y WM. The successful group, unlike the unsuccessful group, had no difference in the measured variables between the 2 measurement points, which suggests that being successful at 3-mo WM is a good predictor for being successful at 1-y WM.

Clearly, obesity is a multifactorial disease. From the current study, we conclude that genetic factors played a role in successful post-weight-loss WM that was seen mainly in subjects who increased their dietary restraint and who were supported by characteristics such as a high baseline BMI, waist circumference, and FM and a more favorable body composition. The different genotypes of the PPARγ2 and GRL genes contribute directly (GRL) or indirectly (PPARγ2 and GRL) to WM, in that they may induce different mechanisms. Both PPARγ2 and GRL play an important biological role in fat cell differentiation, which leads to a higher physiological mechanisms that lead to changes in the TFEQ scores. All of these mechanisms result in better WM.

We thank the subjects for their participation in this study. We thank Lock Wouters, Roy Langeveld, Joan Senden, and Wendy Slijmers for their assistance, and we acknowledge Natalie Lucombe-Marsh for editing the English text.

NV and MW designed the current study. NV carried out the study, collected and analyzed the data, and wrote most of the manuscript. FB contributed to the practical work itself and wrote a part of the subjects and methods section. AK supervised the statistical analysis and reviewed the manuscript. KD reviewed the manuscript. Planning, processing the results, and writing the manuscript were done under general supervision by EM and MW. None of the authors had a personal or financial conflict of interest.

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