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Genetic predisposition, dietary restraint and disinhibition in relation to short and long-term weight loss

Sanne P.M. Verhoef *, Stefan G.J.A. Camps, Freek G. Bouwman, Edwin C.M. Mariman, Klaas R. Westerterp

Maastricht University, Department of Human Biology, Nutrition and Toxicology Research Institute Maastricht, 6200 MD, Maastricht, The Netherlands

HIGHLIGHTS

- A high predisposition score is associated with high body weight
- A high predisposition score is associated with more weight loss
- Long-term weight loss is mainly associated with changes in eating behaviour

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ABSTRACT

Background: Interindividual differences in response to weight loss and maintenance thereafter are ascribed to genetic predisposition and behavioral changes.
Objective: To examine whether body weight and short and long-term body weight loss were affected by candidate single nucleotide polymorphisms (SNPs) and changes in eating behavior or by an interaction between these genetic and behavioral factors.
Methods: 150 healthy subjects (39 males, 111 females) aged 20–50 y with a BMI of 27–38 kg/m^2 followed a very low energy diet for 8-weeks, followed by a 3-month weight maintenance period. SNPs were selected from six candidate genes: *ADRB2*, *FTO*, *MC4R*, *PPARG*, *PPARD*, and *PPARGC1A*. Changes in eating behavior were determined with the Three Factor Eating Questionnaire.
Results: A high genetic predisposition score was associated with a high body weight at baseline and more short-term weight loss. From the six selected obesity-related SNPs, *FTO* was associated with increased body weight at baseline, and the effect allele of *PPARGC1A* was positively associated with short-term weight loss, when assessed for each SNP separately. Long-term weight loss was associated with a larger increase in dietary restraint and larger decrease in disinhibition.
Conclusion: During long-term weight loss, genetic effects are dominated by changes in eating behavior.

1. Introduction

Obesity results from a chronic imbalance between energy intake and expenditure [1]. The increasing prevalence of obesity coincides with changes in dietary habits due to high availability of energy-dense foods, suggesting a causal link [2]. However, some individuals seem resistant to becoming overweight or obese. Inter-individual variation in the susceptibility to develop obesity can be partly explained by genetics. Family and twin studies have shown that the genetic contribution can be 40–70% [3,4]. Genome-wide association studies (GWAS), already identified 52 genetic loci to be unequivocally associated with obesity related-traits [5]. However, the effects of the loci on obesity-susceptibility are small and explain only a small fraction of the total variation with a poor predictive ability [5–7]. Studying the GWAS-identified loci in longitudinal cohort studies can contribute to elucidating new physiological pathways that underlie obesity-susceptibility.

Most association studies focus on single nucleotide polymorphisms (SNPs) in relation to body weight, instead of changes in body weight. Successfully maintaining weight loss, defined as "keeping off an intentional loss of at least 10% body weight for at least one year" is only achieved in around 20% of the cases [8,9]. Individual differences in weight loss and regain may in part be caused by a genetic predisposition to resist weight loss or promoting weight gain [10]. Twin studies on the response to long-term negative energy balance have demonstrated a much larger variability between pairs than within pairs [11,12], suggesting that there is also a genetic contribution in the resistance for body weight loss and maintenance.

* Corresponding author. Tel.: +31 43 3881617; fax: +31 43 3670976.
E-mail address: s.verhoef@maastrichtuniversity.nl (S.P.M. Verhoef).

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In this study, we tested the combined and individual effect of six genetic variants, which had shown associations with obesity-related traits: rs9939609 of fat mass and obesity associated (*FTO*) gene; rs17782313 of melanocortin 4 receptor (*MC4R*) gene; rs1042713 of β2-adrenergic receptor (*ADRB2*) gene; rs1801282 of peroxisome proliferator-activated receptorγ2 (*PPARγ2*) gene; rs8192678 of peroxisome proliferator-activated receptorγ coactivator-1α (*PPARGC1α*) gene; and rs2076168 of peroxisome proliferator-activated receptorδ (*PPARδ*) gene. The aim of the study was to examine whether body weight changes during an 8-week weight loss period and subsequent follow-up of 3-months were affected by the six selected SNPs and by changes in eating behavior, or by an interaction between these genetic and behavioral factors.

2. Material and methods

2.1. Subjects

150 healthy subjects (39 males, 111 females) aged 20–50 y with a BMI of 27–38 kg/m^2 participated in the study, which started in February 2010. The weight loss diet consisted of 8 weeks of very low energy diet providing 2.1 MJ/day (Modifast; Nutrition et Santé Benelux, Breda, The Netherlands). This diet was a protein-enriched formula diet that provided 50 g carbohydrates, 52 g protein, 7 g fat and a micronutrient content, which meets the Dutch recommended daily allowance. Vegetables were allowed in addition to the diet. The weight loss period was followed by a weight maintenance period of 3 months, in which subjects were instructed to maintain their newly achieved body weight. Measurements were done at rest and following an overnight fast at three time points; before weight loss, after weight loss and after 3 months follow-up. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Central Committee on Human Research and by the Medical Ethical Committee of Maastricht University. Written informed consent was obtained from all subjects. The study was registered in ClinicalTrials.gov (registration number: NCT01015508).

2.2. Anthropometry

Height was measured at screening to the nearest 0.1 cm with the use of a wall-mounted stadiometer (model 220; Seca, Hamburg, Germany). Body weight was measured with subjects in underwear after an overnight fast using a calibrated scale of the BodPod®. Body mass index (BMI) was calculated by dividing body weight by height squared (kg/m^2).

Body composition was calculated from body volume (BodPod®, Life measurement, Concord, CA, USA) [13] and total body water (TBW) [14] as assessed with the deuterium dilution technique, using Siri's three-compartment model [15]. The dilution of the deuterium isotope (^2H_2O) is a measure for total body water. Subjects wore tightly fitting bathing suits and a swim cap during the volume-measurements in the BodPod®, and had not engaged in exercise at least 1 h prior to the test.

2.3. Questionnaires

To determine whether attitude toward food intake changed during weight loss and maintenance, a validated Dutch translation of the three-factor eating questionnaire (TFEQ) was used [16]. Changes in dietary restraint and disinhibition scores were used as indicators for changes in eating behavior and different disinhibition and restraint outcomes have been associated with distinct weight and behavior outcomes [17].

2.4. DNA isolation and genotyping

Blood was collected in an EDTA tube during screening and the buffy coat was stored at −80 °C. Genomic DNA was isolated from the buffy coat using the QIAamp mini blood kit (Qiagen, Amsterdam, The Netherlands). Six SNPs were selected based on GWAS and intervention studies, which associated them with obesity (Table 1). Genotypes were coded 0, 1 or 2 according to the number of risk alleles for each SNP. From these codes a genetic predisposition score (GPS) was constructed for each individual by summing the risk alleles across the six SNPs, as previously done by other authors [5,18,19].

Genotyping of five SNPs was performed using commercially available TaqMan SNP genotyping assays from Applied Biosystems (Foster City, California, USA). The procedure was performed according to the manufacturer's protocol and measured on an Applied Biosystems 7900 HT Fast Real-Time PCR system. Allelic calls were determined semi-automatically using the allelic discrimination software of Applied Biosystems. The Pro12Ala polymorphism of the *PPARγ2* gene was characterized using the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) assay. The primers used were 5′-GCCAATTC AAGCCCAGTC-3′ and 5′-GATATGTTTGCAGACAGTGTATCAGTGAAGGAAT CGCTTTCCG-3′. The cycling conditions were 95 °C for 5 min, 30 cycles of 95 °C/30 s, 56 °C/45 s, 68 °C/45 s and followed by 68 °C for 7 min. The restriction enzyme BstU-I was used, which generated the following fragments: 270 bp (Pro12Pro); 270, 227, 43 bp (Pro12Ala) and 227, 43 bp (Ala12Ala).

Table 1
Subject characteristics (mean ± SD) on baseline (t0), after weight loss (t2) and after 3-month (t5).

	t0	t2	t5	P-value[a]
Body weight (kg)	92.6 ± 12.3	83.2 ± 10.9[b]	84.7 ± 11.7[b]	<0.001
BMI (kg/m^2)	32.0 ± 3.1	28.7 ± 3.0[b]	29.2 ± 3.2[b]	<0.001
Fat mass (kg)	38.6 ± 7.8	31.2 ± 7.8[b]	30.9 ± 8.6[b]	<0.001
Percentage fat mass (%)	41.6 ± 6.6	37.4 ± 7.4[b]	33.5 ± 8.5[b]	<0.001
Dietary restraint	7.5 ± 3.8	12.4 ± 4.2[b]	12.0 ± 4.2[b]	<0.001
Disinhibition	6.5 ± 2.7	4.9 ± 2.6[b]	5.3 ± 2.8[b]	<0.001
Hunger	5.1 ± 3.0	3.7 ± 3.0[b]	3.4 ± 2.9[b]	<0.001

BMI: body mass index.
[a] Difference over time (repeated measures ANOVA).
[b] Significantly different from baseline, P < 0.01.

2.5. Statistical analysis

Data are presented as mean and their standard deviations, unless otherwise indicated. A Chi-square test was used to check whether the allele frequencies were in Hardy Weinberg equilibrium. ANOVA repeated measures was carried out to determine changes over time. Mean baseline values and changes in weight during weight loss and follow-up periods were compared between groups with ANOVA. Corrections for multiple testing were performed by using Bonferroni correction. Each SNP was tested individually, with age, sex and baseline value for that particular dependent variable as covariates. Linear regressions were used to test for associations. Significance was defined as P < 0.05. All of the statistical analyses were executed with SPSS version 16.0 for Macintosh OS X (SPSS Inc., Chicago, IL).

3. Results

Body weight, BMI, fat mass, percentage fat mass, and waist and hip circumference decreased significantly during weight loss and remained significantly lower after 3-month follow-up compared to baseline (Table 1). Dietary restraint increased and disinhibition and hunger decreased significantly during weight loss and remained significantly below baseline values during follow-up.

3.1. Genetic predisposition

All SNPs were in Hardy Weinberg equilibrium (Table 2). To determine the genetic contribution of the selected SNPs, differences in body weight at baseline and body weight changes during short and long-term weight