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

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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.

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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

Table 2
Genotypic and allelic distributions per single nucleotide polymorphism.

Gene	SNP	G	F (N)	F (%)	Allele[a]	F (%)	HWE
FTO	rs9936909	AA	25	16.9	**A**	38.9	0.65
		AT	65	43.9	T	61.1	
		TT	58	39.2			
MC4R	rs17782313	CC	15	10.1	**C**	24.1	0.19
		CT	46	31.1	T	75.9	
		TT	87	58.8			
ADRB2	rs1042713	GG	56	37.8	**G**	62.3	0.92
		GA	71	48.0	A	37.7	
		AA	21	14.2			
PPARD	rs2076168	GG	16	10.9	**G**	28.1	0.33
		GT	52	35.4	T	71.9	
		TT	79	53.7			
PPARGC1A	rs8192678	AA	20	13.6	**A**	37.2	0.95
		AG	70	47.6	G	62.8	
		GG	57	38.8			
PPARG2	rs1801282 (Pro12Ala)	Ala12Ala	1	0.7	**Ala**	10.7	0.83
		Pro12Ala	30	20.1	Pro	89.3	
		Pro12Pro	118	79.2			

G, genotype; F, frequency, both absolute (N) and relative (%).
P-values obtained from the χ^2-test of Hardy Weinberg equilibrium (HWE).
[a] Effect allele in bold.

loss were compared between the different genotypes (Table 3). Furthermore, a GPS was calculated by summing the risk alleles across the six SNPs. Multiple regression showed a positive association between GPS and body weight at baseline (Table 4), with a higher GPS associated with a higher body weight at baseline. There was no unifying effect on body weight as the GPS might have suggested when the effect of the SNPs separately was assessed (Table 3). There was a significant difference in body weight at baseline between *FTO* genotypes, with a higher body weight with the effect allele. More weight loss during energy restriction was associated with a high GPS (Table 4), thereby taking into account baseline body weight. Multiple regression with the percentage weight loss showed the same results (results not shown). Subjects with the effect allele for *PPARGC1A* had more short-term weight loss. During long-term weight loss there were no significant associations with GPS. Long-term weight loss was significantly different between *MC4R* genotypes, with less weight loss after 3-month follow-up compared to baseline in subjects with the effect allele.

Additionally, results for differences in fat mass and percentage fat mass between genotypes were comparable to those for body weight as reported above (data not shown). For dietary restraint, disinhibition and hunger scores, there were no significant differences between genotypes.

3.2. Eating behavior

Changes in dietary restraint were inversely correlated with changes in disinhibition during both short and long-term weight loss (respectively $R^2 = 0.044$ $P = 0.011$ and $R^2 = 0.082$ $P < 0.001$). Body weight at baseline was significantly correlated with dietary restraint and disinhibition, but did not reach significance after adjusting for age and gender (Table 5). In a multiple regression together with SNPs that showed a significant effect, body weight at baseline was associated with gender and *FTO*. Short-term weight loss was associated with body weight at baseline, gender and *PPARGC1A*. Long-term weight loss was associated with the amount of weight lost during energy restriction, gender and the change in dietary restraint and disinhibition after 3-month follow-up. No significant interaction effects between the genetic and behavioral factors were found.

4. Discussion

A high GPS was associated with a high body weight at baseline and more short-term weight loss. From the six selected obesity-related SNPs in this study, *FTO* was associated with increased body weight at baseline. The effect allele of *PPARGC1A* was 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.

Based on literature six SNPs were selected as being related to obesity associated-traits, and thus suggested to be candidates for associations with body weight changes. The correlations with GPS indicate that the SNPs have a negative effect on body weight, but a positive effect on short-term weight loss, with subjects with the most effect alleles losing more weight during energy restriction. However, when assessed for each SNP separately merely *FTO* and body weight and *PPARGC1A* and short-term weight loss were significantly associated. For *FTO* rs9936909, body weight at baseline was higher in A-allele carriers, while there were no differences in weight loss consistent with previous studies

Table 3
Baseline and changes in body weight (kg) during short- and long-term weight loss.

Gene	Effect allele	Genotype	Baseline weight (t0)[a]		Short-term weight loss (t2 − 0)[b]		Long-term weight loss (t5 − 0)[c]	
			Mean ± SE	P-value	Change ± SE	P-value	Change ± SE	P-value
FTO	A	AA	96.0 ± 2.4	0.017	−9.9 ± 0.8	0.333	−8.8 ± 0.6	0.411
		AT	93.9 ± 1.3		−9.7 ± 0.4		−8.0 ± 0.4	
		TT	90.5 ± 1.3		−8.9 ± 0.4		−7.8 ± 0.4	
MC4R	C	CC	96.6 ± 3.1	0.353	−8.2 ± 1.0	0.422	−7.5 ± 0.9	0.049
		CT	91.3 ± 1.6		−9.6 ± 0.5		−7.2 ± 0.4	
		TT	92.6 ± 1.2		−9.5 ± 0.4		−8.6 ± 0.3	
ADRB2	G	GG	93.5 ± 1.6	0.208	−9.9 ± 0.5	0.346	−7.3 ± 0.4	0.190
		GA	93.1 ± 1.3		−9.0 ± 0.4		−8.1 ± 0.4	
		AA	89.4 ± 2.2		−8.8 ± 0.7		−8.6 ± 0.6	
PPARD	G	GG	91.8 ± 2.8	0.530	−9.9 ± 0.9	0.525	−8.4 ± 0.8	0.385
		GT	91.4 ± 1.6		−9.5 ± 0.5		−7.4 ± 0.4	
		TT	93.7 ± 1.2		−9.0 ± 0.4		−8.1 ± 0.3	
PPARGC1A	A	AA	92.9 ± 2.6	0.112	−10.7 ± 0.8	0.023	−9.1 ± 0.7	0.290
		AG	94.2 ± 1.3		−9.8 ± 0.4		−7.9 ± 0.4	
		GG	91.4 ± 1.4		−8.5 ± 0.4		−7.8 ± 0.7	
PPARG2	Ala	Pro12Ala	93.8 ± 2.1	0.725	−10.1 ± 0.7	0.189	−7.6 ± 0.6	0.525
		Pro12Pro	92.3 ± 1.0		−9.2 ± 0.3		−8.0 ± 0.3	

[a] Adjusted for age and sex.
[b] Adjusted for age, sex and baseline weight.
[c] Adjusted for age, sex, baseline weight and weight loss (t2 − 0).

Table 4
Multiple regression between body weight and body weight changes with GPS.

Response	Parameter	B ± SE	β	P-value
Baseline weight (t0)	GPS	1.14 ± 0.57	0.15	0.049
	Gender	−15.38 ± 2.28	−0.52	0.000
	Age	−0.03 ± 0.11	−0.02	0.821
Short-term weight loss (t2 − 0)	GPS	−0.52 ± 0.18	−0.21	0.004
	Gender	2.86 ± 0.82	0.30	0.000
	Baseline weight (t0)	−0.11 ± 0.03	−0.30	0.001
	Age	0.04 ± 0.04	0.07	0.317

Response; dependent variable.
Parameter; independent variable.
B; unstandardized regression coefficient.
β; standardized regression coefficient.

[20–22]. During short-term weight loss subjects with the A-allele of *PPARGC1A* rs8192678 lost more weight, but this effect was lost during long-term weight loss. There were also no differences in baseline body weight between *PPARGC1A* genotypes. These results were in contrast to previous studies, which showed associations with body weight and not with weight changes [23,24]. Long-term weight loss was significantly lower in subjects with the C-allele of *MC4R* rs17782313, while others have shown that this SNP was associated with body weight and not weight changes [25,26]. In contrast to what we expected from the literature, there were in addition to *PPARGC1A* and *MC4R* also no significant differences in body weight for the *ADRB2* rs1042713 and *PPARD* rs2076168 [27,28]. Although not many studies determined the relation between SNPs and weight changes, most associations were found with *PPARG2* rs1801282 [29–33], but our results could not confirm this. Many explanations for the inconsistent results in the literature have already been proposed, like low sample size, limitations of study populations and different study designs. However, a probably more important factor is the largely unknown gene–environment interactions that can mask the effect of a genetic variant, as described by Andreasen et al. [34]. Especially during a period of conscious weight loss, behavioral changes might dominate genetic effects. Furthermore, comparing studies using GPS is difficult, because a calculated GPS is not a constant variable and is different in each study depending on the different SNPs selected.

Dietary restraint and disinhibition have emerged from the literature as important indicators for eating behavior and different disinhibition and restraint outcomes have been associated with distinct weight and behavior outcomes [17]. Here, changes in dietary restraint and disinhibition were inversely correlated with each other, consistent with previous studies [35–38]. Both changes in dietary restraint and disinhibition were correlated with long-term weight loss, emphasizing the importance of both factors during periods of weight maintenance. These results confirm findings of previous studies that already have shown that the increase in dietary restraint was associated with more success in weight maintenance [37,39,40]. There was no effect of the SNPs on dietary restraint and disinhibition or changes in these factors, so changes in eating behavior independently predict success in long-term weight loss.

From these results we cannot exclude whether there were gene–environment interactions masking effects of a genetic variant. In turn, dietary restraint and disinhibition do not fully cover behavioral factors, though widely used to characterize eating behavior. In addition, six SNPs as measured in 150 subjects are low compared to other genetic studies. However, this is a consequence of the design of our study, since accurate assessment of short and long-term weight loss was a limiting factor. Since these measurements are part of a larger intervention study, the selection of the SNPs comprised those previously associated with obesity-related traits in general and not specifically personality traits.

In conclusion, long-term weight loss is mainly determined by changes in eating behavior.

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K.R. Westerterp and S.P.M. Verhoef designed the study. S.P.M. Verhoef, S.G.J.A. Camps and F.G. Bouwman collected the data. S.P.M. Verhoef analyzed the data and wrote the manuscript. K.R. Westerterp and E.C.M. Mariman contributed to the interpretation of the data and reviewed the manuscript. The study was executed under supervision of K.R. Westerterp. All authors read and approved the final manuscript. None of the authors had any conflict of interest.

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Table 5
Multiple regression between body weight at baseline and body weight changes with SNPs, dietary restraint and disinhibition.

Response	Parameter	B ± SE	β	P-value
Body weight (t0)	Age	0.01 ± 0.10	0.00	0.959
	Gender	−13.69 ± 2.17	−0.49	0.000
	FTO	3.26 ± 1.29	0.18	0.012
	Dietary restraint (t0)	0.11 ± 0.24	0.03	0.654
	Disinhibition (t0)	−0.48 ± 0.33	−0.11	0.156
Short-term weight loss (t2 − 0)	Age	0.03 ± 0.03	0.06	0.410
	Gender	2.70 ± 0.78	0.29	0.001
	PPARGC1A	−1.15 ± 0.42	−0.20	0.008
	Body weight (t0)	−0.11 ± 0.03	−0.33	0.000
	Dietary restraint (t2 − 0)	−0.06 ± 0.06	−0.07	0.346
	Disinhibition (t2 − 0)	0.01 ± 0.12	0.01	0.912
Long-term weight loss (t5 − 0)	Age	−0.05 ± 0.03	−0.08	0.077
	Gender	−1.94 ± 0.61	−0.17	0.002
	MC4R	0.57 ± 0.37	0.07	0.123
	Weight loss (t2 − 0)	1.02 ± 0.07	0.82	0.000
	Dietary restraint (t5 − 0)	−0.23 ± 0.07	−0.18	0.001
	Disinhibition (t5 − 0)	0.25 ± 0.11	0.12	0.024

Response; dependent variable.
Parameter; independent variable.
B; unstandardized regression coefficient.
β; standardized regression coefficient.

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