Genetics and Molecular Biology, 37, 1, 15-22 (2014)

www.sbg.org.br

Research Article

Obesity-related gene *ADRB2*, *ADRB3* and *GHRL* polymorphisms and the response to a weight loss diet intervention in adult women

Louise F. Saliba[1,2], Rodrigo S. Reis[2,3], Ross C. Brownson[4,5], Adriano A. Hino[2,3], Luciane V. Tureck[1], Cheryl Valko[4], Ricardo L.R. de Souza[1] and Lupe Furtado-Alle[1]

[1]*Departamento de Genética, Universidade Federal do Paraná, Curitiba, PR, Brazil.*
[2]*Escola de Saúde e Biociências, Pontifícia Universidade Católica do Paraná, Curitiba, PR, Brazil.*
[3]*Departamento de Educação Física, Universidade Federal do Paraná, Curitiba, PR, Brazil.*
[4]*Prevention Research Center in St. Louis, Brown School, Washington University in St. Louis, St. Louis, MO, USA.*
[5]*Division of Public Health Sciences and Alvin J. Siteman Cancer Center, School of Medicine, Washington University in St. Louis, St. Louis, MO, USA.*

Abstract

The individual response to diet may be influenced by gene polymorphisms. This study hypothesized that ADRB2 (Gln27Glu, rs1042714 and Arg16Gly, rs1042713), *ADRB3* (Trp64Arg, rs4994) and *GHRL* (Leu72Met, rs696217) polymorphisms moderate weight loss. The study was a seven weeks dietary weight loss intervention with Brazilian adult obese women (n = 109). The body mass index (BMI) was calculated and polymorphisms in these genes were assessed by real-time PCR assays. Two-way repeated-measures ANOVA (2 x 2) were used to analyze the intervention effect between polymorphisms and BMI over the period and after stratification for age and socioeconomic status (SES). The weight loss intervention resulted in decreased BMI over the seven-week period ($p < 0.001$), for high and low SES ($p < 0.05$) and mainly for participants with 30-49 y. The intervention did not result in a statistically significant difference in weight loss between polymorphism carriers and non-carriers, and although, the *ADRB2*, *ADRB3* and *GHRL* polymorphisms did not moderate weight loss, the Gln27Glu polymorphism carriers showed a lower BMI compared to non-carriers in the low SES ($p = 0.018$) and the 30-39 y ($p = 0.036$) groups, suggesting a role for this polymorphism related to BMI control.

Key words: obesity, weight loss, adrenergic receptor polymorphism, ghrelin polymorphism, nutrigenetics.

Received: July 4, 2013; Accepted: November 12, 2013.

Introduction

Many diseases and health conditions have been consistently associated with obesity (Swinburn *et al.*, 2004). Because of the burden represented by obesity and its increasing prevalence (Swinburn *et al.*, 2011) and the associated economic costs (Finkelstein *et al.*, 2005), this condition remains a challenge for many countries worldwide (Swinburn *et al.*, 2004). Over the last few decades, developing countries have experienced an increase in obesity among their population (Hossain *et al.*, 2007), particularly among the upper middle-income population (Dinsa *et al.*, 2012).

Although certain obesity treatments and recommendations for its prevention and control are well established (Avenell *et al.*, 2006; Seagle *et al.*, 2009), less than one out of five patients succeed in maintaining their weight loss (Wing and Phelan, 2005). Individual engagement (Avenell *et al.*, 2006), environmental factors (*e.g.* access to food healthy choices) (Booth *et al.*, 2001), and public policies also affect weight control (Hill *et al.*, 2005) and help to explain why weight loss interventions are often ineffective. These characteristics represent a greater challenge for groups at risk for obesity, such as women, for whom obesity is more common than for males in many countries (Wells *et al.*, 2012). Furthermore, in developing countries, such as Brazil, gender inequality remains a major challenge to promoting healthy habits (Wells *et al.*, 2012).

Social and environmental factors are important mediators for weight control, and the environment may affect the control of food intake. For instance, appetite is regulated by physiological mechanisms, but an obesogenic environment may lead to overconsumption of food, thus affecting weight gain (Blundell, 2006). Additionally, the

Send correspondence to Louise Farah Saliba. Rua Imaculada Conceição, 1155, Escola de Saúde e Biociências, Pontifícia Universidade Católica do Paraná, 80215-901 Curitiba, PR, Brazil. E-mail: louise.saliba@pucpr.br.

individual response to an obesogenic environment and to different diets may be related to gene polymorphisms (Hetherington and Cecil, 2010; Rudkowska and Perusse, 2012). In this context, the identification of genes and polymorphisms associated with obesity may predict a person's genetic risk for developing obesity. For instance, a personal genome profiling test may identify specific individuals as carriers (Loos, 2012) thus providing the basis for a "personalized" genetic approach to prevent or treat obesity (Bray, 2008). After years of searching for obesity-susceptibility genes (Loos, 2012), several specific genes have been identified.

Among the so-called obesity candidate genes, three genes, *ADRB2*, *ADRB3* and *GHRL* (Rankinen *et al.*, 2006), have been explored because of their link with energy balance. The *ADRB2* and *ADRB3* genes code for β2 and β3 adrenergic receptors, respectively. These receptors are part of the adrenergic system, which stimulates lipid mobilization in adipose tissue (Kurokawa *et al.*, 2008) through the action of catecholamines (epinephrine and norepinephrine) (Insel, 1996; Scofield *et al.*, 2002). The *GHRL* gene codes for ghrelin preprotein, which generates ghrelin, the most powerful orexigenic peptide, that creates a positive energy balance promoting food intake and decreasing energy expenditure (Kojima and Kangawa, 2005).

There are controversies and gaps regarding genes and obesity. Some studies found an association between obesity and polymorphisms of the genes *ADRB2, ADRB3* (Garenc *et al.*, 2003; Pereira *et al.*, 2003; de Luis *et al.*, 2008) and *GHRL* (Korbonits *et al.*, 2002) whereas some did not (Oberkofler *et al.*, 2000; Rawson *et al.*, 2002). In addition, studies comparing the response to a weight loss diet between polymorphism carriers and non-carriers are still lacking, this being a limiting factor for developing a personalized diet for obesity treatment. In the present study we hypothesized that ADRB2 (Gln27Glu, rs1042714 and Arg16Gly, rs1042713), *ADRB3* (Trp64Arg, rs4994) and *GHRL* (Leu72Met, rs696217) polymorphisms may moderate weight loss in adult obese women.

Materials and Methods

Study design

This study was a dietary intervention for weight loss in 109 obese, adult women from southern Brazil. The study design was a quasi-experimental intervention lasting nine weeks (two weeks of pre-intervention and seven weeks of intervention, without a follow-up period) conducted from October to December of 2011 in Curitiba, Brazil.

The weight loss intervention had three components: an individual dietary intervention (three sessions), a nutritional group intervention (two sessions: healthy food choices lecture and nutrition labels reading workshop), and an orientation for physical activity (one session). The six sessions occurred over a period of seven weeks. The individual dietary intervention for weight loss was adapted by a nutritionist from the Nutrient-Gene Interactions in Human Obesity: Implications for Dietary Guidelines (NUGENOB) protocol (http://www.nugenob.org) using the Brazilian Dietary Guidelines (Brasil, 2008) and the American Dietetic Association's position for weight management (Seagle *et al.*, 2009). Diet templates were calculated by a nutritionist and ranged from 1000 kcal to 2200 kcal with two options for dinner - salad, bread and cheese or salad, rice, beans and chicken. Each participant received one diet based on her estimated energy needs, with a 600 kcal caloric deficit. The dinner option was based on previous dietary habits reported at pre-intervention. The individual dietary intervention was supervised by a nutritionist and delivered by undergraduate students of the Nutrition Course at Pontifícia Universidade Católica do Paraná The nutritional group intervention was designed and delivered by a nutritionist, and the physical activity orientation session was designed and supervised by a physical educator.

Participants

The participants were recruited through an advertisement tailored to adult obese women to take part in a research study aiming to reduce and control weight through educational strategies and behavioral changes on local television and radio stations. Those interested in participating attended a study screening at the University Pontifícia Universidade Católica do Paraná. The subjects who met the eligibility criteria were enrolled in the study.

Eligibility criteria for the study included: age ≥ 20 years, female, obese class ≥ I (body mass index ≥ 30 kg/m^2), generally healthy (*e.g.* no co-morbidities reported), pre-menopause (self-reported), not pregnant, non-lactating, ability to read and write and to consent to taking part in the research study. Subjects were excluded if on medication or dietary treatment for weight loss, if suffering from type I diabetes, hypothyroidism, chronic kidney disease or other uncontrolled chronic disease, if have had bariatric surgery, were vegetarian, or were not available to attend the study meetings.

Anthropometric measures

Height was measured at pre-intervention and weight at pre-intervention and post-intervention. The participants were measured without shoes and wearing light clothes. The body mass index (BMI) was calculated as weight (kg)/height^2 (m), and the participants were classified according to obesity class (I to III) (WHO, 2000).

DNA and plasma analysis

Blood samples were collected from participants into tubes with EDTA, and DNA was extracted by a salting out method (Lahiri and Nurnberger, 1991) and diluted to 20 ng/μL final concentration. Genotyping of *ADRB2* (Arg16Gly and Gln27Glu, rs1042713 and rs1042714, re-

spectively) *GHRL (L72M, rs696217)* and *ADRB3* (Trp64Arg, rs4994) polymorphisms were achieved using a TaqMan® SNP Genotyping Assay (*Applied Biosystems*). Reactions were performed in a Mastercycler Realplex 2 system (Eppendorf) with the following protocol: 50 °C for 2 min, 95 °C for 10 min, and 50 cycles of 95 °C for 15 s and 62 °C for 1 min. Previously sequenced control samples representing of each of the possible genotypes (normal homozygote, heterozygote and mutant homozygote) were included in every reaction for each of the four polymorphisms studied.

Statistical analysis

Descriptive data for age, socioeconomic level and employment/study status were presented in categorical levels. Two-way repeated-measures ANOVA (2 x 2) were used to analyze the intervention effect between polymorphisms and the BMI over the period - two groups (carrier and non-carrier subjects) for each polymorphism (Arg16Gly, Gln27Glu, Trp64Arg and Leu72Met) and two periods (pre-intervention and post-intervention) - analyzing the effect of period, group, and the interaction between period and group. Subsequently, socioeconomic status (SES), age and baseline BMI were added as covariates. The same ANOVA analysis was then conducted after stratification for age and SES. SPSS version 19 for Windows was used for all statistical analyses and $p < 0.05$ was considered significant.

Ethical Issues

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation from Pontifical Catholic University of Parana's Institutional Ethics Board and the experiment complied with the current laws of Brazil. Informed consent was obtained from all participants. IEB approval number: (0005306/11).

Results

After advertising the study, 380 subjects attended the screening, 87 were considered ineligible (most with BMI < 30 kg/m^2). Among the 293 eligible participants, 208 attended data collection, 200 started the intervention, and 109 had anthropometrical data collected and gene polymorphisms assessed at the end of the study. Most of the participants were between 30 and 39 years old, with a high socioeconomic level and were employed (Table 1). Regarding the BMI level, Obesity Class I was the most prevalent for participants at pre-intervention and post-intervention, with a shift from Obesity Class I to pre-obese after the intervention.

The weight loss intervention resulted in a statistically significant decrease in BMI over the seven-week period ($p < 0.001$) (Figure 1). Whereas most of the participants (76.9%) had not moved to another BMI, 21.4% of the participants had dropped to a lower BMI category, and 1.7% had gone up one class.

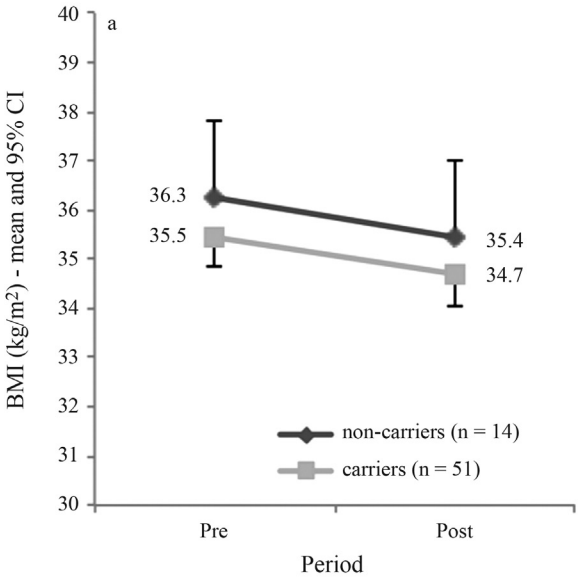
Genotype distributions were in Hardy-Weinberg equilibrium for the four polymorphisms. There was no statistically significant different response to the weight loss intervention between polymorphism carriers and non-carriers (Figure 1). The ADRB2 (Gln27Glu, rs1042714 and

Table 1 - Characteristics of obese women participants in a weight loss intervention study with polymorphisms of the *ADRB2*, *ADRB3* and *GHRL* genes, done in 2011 in Curitiba, Brazil (n = 109).

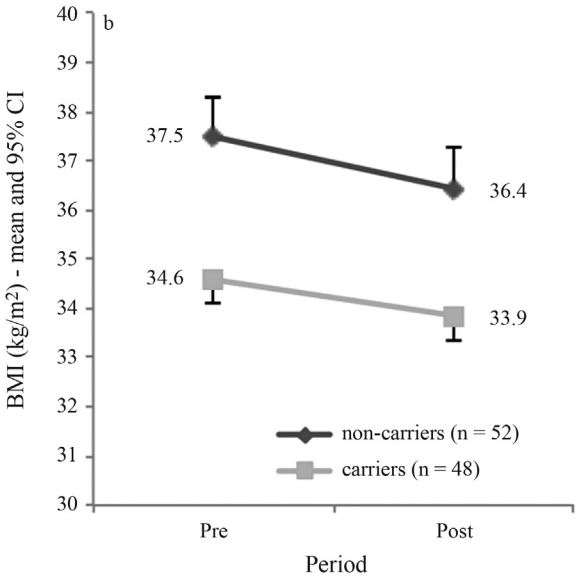
Characteristics	n	%	% missing
Age (years)			
20-29	17	15.6	
30-39	49	45.0	
40-49	35	32.1	
≥ 50	8	7.3	
Socioeconomic status			
High	65	59.6	
Intermediate and Low	44	40.4	
Currently employed (paid job)			
No	29	29.6	10.1
Yes	69	70.4	
Currently enrolled in school/college			
No	77	80.2	11.9
Yes	19	19.8	
Pre-intervention			
Obese Class I (30-34.9 kg/m^2)	61	56.0	
Obese Class II (35-39.9 kg/m^2)	27	24.8	
Obese Class III (≥ 40 kg/m^2)	21	19.2	
Post-intervention			
Pre-obese (25-29.9 kg/m^2)	13	11.9	
Obese Class I (30-34.9 kg/m^2)	53	48.6	
Obese Class II (35-39.9 kg/m^2)	25	23.0	
Obese Class III (≥ 40 kg/m^2)	18	16.5	
Genes			
ADRB2 gene Arg16Gly polymorphism			
Non-carrier	14	21.5	40.4
Carrier	51	78.5	
ADRB2 gene Gln27Glu polymorphism			
Non-carrier	52	52.0	8.3
Carrier	48	48.0	
ADRB3 gene Trp64Arg polymorphism			
Non-carrier	78	77.2	7.3
Carrier	23	22.8	
GHRL gene Leu72Met polymorphism			
Non-carrier	75	72.1	4.6
Carrier	29	27.9	

Arg16Gly, rs1042713), *ADRB3* (Trp64Arg, rs4994) and *GHRL* (Leu72Met, rs696217) polymorphisms did not moderate weight loss in the adult obese women. As no interaction was found between the gene polymorphisms and weight loss, the analysis was adjusted for the covariates SES, age and baseline BMI, but again, no difference was found. Hence only the not adjusted data are presented. Nonetheless, the *ADBR2* gene Gln27Glu polymorphism carriers showed a statistically significant (p = 0.006) lower mean BMI compared to the non-carriers (Figure 1b), thus suggesting a protective effect of the polymorphism.

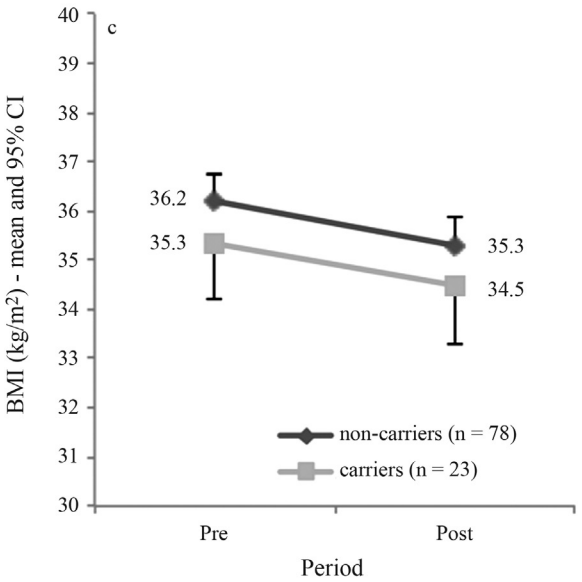
The within-subject analysis for BMI stratified for age did not result in a significant weight loss for younger (20-29 y group) and for older participants (≥ 50 y). The



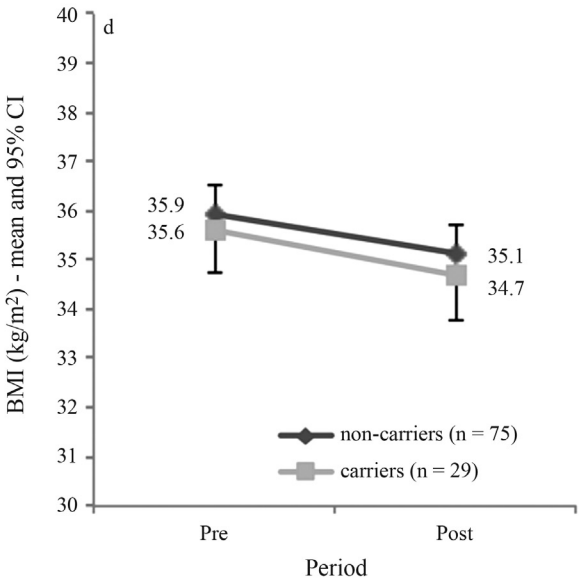
1a) Arg16Gly (for period F = 16.95; p < 0.001; for polymorphism F = 0.28; p = 0.596; for period vs. polymorphism F = 0.05; p = 0.830).



1b) Gln27Glu (for period F = 49.79; p < 0.001; for polymorphism F = 7.87; p = 0.006; for period vs. polymorphism F = 1.22; p = 0.272).



1c) Trp64Arg (for period F = 31.57; p < 0.001; for polymorphism F = 0.47; p = 0.494; for period vs. polymorphism F = 0.02; p = 0.877).



1d) Leu72Met (for period F = 39.05; p < 0.001; for polymorphism F = 0.14; p = 0.709; for period vs. polymorphism F = 0.13; p = 0.718).

Figure 1 - Relationship of body mass index (BMI) and pre and post (period) weight-loss diet intervention and the polymorphisms carrier and non-carriers of (a) the ADRB2 gene Arg16Gly polymorphism, (b) the *ADRB2* gene Gln27Glu polymorphism, (c) the *ADRB3* gene Trp64Arg polymorphism, and (d) the *GHRL* gene Leu72Met polymorphism in the adult obese women.

BMI pre and post-intervention significance was lost for the ≥ 50 y group, except for the Gln27Glu polymorphism of the *ADRB2* gene ($p = 0.013$). For the SES stratified analysis, the weight loss diet intervention resulted in changes in BMI for both high and low SES ($p < 0.05$). The between-subjects analysis for BMI stratified for SES and age, comparing carriers and non-carriers of the *ADBR2* gene Gln27Glu polymorphism, showed a different result. A likely protective effect found for carriers was seen only for the low SES ($p = 0.018$) and the 30-39 y group ($p = 0.036$). The mean BMI difference for the Gln27Glu allele group was 0.43, 0.88, 1.1 and 1.24 kg/m^2 for the 20-29 y, 30-39 y, 40-49 y and ≥ 50 y categories, respectively. The addition of age as covariate to the model ($p = 0.03$) confirmed the tendency shown for the Gln27Glu allele group, showing a concomitant increase in the mean BMI difference across age group.

Discussion

In this study, the polymorphism Arg16Gly, Gln27Glu, Trp64Arg and Leu72Met carriers and non-carriers did not respond differently to the weight loss diet intervention. There was no interaction effect between weight loss and genetic polymorphisms. The differences in genotype did not lead to greater or lesser weight loss. The diet intervention done with adult obese women resulted in a statistically significant weight loss for the groups 30-39 y and 40-49 y, for the Gln27Glu carriers in the ≥ 50 y group, but not for the 20-29 y group. Perhaps due to the small number of participants, the significance was lost in the ≥ 50 y group. Such reasoning may, however, not apply to the 20-29 y group, as the mean BMI difference stratified for age was smaller when compared with the non-stratified analysis. In other words, it seems that the intervention did not result in a significant weight loss for participants with age between 20 to 29 years.

Although the Gln27Glu allele carriers did not respond differently to the intervention, the low SES and the 30-39 y groups showed a lower mean BMI at pre-intervention and after intervention when compared to non-carriers. This difference between carriers and non-carriers suggests a protective effect for the polymorphic allele. It thus seems that Gln27Glu polymorphism carriers in a low SES condition were somewhat protected against a higher BMI when compared to non-carriers. With respect to age, it seems that older individuals responded more strongly to the weight loss intervention. This may be related to a different perception of disease risks and their implications. For the 30-39 y group, the significant result is possibly due to the larger number of participants in this group when compared to the other age categories. Probably there is an interaction effect between weight loss and age, but due to the low number of participants in the other age categories this could not be revealed. This study contributes to the field of nutrigenetics and to the knowledge of obesity-related genotype and the potential weight loss response aiming a personalized diet for obesity treatment.

The ADRB2 and ADRB3 adrenergic receptors play a role in the lipolysis regulation activating lipid mobilization from fat stores (Enocksson *et al.*, 1995; Takenaka *et al.*, 2012), with ADRB2 apparently being the main receptor in this function (Enocksson *et al.*, 1995). Although both are related to the lipid metabolism, and polymorphisms of these genes were seen to cause differences in energy expenditure (Takenaka *et al.*, 2012), we did not find any effect of the *ADRB2* and *ADRB3* polymorphisms in response to a weight loss intervention. For ghrelin, which has a unique capacity to increase food intake and is a central modulator of energy homeostasis (Castaneda *et al.*, 2010), we also did not find an effect between the Leu72Met polymorphism and weight loss response.

Although it is well known that genes are associated with obesity-related traits (Moreno-Aliaga *et al.*, 2005; Rankinen *et al.*, 2006), the understanding is not complete. The results are controversial and most of the studies with *ADRB2*, *ADRB3* and *GHRL* polymorphisms are observational studies. For instance, an observational study by Daghestani *et al.* (2012) found an association between weight gain and the Arg16Gly polymorphism of the *ADRB2* gene, and another (Mattevi *et al.*, 2006) found an association with higher body mass index and waist circumference among men. However, Jalba *et al.* (2008) did not find an association between this polymorphism and obesity, and Lange *et al.* (2005) did not find an association with any of adiposity measures.

Several intervention studies have been conducted, but they are lacking consistent results and an in-depth understanding of the relationship between genes and obesity. Two intervention studies found no differences between carriers and non-carriers and weight loss and weight gain response, respectively (Ukkola *et al.*, 2001b; Ruiz *et al.*, 2011), and their results are consistent with our results, suggesting that the Arg16Gly polymorphism may not be associated with weight loss.

For the Gln27Glu polymorphism of the *ADRB2* gene, the observational studies showed controversial results. For instance, no significant differences were found for obesity-related traits between subjects with and without the *ADRB2* polymorphism (Mattevi *et al.*, 2006) and neither showed an association with obesity in a meta-analysis (Jalba *et al.*, 2008). However, Lange *et al.* (2005) found that the Glu27Glu genotype was associated with higher BMI. Considering intervention studies, the Gln27Glu polymorphism seems to be protective to weight balance, and the results, including ours, show some consistency in this respect. One study (Ukkola *et al.*, 2001b) found that non-carriers of the Gln27Gln polymorphism gained more weight when exposed to long-term overfeeding, and another more recent study (Ruiz *et al.*, 2011) found that women carrying the Gln27Glu allele lost more weight than

non-carriers. These results are consistent with ours - we found that the carriers had a significantly lower BMI at pre-intervention and post-intervention in comparison to non-carriers - although there was no difference in weight loss response between carriers and non-carriers.

The studies on the Trp64Arg polymorphism of the *ADRB3* gene and obesity-related traits also showed contradictory results. Whereas one study found such an association for obese males and females, with the carrier group having a higher weight and BMI than the non-carrier group (de Luis *et al.*, 2008), two studies found no association. In accordance with our results, Rawson *et al.* (2002) found no difference for BMI between Trp64Arg mutation carriers and non-carriers, although, differently from ours, their patients were post-menopausal, and Mattevi *et al.* (2006) found no association between BMI and waist circumference.

For the Leu72Met polymorphism of the *GHRL* gene, the results are even more divergent. One study has shown that the Leu72Met polymorphism is associated with early onset of obesity (Ukkola *et al.*, 2001a), but another (Ando *et al.*, 2007) found no significant differences between the Leu72Met genotype and anthropometric measures relevant to obesity. In addition, this polymorphism seems to be protective for fat accumulation (Ukkola *et al.*, 2002). The lack of diet-induced weight-loss intervention studies and *GHRL* gene polymorphisms limits the comparison with our study.

Candidate gene and genome-wide linkage approaches are used for more than 15 years in the search for genes related to obesity (Loos, 2012). Such studies are useful for identifying the possible genes or related polymorphisms. Once the possible genes or polymorphisms are identified they can be investigated in observational designs and have their hypothesis tested in intervention studies. Our study is a well-controlled intervention, with four important polymorphisms, and adds to understanding the relationship between genes and the weight loss response. This is especially so for Brazil, an emerging country in a nutrition transition (Popkin, 2004), where, to our knowledge, only few studies exist on nutrition and genetics, specifically nutrigenetics, and where most studies were not developed to assess gene effects on weight loss as a primary aim (Moreno-Aliaga *et al.*, 2005).

Notwithstanding, several limitations need to be considered: the lack of intervention studies for comparing the results, especially with *GHRL* genes; the duration of intervention may have been too short, or more specific markers (*i.e.* biochemical or ones related to energy expenditure) are needed to capture an effect. Other limitations are the convenience sample, sample size and missing data for some key variables (*i.e.*, Arg16Gly polymorphism of the *ADRB2* gene) that may have undermined the power to explain negative effects. Furthermore, considering that each genetic polymorphism has some contribution to differences in BMI (Kurokawa *et al.*, 2008), an interaction assessment between genes and polymorphisms should give a better understanding on this relationship. Finally, the lack of data on the external food environment and dietary intake may limit the comprehension of the genes-nutrition interaction.

To better understand the relationship between nutrition and genes, more intervention studies with specific markers, based on functional pathways (Bray, 2008) are needed. In addition, studies identifying the functional significance of a polymorphism, as suggested for a ghrelin single nucleotide polymorphism (SNP) (Ukkola, 2011), including the role of the polymorphisms studied on BMI control, may help to elucidate divergent results and could provide support in hypothesis testing of specific polymorphisms in clinical trials. Studies that assess the food environment may also help to explain results showing the relationship between obesity and genes and environmental factors (Ukkola, 2011; Drong *et al.*, 2012).

Although a personalized nutrition and genetic approach to obesity intervention is expected in the future (Bray, 2008; Abete *et al.*, 2012), it is too early to apply this (Isaak and Siow, 2013). This study was developed specifically to observe the effect of genes on weight loss and adds to the understanding of the relationship between genes, nutrition and obesity. In summary, we did not find an effect between the Arg16Gly, Gln27Glu, Trp64Arg and Leu72Met polymorphisms and the weight loss response to a diet-induced energy restriction in obese women. But the *ADRB2* Gln27Glu polymorphism seems to have a role related to BMI control, as polymorphism carriers in the low SES and 30-39 y groups had a lower BMI compared to non-carriers, suggesting a need for further in-depth investigation. In the context of a personalized diet, this study helps to build the knowledge needed to translate this into evidence-based practice.

Acknowledgments

The study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) scholarship (0194/12-3). The authors are thankful to all study participants and all undergrad students contribution on data collection and analyses.

References

Abete I, Navas-Carretero S, Marti A and Martinez JA (2012) Nutrigenetics and nutrigenomics of caloric restriction. Progr Mol Biol Translational Sci 108:323-346.

Ando T, Ichimaru Y, Konjiki F, Shoji M and Komaki G (2007) Variations in the preproghrelin gene correlate with higher body mass index, fat mass, and body dissatisfaction in young Japanese women. Am J Clin Nutr 86:25-32.

Avenell A, Sattar N and Lean M (2006) ABC of obesity. Management: Part I - Behaviour change, diet, and activity. BMJ 333:740-743.

Blundell JE (2006) Perspective on the central control of appetite. Obesity (Silver Spring) 14 Suppl 4:160S-163S.

Booth SL, Sallis JF, Ritenbaugh C, Hill JO, Birch LL, Frank LD, Glanz K, Himmelgreen DA, Mudd M, Popkin BM, *et al.* (2001) Environmental and societal factors affect food choice and physical activity: Rationale, influences, and leverage points. Nutr Rev 59:S21-S39; discussion S57-S65.

Brasil (2008) Guia alimentar para a População Brasileira: Promovendo a Alimentação Saudável. Ministério da Saúde, Brasília, 210 pp.

Bray MS (2008) Implications of gene-behavior interactions: Prevention and intervention for obesity. Obesity (Silver Spring) 16 Suppl 3:S72-S78.

Castaneda TR, Tong J, Datta R, Culler M and Tschop MH (2010) Ghrelin in the regulation of body weight and metabolism. Front Neuroendocrinol 31:44-60.

Daghestani MH, Warsy A, Al-Odaib AN, Eldali A, Al-Eisa NA, Omer SA and Hassan ZK (2012) Arginine 16 Glycine polymorphism in beta2-Adrenergic Receptor Gene is associated with obesity, hyperlipidemia, hyperleptinemia, and insulin resistance in Saudis. Int J Endocrinol 2012:945608.

de Luis DA, Aller R, Izaola O, Gonzalez Sagrado M and Conde R (2008) Relation of Trp64Arg polymorphism of beta 3-adrenergic receptor gene to adipocytokines and fat distribution in obese patients. Ann Nutr Metab 52:267-271.

Dinsa GD, Goryakin Y, Fumagalli E and Suhrcke M (2012) Obesity and socioeconomic status in developing countries: A systematic review. Obes Rev 13:1067-1079.

Drong AW, Lindgren CM and McCarthy MI (2012) The genetic and epigenetic basis of type 2 diabetes and obesity. Clin Pharmacol Ther 92:707-715.

Enocksson S, Shimizu M, Lonnqvist F, Nordenstrom J and Arner P (1995) Demonstration of an *in vivo* functional beta 3-adrenoceptor in man. J Clin Invest 95:2239-2245.

Finkelstein EA, Ruhm CJ and Kosa KM (2005) Economic causes and consequences of obesity. Annu Rev Public Health 26:239-257.

Garenc C, Perusse L, Chagnon YC, Rankinen T, Gagnon J, Borecki IB, Leon AS, Skinner JS, Wilmore JH, Rao DC, *et al.* (2003) Effects of beta2-adrenergic receptor gene variants on adiposity: The HERITAGE Family Study. Obes Res 11:612-618.

Hetherington MM and Cecil JE (2010) Gene-environment interactions in obesity. Forum Nutr 63:195-203.

Hill JO, Thompson H and Wyatt H (2005) Weight maintenance: What's missing? J Am Diet Assoc 105:S63-S66.

Hossain P, Kawar B and El Nahas M (2007) Obesity and diabetes in the developing world - A growing challenge. N Engl J Med 356:213-215.

Insel PA (1996) Seminars in medicine of the Beth Israel Hospital, Boston. Adrenergic receptors - Evolving concepts and clinical implications. N Engl J Med 334:580-585.

Isaak CK and Siow YL (2013) The evolution of nutrition research. Can J Physiol Pharmacol 91:257-267.

Jalba MS, Rhoads GG and Demissie K (2008) Association of codon 16 and codon 27 beta 2-adrenergic receptor gene polymorphisms with obesity: A meta-analysis. Obesity (Silver Spring) 16:2096-2106.

Kojima M and Kangawa K (2005) Ghrelin: Structure and function. Physiol Rev 85:495-522.

Korbonits M, Gueorguiev M, O'Grady E, Lecoeur C, Swan DC, Mein CA, Weill J, Grossman AB and Froguel P (2002) A variation in the ghrelin gene increases weight and decreases insulin secretion in tall, obese children. J Clin Endocrinol Metab 87:4005-4008.

Kurokawa N, Young EH, Oka Y, Satoh H, Wareham NJ, Sandhu MS and Loos RJ (2008) The ADRB3 Trp64Arg variant and BMI: A meta-analysis of 44 833 individuals. Int J Obes 32:1240-1249.

Lahiri DK and Nurnberger Jr JI (1991) A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Nucleic Acids Res 19:5444.

Lange LA, Norris JM, Langefeld CD, Nicklas BJ, Wagenknecht LE, Saad MF and Bowden DW (2005) Association of adipose tissue deposition and beta-2 adrenergic receptor variants: The IRAS family study. Int J Obes 29:449-457.

Loos RJ (2012) Genetic determinants of common obesity and their value in prediction. Best Pract Res Clin Endocrinol Metab 26:211-226.

Mattevi VS, Zembrzuski VM and Hutz MH (2006) Impact of variation in ADRB2, ADRB3, and GNB3 genes on body mass index and waist circumference in a Brazilian population. Am J Hum Biol18:182-186.

Moreno-Aliaga MJ, Santos JL, Marti A and Martinez JA (2005) Does weight loss prognosis depend on genetic make-up? Obes Rev 6:155-168.

Oberkofler H, Esterbauer H, Hell E, Krempler F and Patsch W (2000) The Gln27Glu polymorphism in the beta2-adrenergic receptor gene is not associated with morbid obesity in Austrian women. Int J Obes Relat Metab Disord 24:388-390.

Pereira AC, Floriano MS, Mota GF, Cunha RS, Herkenhoff FL, Mill JG and Krieger JE (2003) Beta2 adrenoceptor functional gene variants, obesity, and blood pressure level interactions in the general population. Hypertension 42:685-692.

Popkin BM (2004) The nutrition transition: An overview of world patterns of change. Nutr Rev 62:S140-143.

Rankinen T, Zuberi A, Chagnon YC, Weisnagel SJ, Argyropoulos G, Walts B, Perusse L and Bouchard C (2006) The human obesity gene map: The 2005 update. Obesity (Silver Spring) 14:529-644.

Rawson ES, Nolan A, Silver K, Shuldiner AR and Poehlman ET (2002) No effect of the Trp64Arg beta(3)-adrenoceptor gene variant on weight loss, body composition, or energy expenditure in obese, caucasian postmenopausal women. Metabolism 51:801-805.

Rudkowska I and Perusse L (2012) Individualized weight management: What can be learned from nutrigenomics and nutrigenetics? Progr Mol Biol Translational Sci 108:347-382.

Ruiz JR, Larrarte E, Margareto J, Ares R and Labayen I (2011) Role of beta(2)-adrenergic receptor polymorphisms on body weight and body composition response to energy restriction in obese women: Preliminary results. Obesity (Silver Spring) 19:212-215.

Scofield MA, Deupree JD and Bylund DB (2002) Adrenergic receptor genes: cDNA and genomic library construction. Mol Biotechnol 21:171-197.

Seagle HM, Strain GW, Makris A and Reeves RS (2009) Position of the American Dietetic Association: Weight management. J Am Diet Assoc 109:330-346.

Swinburn BA, Caterson I, Seidell JC and James WP (2004) Diet, nutrition and the prevention of excess weight gain and obesity. Public Health Nutr 7:123-146.

Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML and Gortmaker SL (2011) The global obesity pandemic: Shaped by global drivers and local environments. Lancet 378:804-814.

Takenaka A, Nakamura S, Mitsunaga F, Inoue-Murayama M, Udono T and Suryobroto B (2012) Human-specific SNP in obesity genes, adrenergic receptor beta2 (ADRB2), Beta3 (ADRB3), and PPAR gamma2 (PPARG), during primate evolution. PLoS One 7:e43461.

Ukkola O (2011) Genetic variants of ghrelin in metabolic disorders. Peptides 32:2319-2322.

Ukkola O, Ravussin E, Jacobson P, Snyder EE, Chagnon M, Sjostrom L and Bouchard C (2001a) Mutations in the preproghrelin/ghrelin gene associated with obesity in humans. J Clin Endocrinol Metab 86:3996-3999.

Ukkola O, Tremblay A and Bouchard C (2001b) Beta-2 adrenergic receptor variants are associated with subcutaneous fat accumulation in response to long-term overfeeding. Int J Obes Relat Metab Disord 25:1604-1608.

Ukkola O, Ravussin E, Jacobson P, Perusse L, Rankinen T, Tschop M, Heiman ML, Leon AS, Rao DC, Skinner JS, *et al.* (2002) Role of ghrelin polymorphisms in obesity based on three different studies. Obes Res 10:782-791.

Wells JC, Marphatia AA, Cole TJ and McCoy D (2012) Associations of economic and gender inequality with global obesity prevalence: Understanding the female excess. Soc Sci Med 75:482-490.

WHO (2000) Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 894, 253 pp.

Wing RR and Phelan S (2005) Long-term weight loss maintenance. Am J Clin Nutr 82:222S-225S.

Associate Editor: Mara H. Hutz