

# Genetic variants influencing effectiveness of weight loss strategies

Variantes genéticas influenciando a efetividade das estratégias de perda de peso

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## ABSTRACT

Body weight excess has an increasingly high prevalence in the world. Obesity is a complex disease of multifactorial origin with a polygenic condition affected by environmental factors. Weight loss is a primary strategy to treat obesity and its morbidities. Weight changes through life depend on the interaction of environmental, behavioral and genetic factors. Interindividual variation of weight loss in response to different types of interventions (behavioral, caloric restriction, exercise, drug or surgery) has been observed. In this article, currently available data on the role of candidate gene polymorphisms in weight loss are reviewed. Even though control of weight loss by genotype was described in twin and family studies, it is premature to recommend use of genotyping in the design of therapeutic diets or drug treatment. Future studies will have to be large in order to assess the effects of multiple polymorphisms, and will have to control factors other than diet. *Arq Bras Endocrinol Metab.* 2009;53(2):129-138.

## Keywords

Polymorphisms, genetic; gene variant; weight loss; obesity

## RESUMO

A prevalência do excesso de peso cresce no mundo todo. De origem multifatorial, a obesidade é uma doença complexa, com condição poligênica afetada por fatores ambientais. A perda de peso é a estratégia primária utilizada para prevenir e tratar a obesidade bem como suas comorbidades. Mudanças de peso durante a vida dependem da interação entre fatores ambientais, comportamentais e genéticos. Observa-se grande variação da perda de peso entre indivíduos em resposta a diferentes modelos de intervenções (comportamentais, restrições da ingesta calórica, exercícios físicos, drogas antiobesidade ou cirurgias). Este artigo é uma revisão atual da literatura disponível, que busca abordar o papel dos polimorfismos dos genes candidatos à obesidade e sua influência na perda de peso. Apesar da interação do genótipo na perda de peso corporal, descrita nos estudos de gêmeos e familiares, é prematuro recomendar o uso da genotipagem para estratégias de perda de peso. É necessário ampliar as pesquisas sobre os efeitos sinérgicos dos polimorfismos genéticos com coorte maior e associá-los não somente à restrição alimentar mas também às outras intervenções que auxiliam na perda de peso. *Arq Bras Endocrinol Metab.* 2009;53(2):129-138.

## Descritores

Polimorfismo, genético; diversidade genética; perda de peso; obesidade

## INTRODUCTION

Excess body weight is highly prevalent in most countries and the rapid weight gain in the population is likely due to a changing environment (obesogenic environment and behavior), with a misbalance between energy consumption and energy expenditure and individual genetic sensibility to weight gain. Numerous

epidemiological studies have reported that an excess of body weight is associated with a higher risk of developing a number of chronic diseases, such as type 2 diabetes, cardiovascular disease and increased incidence of certain forms of cancer. Treatment or prevention of obesity is advised to reverse or avoid the onset of type 2 diabetes and other obesity-related diseases, and the

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current management of obesity is directed primarily to reduce energy intake and increase energy expenditure. Regulation of body weight and energy homeostasis is subject to complex regulatory mechanisms maintaining balance between energy intake, energy expenditure and energy stores.

There are a number of strategies that can be used to induce negative energy balance and weight loss, such as lifestyle modification including a reduction of energy intake, an increase in physical activity, a behavioral approach, and pharmacological or surgical treatment. Those strategies may result in significant weight loss in obese subjects, however the individual response is very variable. Existence of hypo or hyper responders supports the hypothesis that response to weight loss intervention is related to genetic variation and reliable predictors of successful weight loss are still not well understood. Weight loss is a complex trait that depends on many environmental, behavioral and genetic influences. The gene-environment interaction explains why some individuals are more prone to weight gain than others in a similar environment.

Genetic factors play an important role in weight regulation, since there are genes involved in regulation of energy expenditure, appetite, lipid metabolism, adipogenesis, thermogenesis, cell differentiation.

Association and linkage studies indicate links between candidate obesity genes and body weight, body mass index (BMI), body fat, fat distribution, energy expenditure, fuel oxidation and several other phenotypic characteristics of obesity, including obesity related health risks. More than 600 genes and chromosomal regions have been reported to participate in body weight and energy metabolism regulation. Genes that have been associated or linked to human obesity are numerous, whereas gene-environment interaction in relation to weight change has been studied less frequently.

The strong control of weight loss by genotype was confirmed by studies conducted in monozygotic twins (1). In addition to these, there are studies performed in unrelated subjects evaluating the effect of known genetic polymorphisms on weight loss response after different types of interventions. One must not forget that the candidate genes variants that are associated with weight loss in obese people are often the same variants that were previously associated with obesity and weight gain. These associations among genetic groups might be confounded by differences in baseline measurements of obesity-related variables.

Most studies have focused on weight loss after a single intervention in a relatively homogeneous group where a single or multiple genes were associated and where weight loss was not the primary focus of the study. A few studies were performed where weight loss intervention was primarily carried out in different genotype groups matched by relevant obesity-related variables. Some studies also consisted in controlled intervention trials with different treatment applied to two or more randomized groups, in which weight loss per genotype was not again the primary aim.

These studies relating weight loss interventions are difficult to compare and interpret because they show very heterogeneous populations (men, women, children, obese, overweight, diabetic or pre-diabetic), heterogeneity in the duration and type of treatment (dietary, pharmacological, surgery), difference in the sample size, lack of adequate control groups, contradictory apparent results, difficult to replicate and some possible non-publication of negative results.

Moreover, some groups reported synergetic effects of polymorphisms from different *loci* in the ability or resistance to weight loss therapies. All these interactions increase the complexity of prediction of a response to weight loss with genetic tests approach.

The purpose of this study was to provide an extensive overlook of current evidence, through literature review (2,3) on the role of the genetics on weight loss. This review for time and resource limitation is not an extensive and systematic review. We studied the most plausible candidate genes that are involved in energy balance pathways, body composition changes in response to diet or exercise interventions. We restricted our article to weight loss in excess weight population and didn't focus on weight loss maintenance and weight regain.

A summary of the genes candidates to influencing weight loss in weight loss strategies can be retrieve in Table 1.

## GENES RELATED TO ENERGY EXPENDITURE

Genes encoding proteins that are key regulators of energy balance are likely involved in modulation of body weight response to environmental changes. The change/adaptation of the metabolic rate after weight loss (reduction of fat-free mass) is described as being very variable with individuals: some will decrease and adapt to the new body size, others will decrease more and resist to weight loss. This inter-individual difference suggests genetic make-up effect.

**Table 1.** Selected genes candidates in influencing weight loss in weight loss strategies

Gene	Polymorphism	References first author (year)
<b>Genes related to energy expenditure</b>		
Adreno receptor	<i>ADRB3</i> (Trp64Arg)	Shiwaku and cols. (5), Nakamura and cols. (8), Yoshida and cols. (4), Lee and cols. (10) NEGATIVE: Fumeron and cols. (6), Rawson and cols. (7), Kim and cols. (14); CONTRARY: Xinli and cols. (9)
Uncoupling proteins	<i>UCP1</i> (A-3826G) <i>UCP2</i> (G-866A)	Shin and cols. (16), Yoon and cols. (17)
<b>Genes related to appetite control</b>		
Leptin	<i>LEP</i> (C-2549A) (5'-region)	Mammès and cols. (18)
Leptin receptor	<i>LEPR</i> (Ser343Ser) (T/C)	Mammès and cols. (19), de Luis Roman and cols. (20)
Pro-opiomelanocortin	<i>POMC</i> (R236G)	NEGATIVE: Santoro and cols. 2006 (21)
Serotonin receptor	<i>HTR2C</i> promoter (C-759T)	Pooley and cols. (24)
Neuromedin beta	<i>NMB</i> (Pro73Thr)	Spálová and cols. (25)
Melanocortin receptor	<i>MC4R</i> <i>MCR3R</i> (C17A) (6241A)	NEGATIVE: Hainerová and cols. (22) Santoro and cols. (23)
<b>Adipogenic genes</b>		
Peroxisome proliferator-activated receptor PPAR $\gamma$ 2	<i>PPARG2</i> (Pro12Ala)	Østergård and cols. (33); Adamo and cols. (29); Lindi and cols. (27); NEGATIVE: Niklas and cols. (30), Aldhoon and cols. (31), Stefanski and cols. (32)
<b>Genes related to insulin resistance</b>		
Insulin receptor substrates/insulin-like growth factor	<i>IRS1</i> (Gly972Arg)/ <i>IRS-2</i> (G1057D)/ <i>IGF</i> (GAA1013GAA)	NEGATIVE: Laukkanen and cols. (42)
Insulin 2	Near <i>INSIG2</i> (rs7566605)	Reinehr and cols. (43)
<b>Genes related to lipid metabolism</b>		
Apolipoproteins (apoenzyme)	<i>ApoE e4</i> & <i>ApoB/VNTR</i> <i>ApoA-IV-1/2</i> <i>APO A5</i> (T1131C)	Kee and cols. (34) Lefevre and cols. (35); NEGATIVE: Heilbronn and cols. (36) Aberle and cols. (37), Martin and cols. (38)
Hepatic lipase	<i>LIPC</i> (G-250G)	Todorova and cols. (39)
Perilipin	<i>PLIN</i> (G11482A) <i>PLIN</i> (A14995T)	Corella and cols. (40); NEGATIVE: Deram and cols. (41) Deram and cols. (41)
Acyl-CoA synthetase 5	<i>ACSL5</i> (rs2419621) (C/T)	Adamo and cols. (29)
<b>Other genes potentially related to obesity and synergies</b>		
Plasma factor VII	Arg/Gln353	NEGATIVE: Pankow and cols. (45)
Angiotensin-converting enzyme	<i>ACE1/D</i>	NEGATIVE: Kostis and cols. (46)
Fat mass and obesity associated	<i>FTO</i> (rs9939609)	NEGATIVE: Müller and cols. (47)
<i>ADRB3xIRS-1</i>	Trp64Arg x Gly972Arg	Benecke and cols. (11)
<i>CYP19/COMT</i> (Catechol-O-methyl-transferase)	<i>CYP19</i> 11r/Val108/158Met	Tworoger and cols. (44)
<i>ADRB3xUCP(1or3)</i>	(Trp64Arg) x (A-3826G) or (-55C $\Delta$ ET)	Fogelholm and cols. (13), Kogure and cols. (12); NEGATIVE: Kim and cols. (14)
<b>Genes and drug treatment</b>		
Sibutramine		
Serotonin transporter	<i>SLC6A4</i> (LS/SS)	Vazquez Roque and cols. (49)
G-protein beta 3 subunit	<i>GNB3</i> (C825T)	Hauner and cols. (50)
Phenylethanolamine N-methyltransferase	<i>PNMT</i> (G148A)	Peters and cols. (51)
$\alpha$ 2A adrenoceptor C1291G, 5-HTTLPR, and <i>GNA3</i> C825T genotypes		Grudell and cols. (52)
Mazindol		
Adrenoceptor	<i>ADRB3</i> (Trp64Arg)	Shimizu, Mori (53)
<b>Genes and bariatric surgery</b>		
<i>IL6</i> and <i>UCP2</i>	<i>IL6</i> (G-174C), <i>UCP2</i> (G-866A)	Sesti and cols. (54); Chen and cols. (55)
<i>UCP1</i>	<i>UCP1</i> (A-3826G)	NEGATIVE: Luyckx and cols. (56)
G proteins	<i>GNAS1</i> (T393C), <i>GNB3</i> (C825T) (G814A)	NEGATIVE: Potoczna and cols. (57)

### Adrenergic receptor genes

Adrenergic receptor genes (*ADRB*) play an important role in the adipocyte metabolism, mediating the rate of catecholamine-induced lipolysis. The adrenergic system plays a key role in regulating energy balance through thermogenesis and lipid metabolism.

For the *ADRB3* Trp64Arg polymorphism (the most described), carriers of the Arg64 are more resistant to weight loss for homozygotes (4) or women carrying the allele (5). Other studies did not confirm this association with weight loss studying various *ADRB3* polymorphisms (6,7), nevertheless a resistance to loose visceral fat was described in carriers of Arg64 confirmed by Nakamura and cols. (8). On the other hand, in 2001, Xinli and cols. described a better weight loss in children carriers of Arg64 (9).

An interesting study on Japanese women who completed 12-week lifestyle intervention linked the presence of 64Arg allele to resistance to weight loss, but this association disappeared after adjusting for the percentage change of energy intake (10).

Synergies between *ADRB3* (Trp64Arg) and insulin receptor substrate IRS-1 (Gly972Arg), polymorphisms were described as resistant to weight loss for carriers of both less common alleles (11) in obese women after 13 week intervention.

Synergies between *ADRB3* and *UCP1* were described with a lower loss of weight when both polymorphisms were present (12,13). In 2004, Kim and cols. (14) studied synergies between *ADRB3* and *UCP3* on 224 overweight-obese subjects who underwent a 12-week mild weight reduction program (-300 kcal/day) and separated them in four categories per genotype of *ADRB3* and *UCP3*. Despite similar weight reduction, they observed a higher abdominal adipose reduction in the wild type group and linked the presence of both variants to lower reduction. They observed on a beneficial effect of the weight loss program on wild type and that carriers of variant of *ADRB3* were less beneficial.

*ADRB2*'s polymorphisms were most studied in weight loss maintenance and regain after two years, with a description of the Gly16 carriers being less able to maintain weight loss (15).

### Uncoupling proteins

The uncoupling proteins (UCPs) are a family of carrier proteins located in the inner mitochondrial membrane. Playing an important role in energy metabolism in cells, UCP polymorphisms were described as influ-

encing exercise efficiency, resting energy expenditure, substrate oxidation, energy metabolism, body weight change etc.

*UCP-1* (A3826G) polymorphism was linked to lower weight loss response to a 25% reduction of energy intake (6). This group found that GG homozygotes were more resistant to weight loss. In Korean women, haplotypes of *UCP1* ht3(GAG) was found to be linked to higher weight loss after one month of very low calorie diet (VLCD) intervention (16).

A recent study showed associations with weight loss after VLCD and haplotypes of ten polymorphisms (four of *UCP2* and six of *UCP3*) (17) and concluded that *UCP2-3* polymorphisms were good predictors of reduced body fat in response to VLCD.

## GENES AND CONTROL OF APPETITE

The regulation of food intake involves several genes and the mechanisms are coming clearer. Lately, much attention has been focused on the role of the hypothalamic leptin-melanocortin system.

### Leptin

Lower weight loss was described for the leptin (*LEP*) gene polymorphism in the promoter region 5' (18) and for the carriers of the -2549A allele at position C-2549A, after low-calorie diet in obese women.

### Leptin receptor

Two studies linked effect of polymorphism of leptin receptor (*LEPR*) and weight loss: overweight women carrying the C allele of the Ser (T) 343 Ser (C) polymorphism lost more weight after low calorie diet than non-carriers (19), and the Lys656Asn was shown not to have influence in weight loss (20).

### Melanocortin system genes

Proopiomelanocortin (POMC) polymorphism R236G, even though linked with early onset obesity, showed no influence on the ability to loose weight in three children heterozygous (21).

Mutations on *MC4R*, associated with intense feeling of hunger and hyperphagia in childhood that decrease with aging, were described as not impacting ability to loose weight with a study evaluating influence on weight loss (22).

A clear gene-diet interaction between MC3R Thr6Lys and Val118Ile was recently described in the ability to lose weight (23) in obese children.

### Serotonin receptor HTR

Serotonin is involved in food intake regulation in the central nervous system (CNS). Heterozygous at the *HTR2C* (C759T) promoter is linked to more resistance to weight loss than homozygous CC or TT after weight loss program; some studies concluded that heterozygosity impairs the ability to lose weight (24).

### Neuromedin beta

Neuromedin beta (NMB) is a member of the bombesin-like peptide family expressed in brain, gastrointestinal tract, pancreas, adrenals and adipose tissue. The polymorphism (Pro73Thr) has been linked to higher disinhibition and more hunger and greater body fat accumulation, and was described as influent on the change in fat mass in the Québec Family Study (QFS). Recently, a study linked male T allele carriers of the (P73T) polymorphism to resistance to weight loss, but not in women (25).

## ADIPOGENIC GENES

### Peroxisome proliferator-activated receptor (PPAR)

These genes are involved in regulation of adipocyte growth and differentiation and were already associated with body weight control (26).

PPARG2 is a key transcription factor implicated in adipogenesis, glucose and lipid homeostasis. The polymorphism Pro12Ala was already linked positively to BMI and subjects with impaired glucose tolerance. Homozygotes for Ala12 allele were more successful in losing weight (27) in a three-year study and success in weight maintenance (28). Finally, a recent study (29) observed that this polymorphism was associated in obese women with diet resistance even after correction for baseline BMI.

However, others studies (30) described no differences in weight loss for carriers of Ala12: a study of postmenopausal obese women after six months of hypocaloric diet (they had a higher weight regain after 12 months follow-up), another (31) in obese patients in a four-year period and also in obese with type 2 diabetes (32).

An interesting finding is that diet and exercise have opposite effects on weight loss in Ala12 carriers: they appear more resistant to diet-induced weight loss but more prone to loss on standard exercise training intervention (33).

## GENES OF THE LIPID METABOLISM

### Apolipoproteins

Kee and cols. (34) showed that subjects carrying variant of the Apolipoprotein E (apoE) e4 are more resistant to weight loss.

Apolipoprotein A (apoA-IV) was described to be involved in the regulation of food intake and a study evaluating effect of polymorphism (T-1131C) on weight loss showed that C carriers are more prone to loose weight (35). On the other hand, another study (36) found no difference in weight loss.

Apolipoprotein A5 (ApoA5) plays a role in triglycerides metabolism, and the T-1131C polymorphism was found to be associated with weight loss after short-term dietary restriction in hyperlipaemic overweight men (37) with C carriers showing a higher BMI reduction, factor that was confirmed in another study, in which C carriers lost significantly more weight (38).

### Hepatic lipase gene (LIPC)

Subjects with the G-250A promoter polymorphism showed difference in weight loss, both in control and intervention groups (39).

### Perilipins

Perilipins (PLIN) are a family of proteins that coat the intracellular lipid droplet. They are key regulators of the lipolysis and triglycerides mobilization. Polymorphism (G11482A) was described as influencing weight loss during body weight reduction strategy of low-energy diet; obese patients carrying 11482A allele were more resistant to weight loss after one year (40). This finding was not confirmed in obese children after 20-week lifestyle intervention, although the metabolic syndrome risk was very high among carrier of 11482A allele. Interestingly, another *PLIN* SNP (A14995T) was associated with better weight loss response to the intervention (41). The best response to weight loss was linked to homozygotes of G11482 and 14995T alleles.

### Acyl CoA synthetase 5 (*ACSL5*)

These *ACSL* genes catalyze the production of fatty acyl-CoAs, and a SNP rs2419621 (C/T) was linked to weight loss response to diet in obese women (29).

### GENES OF THE INSULIN PATHWAY

No significant weight reduction was described to genotype in the Finnish Diabetes Prevention Study (DPS), a large study that observed the influence on several variants of genes related to insulin signaling pathway: insulin gene, insulin-like growth factor 1 receptor (*IGF1-IR*), insulin receptor substrate 1 and 2 (*IRS-1* and 2) and more on a lifestyle intervention on overweight subjects with impaired glucose tolerance (42). However, they suggested that lifestyle intervention was not successful in subjects carrying *IGF-IR*, *IRS-1* and *IRS-2* polymorphisms.

Another study described an influence on weight loss when analyzing synergies between carriers of the *IRS-1* (Gly972Arg) polymorphism and *ADRB3* (11).

Recently, a study confirmed that children homozygous CC for the SNP rs7566605 (10kb from the insulin gene 2 (*INSIG2*)) are more resistant to weight loss after one-year lifestyle intervention (43).

### OTHER GENES RELATED TO OBESITY

In 2004, Tworoger and cols. (44) studied two genes and their synergies on weight loss after exercise intervention: subclass 19 cytochrome P450 aromatase (*CYP19*) and catechol-O-methyl-transferase (*COMT*).

*CYP19* contains a tetranucleotide repeat polymorphism (TTTA), from which 11r allele was associated with a higher loss of BMI and total fat after exercise-induced in post-menopausal women intervention. A smaller weight loss was observed in carriers of Met/Met *versus* Val/Val genotype of *COMT*. The best weight loss was linked to carriers of *CYP19* 11r and *COMT* (Val/Val).

The plasma factor VII (Arg-Gln353) gene polymorphism was not linked with ability to lose weight in a six-month intervention in moderately obese men and women (45).

The angiotensin-converting enzyme insertion-deletion (*ACE I/D*) polymorphisms were not linked to weight loss on 86 elderly white overweight hypertensive subjects, but DD carriers showed a significant decrease in blood pressure and therefore weight loss sensitivity (46).

Some very recent strong positive associations with genes like *FTO* and obesity were reported. A recent study did not observe influence on weight loss for the polymorphism (rs9939609) on intervention program for German obese children and adolescents (47).

### GENES AFFECTING RESPONSE TO DRUG TREATMENT OF OBESITY

Studies on drug induced weight loss provide additional evidence that genotyping could be of relevance in predicting efficacy of antiobesity drugs for obesity treatment.

#### Sibutramine

Sibutramine, a promising drug for treatment of obesity, inhibits noradrenaline and serotonin reuptake and also enhances satiety. However a very large variety of weight loss response has been described.

Serotonin transporter is encoded by the gene solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (*SLC6A4*) with long(L) and short(S) alleles.

There is a higher risk of adolescent obesity in S carriers (48) and LS/SS genotype was associated with better weight loss after treatment (49).

The Guanine nucleotide-binding protein (G-protein), beta-3 subunit (*GNB3*) polymorphism C825T was linked to difference in weight loss between control group and group with sibutramine (50) with a higher weight loss on carrier of T allele in the control group and a higher weight loss for the CC homozygotes when treated with Sibutramine.

Phenylethanolamine N-methyltransferase (PNMT) is an enzyme that acts in catecholamine metabolism and catalyses the conversion of norepinephrine to epinephrine. Obese women AA carriers of (G148A) had a better weight loss after 3-month therapy (51) but not after 6 months.

A recent study (52) evaluated overall weight loss effect of placebo vs. sibutramine treatment for 12 weeks on 181 overweight or obese individuals and linked significant response to weight loss for the  $\alpha 2A$  adrenoceptor C1291G, 5-*HTTLPR*, and *GNB3* C825T genotypes. With an enhanced effect with both 5-*HTTLPR* LS/SS and *GNB3* TC/TT, as well as  $\alpha 2A$  CC with *GNB3* TC/TT.

## Mazindol

ADRB3 carriers of the polymorphism (Trp64Arg) showed a resistance to weight loss (53) when treated with mazindol.

## GENES INFLUENCING RESPONSE TO BARIATRIC SURGERY

Interleukin 6 (*IL6*) and *UCP2* genes were linked to weight loss after laparoscopic gastric banding after six-months follow-up (54). Carriers of the C allele of *IL6* G-174C polymorphism and carriers of the G allele of *UCP2* G-866A were more resistant to loose weight.

Several polymorphism of *UCP2* gene were studied and rs660339 (Ala55Val) was linked to greater weight loss after 12 and 24 months for morbidly obese patients who underwent laparoscopic adjustable gastric banding, but this was not observed in the ones who underwent laparoscopic mini-gastric by-pass (55).

*UCP-1* polymorphisms A-3826G was not linked to weight loss after gastroplasty on morbidly obese subjects (56) after three-year follow-up.

None of the G protein (*GNB3*, C825T, G814A and *GNAS1* T393C) polymorphisms were linked to weight loss in a population of 304 obese people, who underwent bariatric surgery (57).

## COMPREHENSIVE MULTI GENE STUDIES

Some comprehensive studies on gene-nutrient interaction have been managed by the Nutrient-Gene Interactions in Human Obesity: Implications for Dietary Guidelines (Nugenob), some are about SNPs others about gene expression.

In 2006, Sørensen and cols. (58), in a study about weight loss, concentrated results from eight clinical centers in Europe (648 obese adults), about 26 obesity candidate genes and 42 SNPs in a ten-week weight loss intervention with low-fat or high-fat diets. The authors did not conclude on any major influence of one particular SNP.

They studied the most frequent genes involved in energy balance regulation and suggested a possible modulation on weight loss of the following genes: pro-hormone convertase subtilisin/kexin type 1 (*PCSK1*), WW domain containing adaptor with coiled-coil (*WAC*), 11-beta hydroxysteroid dehydrogenase type 1 (*HSD11B1*), and tumor necrosis factor-alfa (*TNFA*) –

and also possible link with haplotypes of the glutamic acid decarboxylase 2 (*GAD2*) and ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*). The conclusion was that possibly more severe diet restriction and more duration are required to reveal a possible gene-diet interaction in weight loss intervention.

In 2006, Ruaño and cols. (59) described a significant association with some genes and weight loss during a 4 to 12-week low carbohydrate intervention (CHO 10% of the total energy intake) on 86 normal and overweight healthy adults. Genotyping of 27 SNPs were studied and four had statistically significant association with weight loss: gastric lipase (*LIPF*, rs814628), hepatic glycogen synthase (*GYS2*) (rs2306179), cholesteryl ester transfer protein (*CETP*) (rs5883) and galanin (*GAL*, rs694066).

## CONCLUSION

This review summarizes the current findings on selected genes candidates and their possible role in influencing weight loss in weight loss strategies. The weight loss response to dietary change or to strategies such as exercise, drugs or surgery, is highly complex and with large interindividual variability. The healthy state and prevention of excess weight should have more attention than the bathroom scale.

The real challenge during weight loss is the loss of fat mass, and it is unfortunately accompanied with loss of lean mass; another challenge is a good maintenance of weight loss. Failure to recognize the benefits of exercise independent of weight loss masks opportunities to counsel and educate patients.

The variability of the response to intervention in the numerous interventional studies shows a lack of homogeneous data in order to be able to compare them: ethnicity, physical condition, age, lifestyle differences all are characteristics that combined with length of intervention, sample size make the replication of the studies published difficult. Caution is needed before applying these results to clinical practice. Future studies will have to be large in order to assess the effects of multiple polymorphisms, and will have to control for many factors other than diet.

We reported various contradicting results; for example, in the children population, the results after weight loss intervention are not similar to those observed in adult population (41) – they are even contradictory (9).

This bias could be explained by a different metabolic adaptation to excess weight in young obese, that are not yet in state of resistance to weight loss, but will develop it later in life.

We also reported that losing weight may be more effective for some genotypes than others; furthermore, interventions for weight loss with no apparent effect on weight will have a positive effect on weight will have a benefic effect on metabolic status and were shown to reduce cardiovascular risk factors (36,46). Some individuals will also be hyper responder to weight loss, but will not maintain the weight and, sometimes, the presence of heterozygosity may impair the weight loss success (24).

More and more, the synergies in between genes are being studied and multiple “positive” genotypes can act synergically (44).

Finally, lifestyle factors, such as decrease in energy intake, might mask effect on weight loss (10).

We are still at the beginning of the nutrigenetics studies and this is not enough to start specific personalized nutritional recommendations based on genetic information (60). At present, it is premature to recommend the use of genotyping in the design of therapeutic diets or drug treatment. However, such studies are very useful in identifying the mechanisms by which individuals are successful in losing weight, maintain it and which treatment is the more appropriate. Studies on drug-induced weight loss provide additional evidence that genotyping could be of relevance in predicting efficacy of anti-obesity drugs for obesity treatment.

It is possible that more severe energy restriction and more prolonged weight management program are required to reveal the role played by gene-diet interaction in weight loss programs.

And, a question is raised up about the relation between excess weight and poorer healthy state, since a significant portion of obese individuals can achieve longevity without developing the morbidities associated to obesity. One hypothesis is that total body fat is not the sole source of health complications but the fat distribution is more the determining metabolic risk of the individual. How healthy is it to lose weight for an individual? Is losing too much weight, in a short period of time, health beneficial and more beneficial than losing gradually and maintaining weight loss? What is the toll of yo-yo weight loss on health?

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