Genotype-dependent response to energy-restricted diets in obese subjects: towards personalized nutrition

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Obesity is a complex disease, which in many cases appears as a polygenic condition affected by environmental factors (mainly unbalanced dietary patterns and physical inactivity). In this context, the weight loss response to dietary interventions varies widely and predictive factors of successful slimming including those concerned with the individual’s genetic make-up are poorly understood. Indeed, a number of genes involved in the regulation of energy expenditure, appetite, lipid metabolism and adipogenesis have been reported to affect the risk of treatment failure in some obese subjects. Some candidate genes for the prognosis of weight loss related to energy expenditure are those codifying for the adrenergic receptors (ADBRs) and uncoupling proteins (UCPs), while genes related to appetite potentially affected by energy restriction are leptin (LEP), leptin receptor (LEPR), melanocortin pathways genes (MC3R, POMC) and the serotonin receptor. Furthermore, adipogenesis related genes such as peroxisome proliferator-activated receptor (PPARγ2) and genes related to cytokines such as interleukin-6 (IL-6) and lipid metabolism including hepatic lipase (LIPC), perilipin (PLIN) and lipoprotein lipase (LPL) have also been associated to the weight lowering outcome induced by hypocaloric diets. Therefore, this review shows preliminary evidence from human studies that support the existence of a genetic component in the fat reduction process associated to a negative energy balance.

Key Words: Weight loss, nutrient-gene interaction, obesity, genotype, polymorphism, hypocaloric diets

INTRODUCTION

The personal genetic make-up of humans is involved in body weight homeostasis as well as in body composition stability by regulating processes such as appetite, lipid turnover, adipogenesis, thermogenesis and cell differentiation, etc.¹ Furthermore, the nutrient intake and activity related energy expenditure components of the energy equation are important external factors affecting energy metabolism and utilization, whose metabolic pathways are under the control of specific genes.² In addition, genetic factors may also contribute to the individually differentiated response to energy deficit and the macronutrient intake supplied by hypocaloric diets.³

In fact, several association studies have described interactions between energy-restriction or macronutrient dietary intake with different polymorphisms in obesity candidate genes (β3-adrenergic receptor, PPARγ, UCPs, hormone-sensitive lipase and others) that affect weight loss or obesity risk in genetically predisposed subjects.³ This particular type of nutrient-gene interaction emphasizes the difficulty of examining the impact of polymorphisms in the susceptibility to excessive weight gain. However, it is necessary to establish how environmental factors affect the onset of obesity in individuals with a specific genetic background in order to control the spread of obesity and manage excessive weight gain. This challenge could be successfully approached with the current advances in nutrigenomics and other -omics technologies including the application of bioinformatics tools for genetic, protein and metabolite profiling.⁴ In this context, more than 600 genes and chromosomal regions have been reported to participate in body weight and energy metabolism regulation.⁵ Indeed, the balance in the energy equation, which is continuously challenged by excessive food consumption and sedentary behaviours is, in part, achieved and modulated by changes in gene expression.² Actually, the interactions between genetics and environmental influences such as those concerning dietary intake and physical activity are currently investigated in relation to excessive weight gain and the increasing rates of obesity prevalence.

Furthermore, the weight lowering response of obese subjects to nutritional interventions may vary widely among persons depending on the individual genetic background.³ The characterization of the individual’s genetic background in obese subjects will contribute in the near future to a more

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personalized treatment in situations of excessive body weight as well as to reduce weight regain and yo-yo processes commonly found after weight lowering induced by dietary-based approaches.3

**SUBJECTS AND METHODS**

A selected group of nutritional intervention trials covering previously described nutrient-gene interactions were further analyzed and compared taking into account important variables affecting the energy equation such as BMI changes, fat oxidation, lipolysis and satiety as well as obesity risk and weight loss, maintenance and regain after following a energy–restricted diet.6-18

Thus, data and information concerning several polymorphisms for different genes such as PPAR, ADRB2 and ADRB3, IL-6, LIPC, LEP, LEPR, UCP3 in relation with the role of specific gene variants in the response to the dietary intake on body weight outcomes were reviewed (Table 1).

Phenotypical characteristics such as anthropometrical determinations (BMI, weight changes, waist circumference, etc.), substrate oxidation/lipolysis measurements and dietary intake data were obtained, following validated methods (Table 1) after written consents from all participants, according to the local ethical committees and the Helsinki principles declaration, were obtained.

**RESULTS**

The outcomes resulting from nutrient–gene interactions are variable (Table 1). As a matter of fact, the following are examples in which weight loss is a function of the individual’s genotype affecting a single nucleotide polymorphism (SNP): position C-2549A of the leptin gene, the Arg64 allele of the β3-adrenergceptor gene, the Gln27Glu polymorphism of the β2-adrenergceptor gene, the A-3826G polymorphism of the UCP1, the Ala12 allele of the PPAR gene, a IL-6 polymorphism (-174 G>C), which may interact with the Pro12Ala variant of the PPAR-γ gene and the G-250G promoter polymorphism of the hepatic lipase gene (LIPC). Also, two gene variants of the

<table>
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<td>APO A5</td>
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<td>LEPR De Luis et al.17 (2006)</td>
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MC3R gene have been found to affect weight loss in energy-restricted children, while gene polymorphisms concerning perilipin, Apo A5 and the leptin receptor influence the outcome of different nutritional interventions applicable to fat loss. The genotype-dependent response to energy–restricted diets by obese subjects leading to a personalized nutrition was specifically addressed in the NUGENOB study in which the LIPC–514 C>T polymorphism was identified to be involved in a multiplicative effect depending on the fiber intake, which affects weight gain, while the presence of PPAR and ADIPOQ polymorphisms could also affect the weight loss outcome.

**DISCUSSION**

Nutrigenomics data (i.e nutrient-gene interactions) are often difficult to interpret. Thus, in some studies the hypothesized end–points have been demonstrated, while in others no effect modifications were identified. Some of the discrepancies between experimental trials and association studies may be attributed to differences in the phenotypical characterization (anthropometrical or biochemical determinations, nutrient intake estimations from food frequency questionnaires, food composition databases, etc.), but also by the lack of information about potential confounders such as age and gender as well as by gene-gene interactions. In any case, information concerning the interaction of the macronutrient distribution intake as well as the role of fat or carbohydrate on excessive weight gain that is dependent on genetic make-up is evident for some genes such as PPAR or ADBR.

Furthermore, there are a number of strategies that can be used to induce negative energy balances and weight loss, such as lifestyle modifications including reductions in energy intake, increases in physical activity and behavioural approaches, as well as pharmacological and surgical treatments, which may specifically influence the slimming process in addition to the genetic make-up. In this context, it is worth noting that weight loss can be seen as a complex trait that depends on many environmental, behavioural and genetic factors and that an effective programme for the management of overweight and obesity must take into account all of these factors. Indeed, individual responses to weight loss interventions vary widely and reliable predictors of successful weight loss are poorly understood. Several studies have aimed to identify physiological, behavioural and other predictors of weight loss and/or weight maintenance during dietary, drug or behaviour therapy for obesity. Genetic factors have been described to be associated with a higher risk of treatment failure in some subjects. It would be necessary therefore to take into account the genetic make-up in order to achieve successful long-term weight loss.

A number of genes involved in the regulation of energy expenditure, appetite, lipid metabolism and adipogenesis have been reported to affect body weight regulation and the risk of treatment failure in some obese subjects. Some candidate genes for the prognosis of the weight loss response related to energy expenditure are those codifying for the adrenergic receptors and uncoupling proteins, while genes related to appetite potentially affected by energy restriction are leptin, leptin receptor, POMC, melanocortin and serotonin receptors. Furthermore, adipogenic genes such as PPARγ2 and genes related to lipid metabolism including hepatic lipase and lipoprotein lipase have also been related to the weight lowering outcome induced by hypocaloric diets. Additionally, the large scale European intervention trial NUGENOB concerning the comparison of the impact of more than 40 genetic polymorphisms on weight loss with hypocaloric diets containing different macronutrient distribution revealed that much work is required to be performed in this area and that gene expression profiling is involved in body weight and composition control.

Identification of additional candidate genes may allow for the provision of more “personalized” recommendations (dietary advice, physical activity and/or drug therapy) to achieve effective weight loss and successful long-term maintenance of weight reduction on the basis of an identified genetic predisposition. Therefore, the interactions between the most relevant gene polymorphisms affecting both the amount and composition of weight loss as well as the changes in obesity-associated risk factors depending on the characteristics of the nutritional strategy (energy deficit and dietary macronutrient distribution) are under investigation. Currently, reported gene polymorphisms that may interact with nutrition in successful and long-lasting weight or fat losses are related to appetite control (MC3R, POMC, LEP, LEPR etc.), energy expenditure (UCPs, ADBRs, etc.), lipid metabolism (LIPC, PPAR, APO A5; PLIN etc.) or gene-gene interactions (PPARxIL-6 etc.).

In this context, family history of obesity has also been shown to be a predictor of obesity risk associated with sugar-sweetened beverage consumption affecting specifically BMI changes (kg/m²) in children. Interestingly, the assessment of the potential involvement of the -174 G/C IL-6 variant on weight change derived from the adherence to Mediterranean style based diets (following the PREDIMED intervention study considering groups enriched in either nuts or olive oil), revealed that -174 C allele carriers from a high cardiovascular risk population seem to have protection against weight gain, which was associated to this polymorphism when consuming olive oil or nuts as a part of the prescribed diet.

These observations are consistent with findings from cross-sectional studies that revealed that carbohydrate intake influences obesity risk in carriers of the PPARgamma gene Pro12Ala polymorphism or in women carrying the Gln27Glu beta2-adenreceptor polymorphism.

In the future, the advances in molecular and cell-based genetic biotechnology will ease the way to combine research for new candidate genes, the identification of novel polymorphisms and the profiling of gene expression patterns putatively involved in gene-nutrient interactions concerning weight homeostasis.

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