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Review

Interaction between genes involved in energy intake regulation and diet in obesity

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ABSTRACT

Obesity is a multifactorial, complex, and public health problem worldwide. Interaction between genes and environment as associated with diet may predispose an individual to obesity. In this sense, nutrigenetics appears to be a strategy that can improve understanding of the gene–diet interaction. The aim of this literature review was to summarize data from studies of genes involved in the regulation of energy intake (melanocortin 4 receptor [*MC4R*], fat mass and obesity-associated [*FTO*], ghrelin [*GHRL*], leptin [*LEP*], and cholecystokinin [*CCK*]) and diet interaction in obesity. The presence of polymorphisms in *MC4R, FTO*, leptin, and the respective receptor appear to be associated with higher energy and total lipid consumption. Polymorphisms in *FTO*, leptin, and leptin receptor are also related to increased intake of saturated fatty acids. Individuals with the *MC4R, FTO*, and ghrelin polymorphisms, who submitted themselves for weight loss intervention, appeared to achieve weight loss similar to individuals without polymorphisms in these genes. Additionally, protein seems to interact with these genes, which increases or decreases appetite, or to drive or lessen body weight recovery. Additionally, polymorphisms in these genes were found to be associated with inappropriate eating behaviors, such as increased consumption of sweets and snacks, consumption of large food portions, desire to eat, and eating associated with emotional issues. Preliminary data has supported the gene–diet interaction in determining weight loss and gain in individuals with polymorphisms in the genes involved in energy intake. Despite the advent of nutrigenetics in obesity, it is still too early to define the dietary management for weight loss based on the presence or absence of obesity polymorphisms.

Introduction

Obesity, which has increased worldwide and affects ~13% of adults, is characterized by excessive body fat due to energy imbalance caused by increased energy intake, decreased physical activity, or a combination of both [1]. The balance of energy is important for maintenance of body weight, which is the target of the treatment of obesity [2]. The etiology of obesity is multifactorial, involving gene–environment interactions [3], with environment being responsible for an increase in the prevalence of this disease [1].

Obesity may be monogenic when there is a polymorphism on an individual gene or chromosomal region related to the disease, or polygenic when the polymorphism occurs in a different gene related to the disease. The latter is the most common form, and alleles of various genes, each with little effect on body mass index (BMI), determine the weight of an individual [3].

Many genes associated with obesity are involved in the regulation of energy intake, lipid metabolism, adipogenesis, thermogenesis, adipocytokine synthesis, and transcription factors [3]. Energy intake is a crucial point in weight control and as such it is important to study polymorphisms in genes that regulate the interaction between energy intake and diet [4]. Among these genes are the melanocortin 4 receptor (*MC4R*) fat mass and obesity-associated (*FTO*) genes; leptin (*LEP*), ghrelin (*GHRL*), and their receptors; and cholecystokinin (*CCK*) [5–10]. In this context, nutrigenetics, which is the study of the effect of genetic variations on the nutritional requirements of an individual, can potentially improve the understanding of weight control and can contribute to personalized dietary management [3].

Recently, many reviews have been published about this subject. Reviews by Heianza and Qi [11] and Qi [12] verified the interaction between genes and diet and considered metabolome and gut microbiota and the effect of dietary intervention for weight loss and weight maintenance in the presence of polymorphisms, respectively. However, to our knowledge, no reviews have focused on the polymorphisms of genes involved in the interaction

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between energy intake control and diet. The present study reviewed the literature on nutrigenetics of genes involved in the regulation of energy intake as *MC4R, FTO*, *GHRL*, *LEP*, and *CCK* in obesity.

Genes involved in the regulation of energy intake

MC4R *gene*

MC4R is in chromosome 18 q22 and is expressed in adipose tissue, muscles, brain, and the hypothalamus. It is involved in appetite regulation and energy expenditure and is crucial in the maintenance of body weight [13,14]. Polymorphisms in this gene occur between 2.25% to 4% of the population with severe obesity [15–17].

The arcuate nucleus of the hypothalamus is involved in energy balance. Agouti-related peptide (AgRP), neuropeptide Y, and γ-aminobutyric acid showed orexigenic effects stimulating energy intake and maintaining energy expenditure. On the other hand, pro-opiomelanocortin shows anorexigenic effects signaling the brain to stop food intake. This last produces bioactive compounds, such as α-, β-, and γ-melanocyte-stimulating hormone (MSH) that interact with *MC4R. MC4R* activation through α-MSH promotes satiety, increases energy expenditure, and, consequently, causes weight loss. However, activation of *MC4R* by AgRP stimulates food intake and maintains energy expenditure, driving the individual to gain weight [14,18].

MC4R polymorphism was associated with increased energy intake, promoting weight gain [19,20]. Polymorphism rs17782313 was associated with higher energy and fat intake [20–22] and lower carbohydrate and protein intake [21,22]. The high-fat intake and increase in iron intake were associated with more risk for abdominal obesity in individuals with A allele and GG genotype of the rs12970134 variant, respectively [23] (Table 1).

A high-protein diet appears to increase appetite and craving in individuals with A allele rs72272552 variant, acting on cravings through interaction with the dopaminergic system [24]. Furthermore, the polymorphism of this gene appears to affect eating behavior. Vega et al. [25] reported that higher food intake scores were associated with emotional issues in individuals with C allele in *MC4R* rs17782313, and only women showed an association between BMI and uncontrolled eating. Lower carbohydrate intake is associated with rs17782313 variant, whereas rs2229616, rs17700633, rs571312, rs17700144 is associated with higher intake [20] (Table 1). Carbohydrate intake appears to be dependent on variant.

MC4R polymorphism appears to affect energy and fat intake, increasing their intake and resulting in weight gain. In people with polymorphism in this gene, this could be used as strategy for reduction in energy, mainly from fat intake. Additionally, carbohydrates can be related to this gene; although it is controversial depending on the variant present in the individual.

After 12 wk, obese women with a risk allele who followed a low-calorie diet of 600 kcal/d showed similar weight loss results and a decrease in fat mass compared with women without presence of the risk allele. This study showed that presence of the risk allele does not harm weight loss after calorie restriction [26].

Table 1
Main polymorphisms of genes and the effects on dietary intake

Gene/Genetic variants	Dietary intake
MC4R	
rs17782313	↑ energy and fat intake ↓ carbohydrate and protein intake
rs1270134	↑ fat and iron intake
rs72272552	↑ appetite and craving in high-protein diet
rs2229616, rs17700633, rs571312, or rs17700144	↑ carbohydrate intake
FTO	
rs9939609	↑ SFA, sugar, sweets, and snack intake ↓ appetite and craving in high-protein diet
rs1421085, rs17817499	↑ refined flour intake
rs1121980	↑ SFA intake
GHRL	
rs26311	↓ dairy product, calcium, phosphorus, zinc, and protein intake ↓ motivation to eat
rs2075356 – intron 2	↓ food, dairy products, sugar and calcium, phosphorus, zinc, and magnesium intake ↑ carbohydrates intake
LEP	
rs7799039, rs1137101, 668 A/G A19G, R109K	↑ energy, fat, and SFA intake ↑ sweet intake

FTO: fat mass and obesity-associated; *MC4R*: melanocortin 4 receptor; SFA, saturated fatty acid; *GHRL*: ghrelin; *LEP*: leptin

FTO *gene*

FTO is a nucleic acid belonging to the AlkB family non-heme iron and 2-oxyglutarate–dependent dioxygenases. It is located in position 16 q12.2 and expressed in the brain, hypothalamic arched, paraventricular, dorsomedial, and ventromedial nucleus, all of which are involved in the regulation of energy balance [27].

Twenty-six single nucleotide polymorphisms in the *FTO* gene were associated with BMI; however, rs9939609 variation is the one most often studied. This variant is composed of alleles A and T, with allele A being associated with body fat accumulation [28]. Frayling et al. [29] observed a frequency of homozygous AA of 16%, with 1.2- and 1.3-fold increase for overweight and obesity, respectively.

The mechanisms by which the *FTO* polymorphism contributes to weight gain remain unknown [20]. However, it has been reported that the presence of the polymorphism in this gene affects the sense of appetite and satiety, promoting intake when there is no presence of hunger. The risk allele (A) appears to be open in serum concentrations of leptin and ghrelin, hormones that are involved in appetite and satiety control [30,31]. Additionally, the *FTO* gene plays an important role in adipogenesis, generating new adipocytes and contributing to their maintenance [32] (Table 1).

Individuals with the *FTO* polymorphism showed an increase in calorie [20,33,34] and fat intake [34–36] and it appears that this macronutrient is responsible for the increase in calorie intake [34]. Sonestedt et al. [37] observed that individuals with the *FTO* polymorphism who consumed high-fat diets and low physical activity were susceptible to obesity (Table 1).

Individuals with a risk allele in the rs1421085 and rs17817449 variants showed higher refined flour intake [35], and those with a risk allele in the rs9939609 variant showed higher consumption of sugar, sweets, and snacks. Corella et al. [38] and Philips et al. [39] reported that an increase in saturated fatty acid (SFA) intake in individuals with the *FTO* polymorphism (rs9939609 and rs1121980) appear to have an increased risk for obesity (Table 1).

Adults with the allele A for the rs9939609 variant who consumed a high-protein diet exhibited fewer cravings and reduced appetite [40]. Another study, which tested the acute effect of snacks containing dairy products on the appetite of men, found that volunteers with risk alleles had higher levels of hunger,

increased food cravings, increased appetite, reports of prospective food consumption, and less fullness. However, significant differences in calorie intake in ad libitum meals were not observed [41]. A third study found a high-protein diet to be protective against an increase in BMI and waist circumference [42] (Table 1). These conflicting results suggest that the effect on polymorphism is dependent of protein source. Additionally, a study using dairy products as the protein source included food sources that were high in fat, especially SFAs. The negative effect that might be attributed to protein can be from fat and SFA.

A low-calorie, high-fat, low-carbohydrate diet appears to reduce the resting energy expenditure of individuals who do not have the risk allele for obesity (TT) compared with those with allele A who consume the same type of diet or a low-calorie, low-fat diet [43]. Calorie restriction in obese women with the *FTO* polymorphism does not interfere with weight loss [26]. A meta-analysis revealed that obese individuals with risk allele (A) showed better weight loss compared with those without this allele, being more significant in individuals with AA after a lifestyle change that included calorie restriction, participation in physical activity, or a combination of both [44].

Hormones related to appetite control: Ghrelin, leptin, and cholecystokinin

Ghrelin

Ghrelin is a hormone encoded by the *GHRL* gene [45]. It is located at position 25.3 in chromosome 3 and is secreted by the stomach [46]. Ghrelin stimulates growth hormone secretion, appetite, and food intake [47]. The frequency of the ghrelin polymorphism most studied to date (Leu72 Met [rs696217]) was 8.6% in individuals with metabolic syndrome [48].

Only a few studies evaluated the association between nutrigenetics and the *GHRL* polymorphism. Women following a low-calorie diet, with a calorie restriction of 600 kcal/d, failed to achieve weight loss in the presence of Leu72 Met polymorphism (rs696217) [49]. Other studies evaluated the effects of protein on body weight in individuals who exhibited the *GHRL* polymorphism. A low-protein diet can decrease weight gain in individuals with the risk allele (G) of the rs17032621 variant. On the other hand, a high-protein diet was associated with greater body weight recovery in individuals with polymorphisms in the *GHRL* gene [50].

One study evaluated the relationship among the *GHRL* polymorphism (Leu72 Met), dietary pattern, and food intake. Results showed that the polymorphism influenced calorie, macronutrient, and fiber intake, as well as the dietary pattern [51]. Despite few studies evaluating calorie, protein, carbohydrate, fat, and fiber intake, the authors failed to determine whether a decrease or increase in these dietary components are associated with the polymorphism.

Takezawa et al. [52] evaluated the relationship between food intake and ghrelin polymorphism (−1500 C> G [rs3755777], −1062 G> C [rs26311], −994 C> T [rs26312] {promoter region}, Leu72 Met [rs696217 − exon 2] and + 3056 T> C [rs2075356 −intron 2]) in women. They observed that women with risk allele −1062 G>C (rs26311) had lower intake of dairy products, calcium, phosphorus, zinc, and protein and lower motivation to eat. Those with risk allele +3056 T> C (rs2075356 − intron 2) had lower intake of food, dairy products, sugar and calcium, phosphorus, zinc, and magnesium. Additionally, this latter polymorphism also showed a higher preference for carbohydrate intake compared with fats and proteins [52] (Table 1).

Leptin and its receptor

The leptin hormone is an adiponectin produced mainly by the adipose tissue and encoded by the leptin gene (*LEP*) that is on chromosome 7 q31.1 [53,54]. Leptin and its receptor are involved in energy balance by controlling food intake and energy expenditure in the hypothalamus [55].

G-2548 A (rs7799039) and Q223 R (rs1137101) are the most studied leptin polymorphisms and its receptor, respectively. Boumaiza et al. [56] reported that the frequencies of the polymorphisms in the *LEP* gene and its receptor were 28.12% and 21.88%, respectively. Sabana and Hasnain [57] found that 20.5% of obese adults had a homozygous allele. Moreover, they reported that the occurrence of the polymorphism was higher among obese individuals than among lean individuals [56,57].

Individuals with homozygous AA and RR for leptin and its receptor, respectively, had high-calorie intake [57]. The presence of polymorphism in 668 A/G leptin receptor was associated with increased intake of fat and SFAs. Individuals with higher intake of fat and SFAs have three times higher risk for obesity than those with adequate intake of total lipids and SFAs [58]. De Luis et al. [59,60] did not observe any differences in weight loss among individuals with and without polymorphisms when consuming low-calorie diets rich in monounsaturated or polyunsaturated fatty acids (Table 1).

One study found an interaction between protein intake and the *LEP* polymorphism. Low- or high-protein diets decrease body weight recovery after a 6-mo weight loss maintenance follow-up [50]. Men with a risk allele of rs7799039 variant had less fullness and greater reports of prospective food consumption, but did not differ in calorie intake in the ad libitum meal of men without a risk allele [41] (Table 1).

Mizuta et al. [61] found an association between polymorphism in A19G leptin gene and R109K leptin receptor and increased intake of sweets. Moreover, the leptin receptor polymorphism was found to be associated with body weight gain through increased intake of sweets . Polymorphisms in *LEP* and its receptor were associated with high-calorie intake at night. Furthermore, the polymorphism in the leptin gene increases propensity to eat unhealthy snacks [62] (Table 1).

Cholecystokinin

Cholecystokinin is an anorexigenic gut hormone that also functions as a neurotransmitter. It is located on chromosome 3 position 22.1 [63]. Only one study was found reporting the frequency of the polymorphism in cholecystokinin as 1.9% [4]. Polymorphism in cholecystokinin (*CCK*) gene shows low prevalence, which be the reason for the lack of studies. However, as the *CCK* gene is associated with energy intake, we are addressing two studies published about nutrigenetic in the cholecystokinin polymorphisms in humans.

One study evaluated the association between the food habits of women and the cholecystokinin polymorphism. Results showed the association between polymorphism (GTAA) and consumption of larger food portions [61]. This variant was associated with higher body weight regain after a low-calorie, low-protein diet during the body weight maintenance period [50]. Only two articles limit any conclusion of the relation between diet or eating behavior and cholecystokinin polymorphism.

Conclusion

Few studies evaluated the association between polymorphisms in genes and food intake and nutrients in humans, making it difficult to present nutritional recommendations/guidelines based on the study of nutrigenetics. However, nutrigenetics studies can help in the understanding of the gene–diet relationship and in the definition of new dietary strategies in the future.

Some genes most prevalent (*MC4R, FTO*, *LEP*, and its receptor) are more studied, suggesting an association between increased calorie, lipids, especially SFA intake, with the development of obesity via gene–nutrient interaction. Some variants of ghrelin seem to prevent obesity by promoting lower food intake. Little knowledge of the interaction between the cholecystokinin gene and diet might be due to the low frequency of occurrence.

It appears that the presence of the risk allele polymorphism for obesity in genes addressed in this review does not interfere in weight loss when individuals follow a low-calorie diet. However, the amount of protein intake might help in weight loss or maintenance. Additionally, a diet balanced in macronutrients could contribute to weight maintenance in individuals with a polymorphism in these genes.

Further studies are needed to identify the genes associated with food intake and to determine the populations with a higher frequency of genetic polymorphisms, thus improving the understanding of the gene–diet interaction and its contribution to obesity. Additionally, long-term intervention studies involving obese and non-obese individuals should be performed to evaluate the actual effect of the polymorphism on the response of the organism to the diet employed and its relation to the disease.

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