

Evidences on three relevant obesogenes: *MC4R*, *FTO* and *PPAR γ* .

Approaches for personalized nutrition.

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Abbreviations: BMI: body mass index, GWAS: genome-wide association study, DNA: deoxyribonucleic acid, MC4R: melanocortin 4 receptor, PPAR γ : Peroxisome proliferator-activated receptor γ , SNP: Single Nucleotide Polymorphism, FTO: fat mass and obesity associated gene, MUFA: monounsaturated fatty acid, P:S: polyunsaturated to saturated fatty acids ratio

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Abstract

Obesity is a complex disease that results from the interaction between lifestyle (dietary patterns and sedentary habits) and genetic factors. The recognition of a genetic basis for human obesity have driven to identify putative causal genes to understand the pathways that control body mass and fat deposition in humans as well as to provide personalized treatments and prevention strategies to fight against obesity. More than 120 candidate genes have been associated with obesity-related traits. GWAS (genome-wide association study) have so far identified over 20 novel loci convincingly associated with adiposity. This review is specifically focused on the study of the effects of *MC4R*, *PPAR γ* and *FTO* gene variants and their interactions with dietary intake, physical activity or drug administration on body weight control. The advances in this field are expected to open new ways in genome-customized diets for obesity prevention and therapy following personalized approaches.

INTRODUCTION

Obesity is a worldwide epidemic that predisposes to a high risk of premature mortality [1]. The increased incidence of obesity, particularly in Western societies, is considered to be the result of a change in lifestyle (i.e. less physical activity) and inadequate eating habits (i.e. high quantity and high energy-yielding foods [2], which leads to an increase in adipose tissue mass and fuel metabolism disturbances. However, there is evidence that within a population the variance in BMI (body mass index) is substantially genetically determined [3].

The recognition of an important genetic influence on human obesity have lead to search causal genes in order to understand not only the pathways and networks that control body mass and composition in humans but also to provide insights that will contribute to improved treatment and prevention strategies [4].

Defining obesity

Obesity is a complex disease, which results from an imbalance between energy intake and expenditure, producing an excessive fat depot accumulation [5]. Human adiposity resolves complex interactions among genetic, developmental, behavioural, and environmental influences [6].

Genetic factors are currently estimated to account for 40–70% of the variance in human adiposity [3]. Two complementary experimental designs have been applied to: the candidate gene approach and the genome-wide association study (GWAS) strategy. Candidate genes are selected to be screened for variants associated with obesity based on the putative role of these gene products on the physiology and molecular mechanisms involved in energy homeostasis [7-8].

IDENTIFYING RELEVANT GENE VARIANTS IN OBESITY

Indeed, human obesity has a strong genetic component and many gene regions that may influence an individual's predisposition to gain weight are apparently not yet known. However, the study of extreme human obesity caused by single gene defects has shed light on the long-term regulation of body weight [9]. Monogenic obesity disorders have confirmed that the hypothalamic leptin–melanocortin system is critical for energy balance in humans, because disruption of these pathways causes the most severe obesity phenotypes [2]. Approximately 20 different genes have been implicated in monogenic causes of obesity; however, they account for less than 5% of all severe obesity cases. This outcome suggests that the genetic basis for human obesity is likely to be very heterogeneous, with low contributions from numerous genes acting by various, yet mainly undiscovered, molecular mechanisms. Thus, in most cases, obesity has a polygenic background, having each causative gene variation a small relevance, but a considerable importance in the development of a personalized treatment [10].

The characterization of potential pathways involved in the pathophysiology of the common forms of obesity by means of the identification of genes and mutations is far from being a reality in the majority of the cases. Although, a few hundred of monogenic forms of obesity, caused by single-gene mutations, have been reported, the true number is assumed to be much larger. So far, eleven genes have been implicated in these single-gene cases [11]: *CRHR1* (corticotrophin-releasing hormone receptor 1), *CRHR2*, *MCHR1* (melanin-concentrating hormone 1), *LEP* (leptin), *LEPR* (leptin receptor), *MC3R* (melanocortin 3 receptor), *MC4R* (melanocortin 4 receptor), *NTRK2* (BDNF high-affinity receptor), *POMC* (proopiomelanocortin), *PCSK1* (Prohormone convertase subtilisin/kexin type 1), and *SIMI* (Single-minded 1).

However, most obesity cases are attributed to the interaction of multiple factors including polymorphisms on several genes. There are a number of studies that have analyzed multiple specific gene variants implicated in different biological processes. That is the case of mutations in genes encoding factors involved in the food intake regulation, such as *NPY* (neuropeptide Y) or *ghrelin*; implicated in energy expenditure, as *ADRB2* (beta-adrenoreceptor) and 3 or *UCP2* (uncoupling protein) and 3, in addition to genes controlling adipogenesis such *adiponectin* or *FABP* (fatty acid binding protein) [12].

In the last years, an association between a low grade inflammation and the development of obesity has been described [13]. Thus, the activity of some cytokines secreted by the adipose tissue seems to be associated with pathways implicated in body weight regulation [14]. In this sense, variants on genes encoding these cytokines are being widely studied such as *interleukin 6 (IL-6)* gene polymorphisms [15-16].

The number of genes implicated in obesity is huge and increases very rapidly. In this review, we report findings and outcomes concerning the study of three well documented genes (*MC4R*, *PPAR γ* and *FTO*) involved in body weight and energy homeostasis. The selection criteria were: the most important causative gene of monogenic obesity (*MC4R*), one of the most investigated gene in candidate gene studies and nutrigenetic studies (*PPAR γ*), and the best example of a loci discovered by GWAS methodology and firmly associated with BMI (*FTO*).

Moreover, findings on the interactions of different gene variants and dietary components or drugs on the treatment of obesity are reviewed.

Candidate gene association studies

Candidate gene selection for the study of obesity is based on the knowledge of the biological and/or pathophysiological implication of the gene on this disease [17].

Several genes have been analyzed on large populations or case control studies because of their implication on energy balance on animal models or extreme monogenic cases.

The advances in the field have been very important in recent years reflected by the fact that the last update of the Human Obesity Gene Map (2006), reported 127 candidate genes for which at least one study described a positive association with obesity-related traits [18]. However, these genes appeared to have small effects in many cases but the variant allele is quite common in the population [11]. Moreover, for many of the potential candidate genes, replication in other studies has been often inconsistent, remaining the association not clear. The main problem of the low rate of replication of candidate gene approach seems to be the small sample size of the studies and environment influences [19]. In order to overcome this problem, in recent years, there have been an increasing number of large population studies and also meta-analysis studies of the available data (Table 1) [17].

MC4R

Obesity-related genes participating in neurohormonal pathways frequently have reciprocal effects on energy intake and expenditure, although their primary effect appears to be on the regulation of appetite and satiety [9]. In this sense, the *melanocortin 4 receptor* (MC4R) is a strong obesity candidate gene. This receptor is a 332-amino acid protein encoded by a single exon on chromosome 18q22 [20-21] and is widely expressed in the brain. The endogenous ligand for MC4R is the α -melanocyte stimulating hormone (α -MSH). *MC4R* mutations have been associated with inherited severe obesity in humans [22-23]. Tao *et al.* (2003), proposed a five-type classification of *MC4R* mutations: truncated nonfunctional receptors, intracellularly trapped mutants, binding defective mutants, signalling defective mutants, and those with unknown defects [21]. More than 100 variants in human MC4R have been reported up to date

[24]. About 50% of these variants have a partial or complete impairment or loss of function *in vitro* [25]. Although defects in MC4R seems to constitute the most common form of monogenic obesity, prevalence rates ranging from 0.5% to 5.8%, [26-27], different penetrance or expressivity of the mutations and potential environment interactions configure a variety of obesity phenotypes [24]. The features concerning MC4R deficiency are characterized by several disorders such as hyperphagia, hyperinsulinemia or increased fat mass [2].

The importance of the MC4R mutations in the development of obesity has been confirmed by researches regarding large populations (meta-analysis) and in the high number of emerged loci in GWAS studies [28-30].

PPAR γ

Peroxisome proliferator-activated receptor γ (PPAR γ) encodes a transcription factor (PPAR γ 2) that controls the expression of genes involved in adipocyte differentiation, lipid storage, and insulin sensitization [31]. This gene is one of the most studied as potentially linked to the development of obesity, and especially related to the interactions with lifestyle factors [6, 32-36].

To date one common variant (Pro12Ala) and 16 rare missense and nonsense mutations in the coding region of the *PPAR γ* gene have been identified and functionally analysed [37] The Pro12Ala polymorphism of the PPAR γ 2 protein is the most frequently found genetic variant of *PPAR γ* , whose frequency has been reported to vary from 2% to 25% depending on ethnicity (table 2).

The effects of the 12Ala allele have been studied in functional analysis revealing that the receptor expressing this allele displays reduced DNA (deoxyribonucleic acid)-binding affinity and impaired transcriptional activity in target genes [38]. Therefore, the 12Ala carriers would be expected to be protected against excessive adiposity due to the

reduced functionality of the receptor. However, there are studies in human subjects showing that the 12Ala allele was associated with increased adiposity [39-41]. These contradictory *in vitro* and *in vivo* results might be explained by a potential enhancing effect of the anti-lipolytic action of insulin, which leads to reduced release of free fatty acids [38]. Moreover, conflicting results in human studies could lead to think that Pro12Ala may be interacting with some factors. Indeed, giving these differential effects, mechanistic studies are needed.

A summary of the positive, null and negative associations of the polymorphism with obesity found in Caucasian populations is reported (table 2).

Genes identified by GWAS

Genome-wide association studies had made a reality the challenge to analyze DNA sequence variants of large populations in a single experiment. The first study using this technology was published in 2005 [42], and the first analysing a complex disease, type 2 diabetes, in 2007 [43]. The genome-wide association approach looks into the entire genome, without any previous consideration. The aim is to identify genetic loci, not *a priori* considered as an implicated region, associated with a disease phenotype. This approach may help to clarify the knowledge of the underlying pathophysiology.

Thus, the advantages and benefits of performing a GWAS are clear: the entire genome of thousand samples can be analyzed in a single assay. Despite the strength of the approach it has some limitations that need to be explained. First of all it has to be considered the possibility of false positives due to multiple testing. Moreover, in the case of complex disease as obesity, the heterogeneity of the trait gets more difficult the finding of specific SNPs. Another limitation is that GWAS consider only common SNPs, thus the contribution of many rare SNPs to the trait may remain ignored [44-45].

Anyway, GWAS have revolutionized the field of genetic epidemiology and has already resulted in an unprecedented chain of discoveries with >300 replicated associations for >70 common diseases and traits [17]. This approach have so far identified over 20 novel loci , including genes as *FTO* or the region near *MC4R*, robustly associated with obesity traits, revealing that GWAS is the most productive approach compared to the other gene-discovery methods previously used for common traits [46].

FTO

Approaches based on GWAS have identified common genetic variants that are robustly associated with higher BMI in adults. To date, *FTO* (fat mass and obesity associated) gene polymorphisms appears to have the most important effects on obesity susceptibility [46]. A GWAS initially performed for type 2 diabetes screening identified a common variant in *FTO* (rs9939609), which conferred increased risk for diabetes secondary to its associations with greater body mass index (BMI) in the adult [47]. Simultaneously, another GWAS in relation to BMI confirmed the association between *FTO* gene variants and this adiposity index [48].

The *FTO* gene is composed of nine exons that span more than 400 kb on chromosome 16. Several SNPs were initially identified by Frayling *et al.*[47], Dina *et al.* [49] and Scuteri *et al.*[48]. They are located in the first intron of the gene, a region where the sequence is strongly maintained across species. It is known that *FTO* encodes a 2-oxoglutarate-dependent nucleic acid demethylase, and that it is located in the nucleus [50]. The biological action of *FTO* in humans remains to be fully established [51], although there is increasing evidence for associations between *FTO* genotype and differences in eating behaviour, satiety and dietary intake, but not in energy expenditure, at least in children [52-53]. The most studied variant in *FTO* gene is the

rs9939609 T/A that has been associated with higher body weight and [52-53] higher risk of obesity in different studies and populations [47-48, 54-56].

This polymorphism is currently being widely studied in children cohorts due to its potential implication in the development of obesity at this early stage [57]. Thus, a summary of the association between rs9939609 and obesity as found in children studies is shown (table 3).

The identification of implicated loci in BMI variation has led to the study of new genetic areas. However the analysis of the genetic predisposition of individuals for obesity taking into account these loci has revealed that they explain a low percentage of variance in BMI. In this sense, the combination of the additive risk of two common variants in *FTO* and near *MC4R* genes widely associated with BMI, account for less than 2% of the variance in adult BMI in a 77000 subjects population [8, 29, 47]. When the effect of other discovered loci as are considered, this percentage does not improve [30], suggesting that although *FTO* and *MC4R* are highly associated with BMI they can not explain *per se* the development of obesity.

Prevention and treatment based on genotyping

Current obesity investigations based on genotyping are directed to prescribe a personalized treatment. Indeed, obesity is infrequently originated by one gene (monogenic obesity), and usually depends on various factors such as several gene variations and their interactions with lifestyle factors. Thus, the prevention and treatment of obesity must be independently considered in each case considering the individual's potential response to lifestyle modification or drug treatment depending on the genotype.

Nutrigenetics

Nutrigenetics is a growing science that studies the response of individuals to a dietary component or components depending on the genotype [58-59]. There are some studies analyzing the interaction between dietary components or dietary patterns and genetic variants on adiposity. Most of these studies are conducted within cross-sectional designs. However, the best approach to analyze the effects of a mutation on obesity parameters appears to be on the frame of a nutritional intervention [60-61].

Probably, the most studied gene in relation to the interactions with dietary components on adiposity features is the *PPAR γ* , and specifically the Pro12Ala gene variant (table 4). The majority of the studies have been directed to the interaction between fat intake and Pro12Ala due to the fact that free fatty acids are natural agonists of the *PPAR γ* transcription factor [62]. Nevertheless, the relationship between the variant and carbohydrate intake or alcohol consumption have been also analyzed in different studies [33, 35, 63].

Related to the total fat intake, in the Quebec Family Study population (2003), an interaction between the Ala12 variant and total fat intake associated with higher BMI and waist circumference was found [64]. Memisoglu *et al.* (2003), found a significant interaction between total fat intake and BMI. The highest quintile of total dietary fat was associated with increased risk of obesity among Pro12Pro subjects [34]

Related to unsaturated fatty acids, Luan *et al.* (2001) found that Ala12 carriers showed an inverse association between the dietary polyunsaturated to saturated fatty acids ratio (P:S) with BMI [32]. In this sense, Franks *et al.* (2004) reported that carriers of the Ala12 allele, who had high dietary P:S and were physically active, had lower fasting insulin levels [65]. Moreover, in a case-control study, Ala12 carriers with increasing intake of arachidonic acid presented a higher risk of obesity [35]. Furthermore,

Memisoglu *et al.* (2003), found that intake of monounsaturated fatty acids (MUFA) was inversely associated with BMI in Ala12 allele-carriers but not in Pro/Pro homozygotes, in a larger population [34]. Additionally, Soriguer *et al.* (2006) found that the low consumption of MUFA in obese Ala carriers was associated with higher HOMA values in a healthy Spanish population [66].

Apart from fat intake, Marti *et al.* (2002) reported an increased obesity risk for Ala12 carriers when consuming more than 49% of total energy from carbohydrates [33]. Furthermore, other studies have analyzed the association of the polymorphism and alcohol intake. Results obtained by the European Project on Genes in Hypertension showed that elevated alcohol consumption in Ala12 carriers was associated with higher serum HDL cholesterol levels [63].

Recently, a substudy of the PREDIMED intervention trial, found that a Mediterranean dietary pattern rich in virgin olive oil or nuts was able to reverse the negative effect that the12 Ala allele had in waist circumference. Thus, 12Ala carriers that consumed a Mediterranean-style diet during 2 years had similar waist circumference enlargement compared to Pro12Pro subjects. In contrast, 12 Ala carriers that followed a conventional low fat diet had a significantly higher waist circumference compared to non mutated subjects [67].

Moreover, also in a recent trial with Pro12Ala mutant knock in mice, it was demonstrated that the effects of *PPAR* γ Pro12Ala variant on metabolic control is diet-dependent, especially when comparing dietary fat content [68].

Currently, the most studied gene in relation to the interactions with lifestyle factors is the *FTO* gene, and especially the rs9939609 variant. Related to dietary interactions, Sonestedt *et al* (2009) found in a crosssectional study that there was a significant interaction between fat intake and *FTO* genotype and also between carbohydrate intake

and *FTO* genotype on BMI [69]. There are also some nutritional intervention studies analyzing interactions with this gene variant [55, 70]. However, most of the interventional studies are directed to a complete lifestyle intervention including physical activity and dietary changes especially in children [54, 71-72].

Physical activity-genotype interactions

The diagnosis of interactions between physical activity level and gene variants tries to find a personalized therapy for subjects genetically predisposed to develop obesity. Given the fact that the *FTO* gene appears might participate in controlling energy expenditure, variations on this gene are receiving attention in the study of gene variation-lifestyle interactions on body weight. Therefore, the outcomes obtained up to now related to the interactions between *FTO* gene variants and physical activity on children and adult populations are reviewed (table 5).

In this context, concerning the rs9939609 Hakanen et al., did not find any significant association between leisure time physical activity in an adolescent cohort of the STRIP study [54]. In contrast, Ruiz et al, found that the rs9939609 was associated with higher BMI, body fat and waist circumference but this effects were attenuated in adolescents who met the daily recommended physical activity [73].

In adults, Andreasen *et al.* (2008), found that physical inactive Danish subjects carrying the A risk allele had higher BMI compared to wild type subjects (TT), suggesting that low physical activity may accentuate the effect of *FTO* rs9939609 on body fat accumulation [74]. However, three adult studies in other European populations [70, 75-76], found no evidence of interaction between physical activity and this *FTO* gene variant on body weight (Table 5).

Other *FTO* gene variants have been investigated in relation to their interactions with physical activity on BMI. Thus, Mitchell *et al.* (2009), found that the A allele of

rs8050136 gene variant was associated with higher BMI at baseline, but after following the physical activity recommendations of the intervention program, AA subjects were found to have a higher weight loss in comparison to CC subjects [77]. In the EPIC-Norfolk cohort, Vimalleswaran *et al* (2009), found that T risk allele of rs1121980 was associated with BMI and waist circumference, but physical activity level was able to attenuate this effect [78]. Moreover, Rampersaud *et al* (2008), found that two *FTO* gene variants, rs1477196 and rs1861868, were associated with BMI and obesity only in those subjects with a low level of physical activity [79] (Table 5).

Drug-genotype interactions

The increasing epidemic of obesity is leading to look for new strategies on the prevention and treatment of this disease. The first approach is to configure lifestyle patterns (including dietary and physical activity changes), however, long-term lifestyle modification suffer from lack of individual's compliance. Moreover, subjects with a potent genetic susceptibility need even more than a radical lifestyle change [80]. In this context, pharmacotherapy appears to be a suitable approach to treat obesity. Three common drug therapies have been applied in the treatment of obesity: orlistat, a lipase inhibitor, rimonabant, a selective cannabinoid-1 receptor antagonist, and sibutramine, a central appetite suppressant. However, only the first one can be now prescribed to fight against obesity in Europe. There are several genes that can be considered good targets for this therapy, but it remains important to take into account gene variants that may modify the effect of the potential therapy. Indeed, pharmacogenetics is the study of how genetically determined variations affect an individual's response to drugs. It is well known that adverse side effects and therapeutic failure of drugs may both have a strong genetic component [81].

Sibutramine, a noradrenergic and serotonergic reuptake inhibitor, has been administered for the long term treatment of obesity [82]. Sibutramine induces satiety, prevents decline in metabolic rate associated with hypocaloric diets and causes weight loss especially when combined with behavioral therapy. Furthermore, there are large differences in weight loss among individuals treated with sibutramine. Thus, there were studies analyzing the potential interactions between this drug and gene variants that may affect weight loss. Grudell *et al.* (2008) found that sibutramine interacted with specific markers of candidate genes controlling serotonergic and adrenergic mechanisms ($\alpha 2A$ -receptor, *5-HTTLPR* (serotonin-transporter-linked promoter region) and *GN β 3* (G-protein β subunit polypeptide 3)). Treatment with sibutramine resulted in significantly greater reduction of weight and body fat for specific $\alpha 2A$ CC and *GN β 3* TC/TT genotype variants [83]. Furthermore, Vazquez Roque *et al.* (2007), also found that response to sibutramine was mediated by the *SLC6A4* (solute carrier family 6 member 2) genotype [84]. Anyway, as stated before, the prescription of this reuptake inhibitor has been forbidden, in Europe, since January 2010.

Although sibutramine was used as a possible treatment for obesity, there are other studies looking for new therapies and, of course, studying the potential interactions with gene variants. In an interventional study with lifestyle modifications and capsinoid administration, Snitker *et al.* 2009, found that the 585Ile allele of *TRPV1* (transient receptor potential cation channel) gene and -866A allele of *UCP* (uncoupling protein) gene are associated with a higher abdominal fat reduction [85]. On the other hand, Spraggs *et al.* (2005), evaluated the efficacy of GW320659 ((2S,3S,5R)-2-(3,5-difluorophenyl)-3,5-dimethylmorpholin-2-ol), a highly selective neuronal norepinephrine and dopamine re-uptake inhibitor, in the treatment of obesity. They found that polymorphisms in *SLC6A2* and *GRIN1* (glutamate receptor, ionotropic, N-

methyl D-aspartate 1) were associated with increased weight loss when treated with GW320659 [86].

All these results suggest that the study of potential interactions between specific polymorphisms and drugs could be used to maximize effective obesity pharmacotherapy by identifying patients that may be predisposed to a particularly treatment weight loss response.

Conclusions and future of individualized treatments of obesity

Obesity is actually a multifactorial disease and, consequently, involves a complex prevention and/or treatment strategies, which means that there is no universal treatment that would be beneficial for every obese patient. All the published studies to date are giving light to the fact of needing a personalized treatment for each obese subject.

As the genetic contribution to the variance in human adiposity is estimated to account 40-70%, it is clear that the prescription of future individualized treatments may need the knowledge of the subject genotype. For this purpose it is important to know now those genes and gene variations that are really important to take into account within a customized therapy. Furthermore, it would be essential to assess if there are interactions with the individual genotype and potentially modifiable lifestyle factors, especially dietary components and physical activity, and/or with potential drug treatments. Moreover, intervention studies have to be carried out on a large number of individuals to find robust results because of the small implication of each single SNP on body weight control.

Moreover, to design an individualized nutrition other factors may have to be considered as epigenetics or nutrigenomics. Epigenetics has been defined as the study of heritable changes in gene expression that occur in the absence of a change in the DNA sequence itself. Increasing evidence indicates that early metabolic programming contributes to

increasing obesity prevalence in children and adults. Metabolic imprinting is involved in the establishment of set points for physiological and metabolic responses in adulthood. Recent studies suggest that changes in the dietary pattern may modify the imprinting.

Considering the results of nutrigenetic, nutrigenomic and epigenetic studies, a personalized intervention for the patient may be defined in the future. At present, it seems an optimistic view, but i.e. there are trials seeking to design DNA microchips that may be used to identify the more relevant mutations in the development of obesity and treatment outcomes.

It seems evident, that individuals genetically predisposed to obesity are going to benefit more from a specific treatment than subjects less susceptible that are benefited from standard treatments. Indeed, the high and increasing prevalence of obesity reveals that traditional treatments do not lead to a successful result in many cases.

At present, the best therapy appears to be a combination of modification in dietary habits and physical activity level and, in severe obesity cases, the application of drug treatment according to subject genotype. But in the future, it is expected that genotype based interventions will be more relevant on the customized obesity therapy.

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