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ETIOLOGY OF OBESITY (JA MARTINEZ, SECTION EDITOR)

Genetics of Obesity

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Abstract Obesity is becoming an escalating global epidemic in many parts of the world and results in a huge rise of sanity costs due to its associate comorbidities. In this sense, body weight regulation depends on a combination of interactions between genetic and environmental factors. Among inheritance factors, body weight is normally a polygenic condition determined by the presence of genes of high prevalence but with a low relevant effect. In the last years, Candidate Genes Analyses and Genome Wide Association Studies (GWAS) have become very useful strategies to detect new polymorphisms and copy number variants (CNVs) associated with obesity and its related comorbidities. From these studies, more than a hundred genetic variants involved in metabolic pathways including adipogenesis, energy intake, lipolysis or energy expenditure have been found. These findings along with epigenetics and nutrigenetics are the basis to the development of new tools that would allow predicting individual obesity susceptibility and weight loss response.

Keywords Genetic variant · Body mass index · Obesity · Genome wide association studies · Copy number variant · Epigenetics · Nutrigenetics · Genetics

Introduction

Obesity and overweight are becoming a growing and global epidemic that is taking over many parts of the world, not only developed, but also developing countries. As such, it involves a serious threat to public health, including a higher risk of developing associated disorders as type 2 diabetes, hypertension, cardiovascular disease or inflammatory disorders among others [1]. Therefore, it also leads to a considerable rise in health costs [2].

Body weight is determined by a combination of genetic and environmental factors related to lifestyle (diet, physical activity or sedentary lifestyle), as well as by interactions between those factors [3, 4]. Therefore, obesity appears as a consequence of a positive energy balance involving any alteration in one or several of these factors.

The hereditary component of body weight regulation was studied for the first time in the first decades of the twentieth century, but until recently, there were no objective and consistent data about specific genes involved in obesity development and onset. In 1994, the discovery of ob gene and leptin by Friedman et al. [5], contributed to promote a significant progress in the knowledge and understanding on the genetic component of body weight regulation. Twin, families and adoption studies have revealed that genetic factors could be responsible of a 50- 80 % of a population BMI variation [6].

Increasing study concerning the genetics of obesity has allowed that in the last two decades, from few genes associated to adipose accumulation known in 1994, more than 50 *loci* that could be related to obesity predisposition have been identified [7].

Monogenic Obesity

From the available data, monogenic obesity caused by a single polymorphism accounts for about a 5 % of the total obesity cases. In those cases is well established that some genetic variations in several genes that codify for proteins implicated in appetite regulation and satiety are responsible for pathologic alterations whose more obvious phenotype is obesity [8]. Up to now, about 11 genes have been associated to this type of obesity (Fig. 1).

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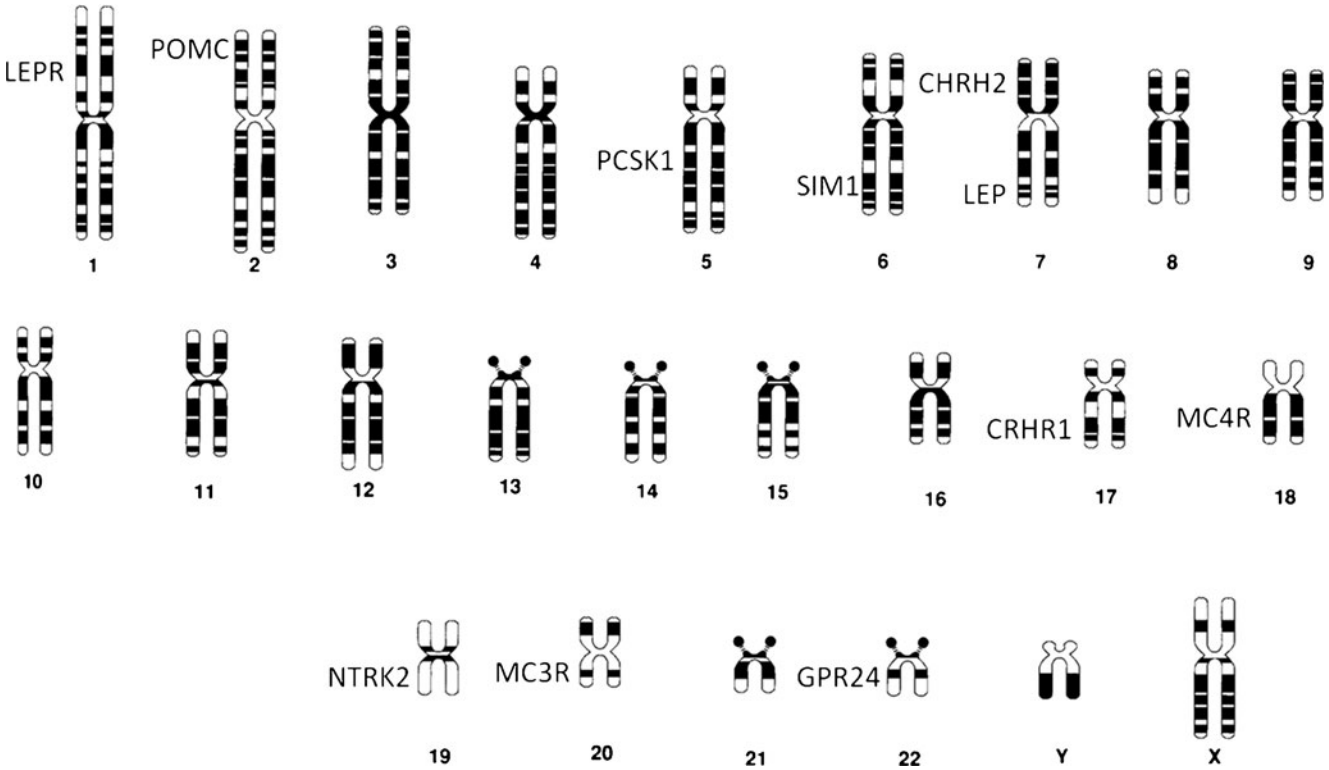

Fig. 1 Genetic map for monogenic obesity genes and its distribution range throughout chromosomes

Among these genetic variants, those in genes *LEP, LEPR, POMC, MC4R* and *PCSK1* are especially important, since this five variants account for the 5 % of severe obesity cases of early development in children [8].

Polygenic Obesity

Concerning the study of polygenic obesity, two main strategies have been applied. Candidate genes studies were the first approach followed by genome wide association studies. Nowadays, these genome wide association studies are the more frequent tool used for the discovery of new genetic variants associated to obesity.

In addition to these two approaches, in the last years, copy number variations (CNVs), a structural alteration of DNA that results in an abnormal number of copies of one or more sections of the DNA as well as epigenetic processes and nutrigenetics have been developed as new strategies to search for obesity causes.

Candidate Genes Studies

Polygenic obesity is determined by the presence of genes of enough prevalence but with a relatively low effect [9]. The last *Human Obesity Gene Map* actualization [7] describes more than a hundred obesity candidate genes in this situation.

The candidate obesity gene approach analyze genes involved in key metabolic pathways or those that have been shown to be important for obesity development in animal studies [6]. However, a significant constraint of these studies is their reduced sample size that prevent them from having the necessary power to identify modest genetic effects on obesity [10]. To overcome this limitation, in the last years, studies with a high number of participants and meta-analyses that gather the published information have been carried out and from them, strong associations between obesity and several genetic variants have been found [10]. Some of the most important polymorphisms involved in obesity found by candidate gene analyses are included (Table 1). These genetic variants are located in genes participating in different fuel homeostatic processes: energy intake (*INS, LEP, MC4R, NPY, POMC, AGRP, CARTPT, FTO* or *LEPR*) [11, 12], energy expenditure (*CLOCK, ADRB2, ADRB3, UCP1, UCP2* or *UCP3*) [13, 14] or adipose tissue growth and development (*PPARG2, CEBPA, IL6, FABP4, CD36, PNAPLA3* or *PLPIN5*) [15, 16].

Genome Wide Association Studies

Nowadays, the most common and useful tool to detect new genetic variants associated with obesity and its related comorbidities are Genome Wide Association Studies

Table 1 Some genes showing polymorphisms involved in obesity development according to candidate genes studies along with their location and their main function within metabolism

Function	Gene	Location
Involved in dietary intake	INS	11p15.5
	LEP	7q31.3
	MC4R	18q22
	NPY	7p15.3
	POMC	2p23.3
	AGRP	16q22
	CARTPT	5q13.2
	FTO	16q12.2
	LEPR	1p31
Involved in energy expenditure	ADBR2	5q31-q32
	ADBR3	8p12
	UCP1	4q28-q31
	UCP2	11q13
	UCP3	11q13.4
	CLOCK	4q12
Adipose tissue growth and development	PPARG2	3p25
	CEBPA	19q13.11
	IL6	7p21-p15
	FAB94	8q21.13
	PNPLA3	22q13.31
	PLPIN5	19p13.3

(GWAS). The basis of these studies is to compare the genome of a group of people with the trait under study (cases) and another group of people without it (controls) in order to detect genetic variants associated with this trait. In comparison with candidate gene studies, the three main advantages of GWAS are that they are more profitable, have much higher resolution and allow the analyses of higher sample sizes providing solid findings [17].

The first gene that was unquestionably related to obesity from GWAS analysis and after being replicated in different populations was *FTO* (fat mass and obesity associated gene) [18–20]. Since then, more waves of GWAS for BMI, with a final sample size of 123,865 individuals, have been performed identifying 32 *loci* significantly associated with this trait [21•, 22–24]. The discovery of these new *loci* is of great importance since it allows that new biological pathways involved in the development and onset of obesity could be studied in depth.

Among the waves of GWAS for BMI, six *loci* have been confirmed to have a strong association with this trait. These *loci* are located in *FTO* gene, near *MC4R*, near *KCTD15*, near *NEGR1*, near *TMEM18* and in *SH2B1* gene [21•]. The *loci* significantly associated with BMI after GWAS are shown in Table 2.

FTO gene (Fat Mass and Obesity Associated Gene)

FTO is a very highly conserved gene among vertebrates [4]. It is composed of nine exons that span more than 400 Kb on chromosome 16. This gene codifies for a 2-oxoglutarate dependent nucleic acid demethylase located in the cellular nucleus [25]. It is mainly expressed in the brain, in a particular area of the hypothalamus, besides muscle, adipose tissue, pancreas and heart among others organs [18].

Fto gene was described for the first time in 2002 in a murine animal model (Ft) with a deletion in the region where this gene is localized [26]. In 2007, two different

Table 2 Nearest genes to *loci* discovered throughout Genome Wide Association Studies (GWAS), and BMI increase (kg/m^2) per risk allele in the genotype

Loci	Genome Wide Association Studies (GWAS)	BMI increase (kg/m^2) per risk allele
FTO	[19–21]	0.39
Near TMEM18	[19–21]	0.31
NearMC4R	[19–21]	0.23
SH2B1	[19–21]	0.15
Near NEGR1	[19–21]	0.13
Near KCTD15	[19–21]	0.06
Near SEC16B	[19–21]	0.22
BDNF	[19–21]	0.19
Near GNPDA2	[19–21]	0.18
NearETV5	[19–21]	0.14
Near FAIM2	[19–21]	0.12
MTCH2	[19–21]	0.06
SLC39A8	19	0.19
Near GPRC5B	19	0.17
Near PRKD1	19	0.17
QCPTL	19	0.15
Near RBJ	19	0.14
TFAP2B	19	0.13
MAP2K5	19	0.13
NRXN3	19	0.13
LRRN6C	19	0.11
Near FLJ35779	19	0.10
Near FANCL	19	0.10
CADM2	19	0.10
Near TMEM160	19	0.09
Near LRP1B	19	0.09
MTIF3	19	0.09
TNN13K	19	0.07
Near ZNF608	19	0.07
Near PTBP2	19	0.06
Near RPL27A	19	0.06
NUDT3	19	0.06

studies demonstrated the relevance of *FTO* gene to humans [19, 20]. Frayling et al. (2007) identified the *FTO* gene through a genome wide association study comprising 1924 type 2 diabetes subjects and 2938 controls. This study associated several *FTO* polymorphisms with diabetes, and this association was mediated by BMI [17]. Another GWAS study regarding BMI in 6148 subjects of Sardinia, found a strong association between several *FTO* gene variants and BMI [20]. Similar results have been subsequently obtained in various Caucasian populations, especially among children [27]. *FTO* polymorphisms have been also related with obesity associated traits as body weight [12, 28], leptin levels [29], body fat mass or waist circumference [28, 30].

In this context, rs9939609 polymorphism is, up to now, the most studied *FTO* gene variant which consists in an adenine per thymine change (A/T) and is associated with several adiposity measurements. The A allele is associated with a higher body weight and obesity risk [4, 12, 19, 27, 31].

Regarding energy intake, this polymorphism appears to interact with several dietary components. A number of studies have associated the polymorphism with an increased intake in children and adolescents, as well as with loss of control over eating [32–34]. Besides total energy intake, Grau et al. (2009) described that the rs9939609 *FTO* genetic variant could interact with dietary macronutrient composition on obesity development, in particular depending on dietary fat intake account [35]. Similar results have been achieved by other authors regarding the influence of fat and carbohydrates intake [36], dietary fatty acid distribution [12], as well as the amount of fatty acids consumed [37] on the polymorphism effect.

Furthermore, the polymorphism effect on anthropometric changes after a dietary intervention has been investigated. Studies carried out both in obese children [38] and overweight/obese adults [31] have not found association between the polymorphism and weight loss after one year of dietary intervention and physical activity recommendations. In relation with weight gain, a study carried out by Razquin et al. (2010) showed that in spite of having a higher BMI at the beginning of the study, risk allele carriers (A allele) of the *FTO* gene rs9939609 polymorphism, showed a higher weight gain after 3 years of a Mediterranean-style dietary intervention [39].

Melanocortin-4 Receptor (MC4R)

Melanocortin-4 Receptor gene (*MC4R*) is localized in chromosome 18q22. It is composed of a single exon that encodes for a 332 amino acids protein mainly expressed in brain and more specifically in hypothalamic neurons acting on the control of energy intake and regulating appetite and satiety feelings [4].

A study carried out by Huszar et al. (1997) demonstrated in a murine model that the absence of this receptor leads to an obesity profile accompanied by hyperphagia, hyperinsulinemia and hyperglycemia as a consequence of a loss of control over eating [40]. At the same year Fan et al. (1997) showed that *MC4R* activation by the administration of a synthetic agonist (MTII) was able to inhibit energy intake proving the implication of this gene in energy metabolism [41].

The first genetic variants of *MC4R* in humans were identified in 1998 through the analysis of obese subjects and their family lineages [42, 43]. Since then, more than 100 different genetic variants with diverse effects on functional gene activity have been found throughout *MC4R* [44].

One of the most studied genetic variants in or near *MC4R* gene is the rs17782313 polymorphism caused by the change of a thymine by a cytosine (T/C) 188 kb downstream *MC4R*. A meta-analysis carried out by Loos et al. in 2008 analyzing GWAS available to that moment, pointed out that this SNP presented the higher association with obesity measurements. In particular, there was an increase of 0.22 kg/m^2 on adult BMI per each C allele present in the genotype. In children over 7 years old, an increase of 0.10-0.13 units of BMI-SDS per C allele in the genotype was observed [45]. This association of the polymorphism with obesity has been later confirmed in other studies carried out in adult [46, 47], adolescent [48] and infant [49] populations.

Regarding the role of the polymorphism on energy intake results are controversial. Some authors like Hasselbalch et al. (2010) did not shown any association between the SNP and eating behavior or food choices [50], while Qi et al. (2008) observed that C allele carriers had a higher total energy and fat intake [51]. In children, Valladares et al. (2010) reported that rs17782313 of *MC4R* gene was associated with satiety responsiveness and enjoyment of food scores [52].

Concerning intervention studies, one study carried out by Haupt et al. (2009) did not found an association between the polymorphism and weight loss after 9 months of intervention [53], however, another study carried out in 2011, revealed that subjects carrying the genetic variant presented a higher BMI decrease after a weight loss intervention [54].

Transmembrane Protein 18 (TMEM18)

The first scientific work concerning *TMEM18* was published in 2008, when Yamashita et al. described that this gene resulted in a protein that inhibits mARN translation in growth arrested cells [55]. After that, based on GWAS studies, *TMEM18* gene was specifically related to obesity. In 2009, several studies demonstrated that a polymorphism located near this gene, rs7561317, was second highest after *FTO* gene in association with BMI [23, 24], especially in children [56, 57].

TMEM18 gene is located in human chromosome 2p25.3. It is a 9466 base pairs (bp) length gene, including introns and seven exons that result to transmembrane protein

TMEM18, composed of 140 amino acids [56]. This gene is active in nearly all tissues, but its expression is especially important in brain, specifically in the hypothalamus, suggesting that it could be responsible of obesity development through the control of eating behavior [58].

Genetic variant rs6548238 downstream *TMEM18* gene is caused by a cytosine per thymine change (C/T). This SNP has been associated with obesity, as well as with other adiposity measurements. In particular, it has been related to increased risk of obesity [56, 59], body weight, BMI, waist circumference and body fat [60]. Moreover, a study carried out by Thomsen et al. (2012) has reported that in addition to being associated with obesity risk, it also remains associated with a higher risk of diabetes risk after adjustment for BMI [61].

SH2B Adaptor Protein 1 (SH2B1)

SH2B1 gene is located in chromosome 16p11.2 and has a total length of 27614 bases. In 2005 it was associated with obesity for the first time [62] and since then it has been demonstrated that it influences a variety of signaling pathways mediated by Janus kinase (JAK) and receptor tyrosine kinases. In 2007, Maurer et al. reported that a deletion in this gene led to severe obesity, leptin and insulin resistance [63]. Subsequent studies showed that its transcript functions as an adapter protein that cross-links actin filaments, leading to modulation of cellular responses to JAK2 activation [64] and that it acts as a positive regulator of leptin receptor (LEPRb) [65].

This gene is expressed in brain, hypothalamus, liver, muscle, adipose tissue, heart and pancreas and it is involved in the regulation of energy balance, body weight, insulin sensitivity and glucose homeostasis. In this sense, Ren et al. showed that in rats, neuron over expression of *SH2B1* protected against high fat diet (HFD) induced obesity and leptin resistance [66].

Results concerning expression levels depending on dietary intake are controversial. While a recent study reported that *SH2B1* expression was not affected by nutritional state in two brain regions implicated in feeding behavior: ventromedial hypothalamus (VMH) / arcuate nucleus (ARC) and substantia nigra (SN) / ventral tegmental area (VTA) [67], other authors have shown that this gene was downregulated in hypothalamus in HFD fed rats [68] or that the expression in the brain specifically increased more than 20 fold in fed mice [69].

The rs7498665 genetic variant of *SH2B1* gene consists on the change of an adenine per guanine at exon 3. This variation translates in an Ala/Thr mutation. In 2007, this polymorphism was associated for the first time with serum leptin levels, total fat, waist circumference and body weight, and these findings led to the hypothesis that it could be a potential target for drug-induced leptin sensitization [70].

From GWAS, where this genetic variant showed one of the highest effect sizes on BMI, several studies have analyzed the association between rs7498665 SNP and obesity risk [71, 72], increased BMI [73], visceral fat [60, 74], decreased insulin sensitivity [75] and type 2 diabetes incidence independently of BMI [76]. Concerning energy intake, the polymorphism is associated with increased total and saturated fat intake [77] and with more servings of dairy products [78]. Finally, a study carried out by Orkunoglu-Suer et al. (2011) reported that females with a copy of the risk allele (G allele) showed less change of subcutaneous fat volume after exercise training than those no carrying this genetic variant [79].

Neuronal Growth Regulator 1 (NEGR1)

NEGR1 gene is in chromosome 1p31.1 which encodes the neuronal growth regulator 1 protein and is highly expressed in brain, mainly in the hypothalamus, but also in subcutaneous adipose tissue (SAT), heart and skeletal muscle. Moreover, Walley et al. (2012) showed a significant correlation between hypothalamus and SAT *NEGR1* expression levels. In SAT, this gene appears to be a central hub in an obesity related transcript network [80], and the nutritional state seems to affect its expression levels [67]. The study of the *NEGR1*-deficient mouse model have demonstrated the role of this gene in the control of body weight and food intake and its implication in body weight control [81].

GWAS carried out by Willer et al. and Thorleifsson et al. in 2009 evidenced that a genetic variant upstream *NEGR1* gene (rs2815752) had one of the biggest effect sizes on BMI values. Several studies have associated the polymorphism with increased BMI both in adults [77, 82] and in children [57]. Also, it has been related to other obesity associated traits as weight, waist circumference [60, 77] and decreased insulin sensitivity [75], whereas other studies have not found association with BMI [73], birth weight [83] or body fat distribution [60].

In addition, rs2815752 genetic variant has been shown to be involved in dietary intake, since A allele carriers had a decreased intake of saturated and monounsaturated fat [77]. Finally, concerning the effect of the polymorphism on weight loss interventions, Delahanty et al. reported an interaction between the SNP and metformin intervention during two years and they also showed that this variant is associated with weight regain after treatment [84].

Potassium Channel Tetramerization Domain Containing 15 (KCTD15)

The *KCTD15* gene is located in chromosome 19q13.11 with a length of 18916 bases and it is expressed in almost all tissues. Studies in rats and mice models have demonstrated that the expression of this gene decreases in hypothalamus of HFD fed rats showing that mRNA levels depend on nutritional status [68]. Yoganathan et al. concurred with that

finding, suggesting that in HFD fed mice, *KCTD15* expression is downregulated in liver, adipose tissue and hypothalamus but not in brain [69].

In relation with obesity, a genetic variant located upstream *KCTD15* gene (rs11084753) have been identified by GWAS as one of the key SNP involved in determining BMI [23, 24]. In this sense, several studies have associated this genetic variant with higher BMI both in adults [76, 77, 85] and in children [57], and also with higher weight, waist circumference and carbohydrate intake [77]. A study conducted in 2010 by den Hoed et al., reported that rs11084753 have a higher effect size in children compared with adult populations [86]. However, Holzapfel et al. (2010) have not seen any relationship of the SNP with obesity in a study carried out in 12462 subjects from the population-based MONICA/KORA Augsburg study [73]. In the same way, negative associations with body fat distribution depots and birth weight have been observed [60, 83].

Copy Number Variants (CNV)

CNV are structural variations of DNA, inherited or "*de novo*", that cause the cell to have an abnormal number of copies of one or more sections of DNA and that sometimes result in an increase to disease susceptibility. These microdeletions or microduplications could range from a few hundred base pairs to several megabases (Mb) [87] and according to genome analysis, there are at least 12000 CNVs overlapping more than 1000 genes. In this sense, any individual has an average of 1000 CNVs covering around 4 million base-pairs and almost 13 % of its genome. In the last years the study of these variations has rapidly increased due to the growing evidence of its influence in disease phenotypes.

Concerning CNVs involved in obesity development, Bochukova et al. reported in 2009 that a deletion extended through 593-kilobase region in chromosome position 16p11.2, is associated with severe obesity. This deletion has been previously related with mental retardation and included the gene *SH2B1*, which is known to be involved in insulin and leptin signaling. Other studies have confirmed this association and have also shown that deletion carriers presented hyperphagia and severe insulin resistance disproportionate for the degree of obesity [88, 89]. Interestingly, a study carried out in 2011, showed that a reciprocal duplication was associated with being underweight and with an unusually high frequency of selective and restrictive eating behavior [90].

Moreover, other CNVs, as deletions in *EKIL3, S1PR5, FOXP2, TBCA, ABCB5* and *ZPLD1* and duplications in *KIF2B* and *ARLI5* has been shown to contribute to genetic susceptibility of common childhood obesity [91].

Finally, in relation to dietary intake, the study of a gene involved in carbohydrate metabolism pathway (*AMY1* gene) has reported a higher number of CNVs in individuals with a high-starch diet compared to those with a low-starch diet, indicating that dietary intake could modulate these microdeletions/microduplications [92].

New Perspectives

In the study of the genetics of obesity, one important issue is the standardization of obesity phenotypes. Some investigators favor the use of BMI as main outcome due to its ease of retrieval and inexpensiveness, however, this measure could be influenced by extrinsic factors unrelated to obesity [93]. Therefore from our point of view, an optimal characterization of obesity would be that including phenotypes that could be reliably and inexpensively measured, as weight, total fat mass and visceral adipose tissue area, allowing the evaluation of large study samples without implying great expenses. The use of biochemical biomarkers involved in CVD or metabolic syndrome risk may also be a useful approach, nevertheless, its higher cost could be a disadvantage for its collection.

A second important issue is the description of an optimal context to detect a genetic effect with clinical relevance. In this sense, taking into account different epidemiologic designs in obesity research, prospective cohort studies seem to be the most suitable in order to increase the power and enhance the validity of observed associations. These studies minimize risk bias from retrospective reporting on diet or lifestyle factors and as a result they could be considered the strongest nonrandomized design. Some of their advantages are a very large size, long term and high rates of follow-up, availability of archived biological samples and repeated measures of body weight and diet. Furthermore, large intervention studies are also a remarkable approach for the study of obesity since they have the intention to improve the condition of an individual or a group of individuals besides its additional contribution to find associations between exposure variables and health outcomes.

Concerning the influence of environmental factors on obesity development, physical activity is the most common environmental factor assessed in gene x environmental studies followed by dietary intake. In this sense, nutrigenetics studies the interaction between genes and nutrients in order to determine the individual susceptibility to diet-related diseases. Some examples are the interaction of rs2943641 polymorphism of *IRS1* gene and carbohydrates and lipids intake on insulin resistance and weight loss [94], rs3135506 genetic variant of *APOA5* gene and vitamin D intake on HDL-cholesterol plasmatic levels [95], rs1801282 of *PPARG* gene and saturated and polyunsaturated fatty acids intake on particle diameter of low-density lipoproteins [96], or the interaction between rs9939609 SNP of *FTO* gene and saturated fatty

acids intake on obesity development [12]. These interaction studies aim to reach personalized nutrition detecting genetic risk profiles that would predict in early stages who would be at risk of developing obesity or promoting effective prevention or management of chronic diseases by accurate diet and lifestyle matched to an individual's genetic profile. Although at the present moment none of the studied genes have meaningful predictive power by themselves, these lifestyle intervention studies are increasing the knowledge of the field enabling to target specific therapies to those subjects most likely to obtain a benefit. Therefore, we might continue moving in that direction to further progress in these areas that would permit us, in a foreseeable future, to develop a "predictive medicine" that will allow to identify individuals at risk of obesity or low/high responders to a given treatment.

In addition to the increasing progress of the knowledge about the influence of genetic variants on obesity development, in the last years, epigenetics have emerged as a new possible therapeutic approach to treat obesity [97]. Epigenetic changes consist on variations in gene expression that occur without changes in the DNA sequence. In relation to body weight determination, more than 20 differentially methylated sites associated with obesity have been described. It has been reported that the effect of some genetic variants, as rs9939609 of *FTO* gene may be mediated through epigenetic changes [98]. Moreover, a recent study has shown that DNA methylation levels in some genes such as *CLOCK, PER2* and *BMAL1* are associated with obesity and the metabolic syndrome as well as monounsaturated fat intake [99••] and in relation to weight loss, Cordero et al. (2011) revealed that *LEP* and *TNF-α* promoter methylation levels could predict the response to a low-calorie diet [100].

Conclusion

In summary, in the last years the developments of GWAS, together with CNVs screening, have accelerated the study of polygenic conditions as obesity allowing the identification of several obesity-associated genetic variants. Nevertheless, despite the highly significant associations it has been demonstrated that the 32 *loci* identified for BMI account for only 1.45 % of the phenotypic variation [21•] suggesting that new approaches such as the study of epigenetic mechanisms involved in obesity and a better knowledge of nutrient x gene interaction are needed.

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- •• Of major importance

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