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Genetic background, nutrition and obesity: a review

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Abstract. – OBJECTIVE: To summarize the latest information on the relationship between genes and common forms of obesity, and to review genetic markers (SNPs and miRNA) that play a role in predisposing to common forms of obesity and related disorders.

MATERIALS AND METHODS: We searched PubMed with the following keywords: (obesity[Title/Abstract]) AND predisposition[Title/Abstract]) AND miRNA[Title/Abstract]) OR polymorphism[Title/Abstract].

RESULTS: From the search we obtained a total of 44 gene loci and 48 miRNAs associated with common obesity.

CONCLUSIONS: It is now widely accepted that obesity involves interactions between environmental risk factors (physical inactivity, excessive calorie intake, chronic stress, taste perception) and a genetic background of risk. Analysis of the genetic background of obese subjects is therefore an important way to determine the molecular mechanisms controlling the link between food intake and obesity, enabling a better understanding of how these interactions may differ from person to person.

Key Words
Obesity, miRNA, Genetic Markers, Metabolic disorders.

Introduction

Obesity is a considerable burden for patient quality of life and public health expenditure. Much has been done from the point of view of prevention and treatment, and more is emerging regarding the genetic component of this disease. Thanks to twin and adoption studies, it is now clear that there is a powerful genetic component correlated with obesity[1]. The overlap between obesity and other metabolic disorders linked to over-accumulation of fat, like diabetes mellitus, metabolic syndrome and polycystic ovarian syndrome (PCOS), is increasingly evident[2]. Indeed, it is becoming increasingly clear that the metabolic syndrome predisposes to the obesity and diabetes, that the obesity favours the diabetes onset and *viceversa* and that PCOS could be considered to all effects as a variant of metabolic syndrome involved in diabetes onset[2]. Relatively to this last disease, defined by the expert conference of Rotterdam in a misleading way as a disease characterized by at least two out of three conditions between oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, or 3) polycystic ovaries[3], its impact on metabolism was little considered for too long time. Only just recently, more importance to the PCOS effects on the metabolic pathways was given and now, in practice, it can be considered belonging to the pre-diabetic states, defined by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus in the 1997 as diabetes predisposing conditions characterized by values of fasting glucose and glucose tolerance higher than normal ones but under the diabetes thresholds[4]. This last assertion is confirmed by the effectiveness of insulin-sensitizing therapies such as the one based on the myo-inositol and d-chiro-inositol ratio 40:1, regularly used for the treatment of this gynaecological disease[5].

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These considerations are even more interesting switching from a clinical to a genetical analysis because the overlapping area between these metabolic diseases results more pronounced. The genes and the modifications of these sequences involved in the several metabolic alterations frequently are the same e.g. the single nucleotide polymorphism (SNP) rs9939609 on the fat mass and obesity associated gene (FTO), involved in obesity, PCOS and diabetes[6,7]. Relatively to the obesity, there is a powerful genetic component in twin and adoption studies[1]. So far, different strategies have been used to determine the genetic factors involved in obesity, exploiting new technologies in the field of human genetics to dissect monogenic and multifactorial genetic disorders. Linkage analysis associated with the candidate gene approach was one of the first and enabled the definition of rare monogenic forms of obesity (e.g., *LEP, LEPR, POMC, PCSK1, SIMI1, NTRK2, BDNF,* and *MC4R*). These genetic anomalies affect pivotal factors related to the leptin-melanocortin pathway and are fundamental in energy balance regulation[8-11]. More recently, forms of oligogenic obesity, characterized by a variable degree of obesity partly dependent on environmental factors, have also been described. This type of obesity is responsible for 2-3% of obesity in adults and children[11]. It is also recognized that "common forms" of obesity are a result of interactions between environmental and genetic factors, reflecting the role of many genes that confer different degrees of susceptibility (polygenic obesity)[12]. Several recent projects using whole-genome sequencing analysis have provided a comprehensive description of genetic variations across the human genome, including SNPs and copy number variations (CNVs).

Materials and Methods

We searched Pubmed with the following keywords: (((obesity[Title/Abstract]) AND predisposition[Title/Abstract]) AND miRNA[Title/Abstract]) OR polymorphism[Title/Abstract].

Results

The search produced a total of 44 genetic loci and 48 miRNA strongly associated with common obesity (Tables I and II).

Genome-Wide Association Studies in Common Obesity

Several recent genome-wide association studies (GWAS) with large samples of patients have enabled the identification of genetic variants associated with increased risk of developing "common forms" of obesity[13]. These advances improve our understanding of common forms of obesity, allowing individual risk prediction and enabling personalization of dietary management[14,15]. Genome-wide association studies have made it possible to identify more than 100 independent loci associated with common obese status in large samples[16] suggesting that almost 21% of variation in body mass index (BMI) can be explained by common genetic variants[17]. Interestingly, these GWAS showed that almost all genes involved in monogenic and oligogenic forms of obesity (*LEPR*, *POMC*, *MC4R*, *BDNF*) have common variants also associated with polygenic obesity. Unfortunately, not all the loci identified in single GWAS were replicated in independent studies, because most SNPs only proved to be associated with obesity in specific ethnic groups or selected populations. On the other hand, a group of loci proved to be associated with obesity in different GWAS performed on specific population samples. If we consider the loci found associated with obesity/BMI in at least two independent samples, the number of chromosome regions with strong evidence of association with the disease drops to 44 (Table I)[16,18]. An example is the fat mass and obesity associated gene (*FTO)*, an obesity susceptibility gene considered a reliable and well-established risk factor for common forms of obesity because it has been identified in more than 20 independent studies[16]. *FTO* is the gene with the greatest effect on obesity, and it is recognized as a powerful genetic susceptibility locus for obesity and related disorders, such as PCOS and diabetes.

Recent technical progresses in metabolomics and GWAS have enabled the analysis and collection of huge data sets in different populations, suggesting that metabolic disorders are only the most severe cases of the variegated influence that genetic variations can exert on human metabolism. In a recent paper, Shin et al[19] provided the most comprehensive analysis of genetic influences on human metabolism, identifying over 100 different blood metabolites influenced by specific genetic markers (SNPs). Interestingly, they found that one-third of these loci were involved with intermediates of lipid metabolism, including sterols, carnitines and intermediates of inositol and fatty acid

Table I. List of genes and SNPs associated with obesity and/or BMI in at least two independent genome-wide association studies. For more details see references[15,17].

Nr.	Gene	SNP	Other associated phenotypes
1	*BDNF*	rs6265, rs4923461, rs10767664, rs2030323, rs988712	
2	*CADM2*	rs13078807	
3	*CDKAL1*	rs2206734, rs9356744	
4	*ETV5*	rs7647305, rs9816226	
5	*FAIM2*	rs7138803, rs7132908	
6	*FANCL*	rs887912, rs12617233	
7	*FOXO3*	rs9400239, rs4946932	
8	*FLJ35779*	rs2112347	
9	*FTO*	rs9939609, rs9930506, rs1121980, rs1421085, rs8050136, rs1558902, rs17817449, rs12149832, rs9940128, rs62033400, rs1421085, rs1121980, rs9936385, rs9941349, rs3751812, rs6499653	Diabetes, type 2; metabolic syndrome
10	*GIPR*	rs2287019, rs11672660, rs11671664	Diabetes, type 2
11	*GNPDA2*	rs10938397, rs13130484, rs348495	
12	*GPRC5BB*	rs12444979	
13	*KCTD15*	rs11084753, rs29941	
14	*HMGCR*	rs6453133	
15	*IQCK*	rs739564	
16	*LRRN6C*	rs10968576	
17	*MAP2K5*	rs2241423, rs4776970, rs997295	
18	*MC4R*	rs17782313, rs571312, rs12970134, rs2331841, rs6567160, rs8089364, rs7234864, rs723486, rs7227255, rs2229616, rs17782313, rs17700144, rs663129, rs571312, rs476828, rs11873305, rs17066846	
19	*MRPS33P4*	rs13041126	
20	*MTCH2*	rs10838738, rs3817334	
21	*NEGR1*	rs2815752, rs2568958, rs1993709	
22	*NLRC3*	rs758747	
23	*NPC1*	rs1805081, rs1788826	Metabolic syndrome
24	*NRXN3*	rs10150332	
25	*NT5C2*	rs11191560, rs3824755	
26	*OLFM4*	rs9568856, rs9568867	
27	*PACS1*	rs564343	
28	*PCSK1*	rs261967, rs6232, rs6234, rs6235	
29	*POMC*	rs713586, rs6545814, rs1561288, rs6752378, rs10182181	Early-onset diabetes, type 2
30	*PRKD1*	rs11847697, rs12885454	
31	*SEC16B*	rs10913469, rs543874, rs574367, rs516636, rs591120	
32	*SH2B1*	rs7498665, rs4788102, rs7359397, rs4788099	Maturity onset diabetes of the young
33	*SLC39A8*	rs13107325	
34	*SMG6*	rs9914578	
35	*SPI1*	rs11570094	
36	*STXBP6*	rs10132280	
37	*TAL1*	rs977747	
38	*TCF7L2*	rs7903146	Diabetes, type 2
39	*TFAP2B*	rs987237, rs734597, rs2272903	
40	*TMEM160*	rs3810291, rs3810291	
41	*TMEM18*	rs6548238, rs7561317, rs2867125, rs12463617, rs4854344	
42	*TNKS*	rs17150703	
43	*TNNI3K*	rs1514175, rs12142020, rs1040070, rs1514174, rs7553158	
44	*TOMM40*	rs2075650	

Table II. List of circulating miRNAs up- or down-regulated in patients with obesity or related disorders. ↑ indicates increased expression of miRNAs ↓ indicates miRNAs showing reduced expression in obese patients.

miRNA	Process	References
↓miR-23a, miR-23b, miR-26a, miR-28-5p, miR-30e-3p, miR-151-5p, miR-151-3p, miR-181a, miR-374b, let-7d, let-7e, let-7f, miR-32, miR-365, ↑miR-197, miR-584, miR-101, miR-144	Obesity	75
let-7b, miR-143, and miR-221	Atherogenic and adipogenic alteration	76
↓miR-17-5p and miR-132	Obesity	77
↓miR-29c, miR-99b, miR-103, miR-221, miR-340; ↑miR-30a-5p, miR-130a, and miR-150	Gestational obesity	78
↑miR-140-5p, miR-142-3p, miR-222; ↓miR-532-5p, miR-125b, miR-130b, miR-221, miR-15a, miR-423-5p, and miR-520c-3p	Obesity	79
↑miR-122	Obesity, Type 2 diabetes	80
↑miR-122, miR-199, miR191, miR-27, miR-378, miR-33, miR-370a, ↓miR-335, miR-143, miR-758	Obesity in children	81,82

metabolism. For instance, the importance of these metabolites is confirmed by the fact that PCOS patients benefit from treatment with myo-inositol and d-chiro-inositol, usually used as insulin-sensitizing therapies[5]. The SNP associated with these loci (Table III) may prove to be a good prognostic marker of metabolic dysfunction associated with obesity and related disorders.

Regulation of the Major Molecular Effectors in Common Obesity

The main molecular effectors of obesity are molecules synthesized by the adipose tissue itself and the gut, in response to food intake. The adipose tissue is not a passive reservoir of energy but is known to express and secrete a variety of bioactive peptides, known as adipokines, which act at both the local (autocrine/paracrine) and systemic (endocrine) level. In addition to these signals, adipose tissue expresses numerous receptors that allow it to respond to signals from traditional hormone systems and the central nervous system[20]. The gastrointestinal tract is the largest endocrine organ in the body and is believed to have an important appetite-regulating role as a source of various regulatory peptide hormones[21].

PPARγ (also known as NR1C3) is expressed in white and brown adipose tissues and is a nuclear receptor that functions as ligand-inducible transcription factors and functions as heterodimer with retinoid X receptors. The process of PPARγ activation is mediated by both natural and synthetic ligands. PPARγ ligands *in vivo* remain unidentified. The expression of PPARγ is highly induced in adipocytes during adipogenesis and this induction is regulated by GAGA, KLF2, and CHOP10, that repress PPARγ in preadipocytes. During the early stage of adipogenesis, C/EBPβ and C/EBPδ induce the expression of PPARγ and C/EBPα. Several other transcription factors: KLF5, KLF9, KLF15, NFI, EBF1, and SREBP1 are required to induce expression of PPARγ during adipogenesis[22].

Leptin is expressed mainly by adipose tissue and is increased by glucocorticoids, and proinflammatory cytokines. In contrast, cold exposure, adrenergic stimulation, growth hormone, thyroid hormone, melatonin, and smoking decrease leptin. Leptin synthesis is greater in subcutaneous than in visceral adipose tissue. Leptin has been implicated also in modulation of the reward circuitry for feeding, glucose metabolism, and lipid oxidation[23].

Tumor necrosis factor, TNF-α, is produced by differentiated adipocytes. However, the major source of adipose derived TNF-α is the macrophages from the stromal vascular fraction. The increased levels of TNF-α in obesity are due to the increased infiltration of adipose tissue with macrophages. The quantity of macrophages in the adipose tissue correlates with the fat mass. In fact, adipocytes secrete MCP-1, MIF-1, MIP-1α, CCL5 and M-CSF factors that support the maturation of monocytes[23]. In humans, approximately 30% of circulating IL-6 originates from adipose tissue. Concentrations are higher in visceral fat as compared to subcutaneous fat. They increase with obesity and are stimulated by TNF and interleukin-1. Elevated levels are associated with increased risk of coronary artery disease, atherosclerosis, and unstable angina[23]. PPARγ activation increases circulating levels of adiponectin at the post-translational

Table III. List of blood metabolites associated with lipid metabolism influenced by specific genetic markers. The SNPs associated with these metabolites could be biomarkers of dysfunctions associated with obesity.

Gene	SNP	Biochemical(s)
ABCC1	rs2062541	Hexanoylcarnitine/octanoylcarnitine
ACADL	rs3738934	Nonanoylcarnitine
ACADM	rs4949874	Acetylcarnitine/hexanoylcarnitine
ACADS	rs2066938	Butyrylcarnitine
AKR1C4	rs17134585	Androsterone sulfate/ epiandrosterone sulfate
ALOX12	rs2271316	12-Hydroxyeicosatetraenoate (12-HETE)
ALX3	rs1466788	Carnitine
APOA5	rs11825181	1-Linoleoylglycerol (1-monolinolein)
APOE	rs445925	Cholesterol
CYP3A5	rs7809615	Androsterone sulfate/ 4-androsten-3beta,17beta-diol disulfate 2
CYP4A11	rs6678639	10-Undecenoate
ELOVL2	rs9393915	Docosapentaenoate
ETFDH	rs4690909	Octanoylcarnitine
FADS1	rs174548 rs2727271	Arachidonate/dihomo-linolenate Docosapentaenoic acid (n6-DPA)
ISYNA1	rs4808136	Myo-inositol
LIPC	rs10468017 rs2070895	1-Palmitoylglycero-phosphoethanolamine 1-Palmitoylglycero-phosphoethanolamine
MARCH8	rs2291429	3-Dehydrocarnitine
MBOAT7	rs2576452	Arachidonate/1-arachidonoylglycero-phosphoinositol
PDXDC1	rs2740	Linoleate/dihomo-linolenate
PEX5L	rs9842133	Carnitine
SCD	rs603424	Myristate (14:0)/ myristoleate
SGPP1	rs7157785	Cholesterol
SLC16A9	rs1171615	Carnitine
SLC17A3	rs1185567	DHEA-S/ 4-androsten-3beta,17beta-diol disulfate 2
SLC27A2	rs1365505	10-Undecenoate (11:1n1)/ X-11438
SLC5A11	rs4787294	Scyllo-inositol
SLCO1B1	rs12829704	Octadecanedioate
SPTLC3	rs4814176	Palmitoyl sphingomyelin
SULT2A1	rs2547231	4-Androsten-3beta,17beta-diol disulfate 2
THEM4	rs6693388	Linoleate/5,8-tetradecadienoate
ZCWPW1	rs13222543	Androsterone sulfate/ 4-androsten-3beta,17beta-diol disulfate 2

level. Adiponectin is assembled and processed in a similar manner as IgM molecules. It is retained in the endoplasmic reticulum by the chaperone ERp44 and released by the oxidoreductase Ero-Lα. This process is highly regulated by these chaperones that are the primary transcriptional target for PPARγ agonists, leading to a more efficient release of the high molecular weight form of adiponectin from the adipocytes[24].

Cholecystokinin is a gut hormone that reduce food intake and in response to meal initiation, cholecystokinin is predominantly synthesized and released from the duodenum and jejunum, where its regulatory effects include inhibition of gastric emptying. In addition, cholecystokinin is distributed within the hypothalamus and is the most abundant neuropeptide in the central nervous system[21]. Ghrelin is a peptide hormone produced predominantly in the stomach. It is an orexigenic hormone. Ghrelin binds to the growth hormone secretagogue receptor, which is highly expressed in the hypothalamus and brain stem. Ghrelin has been proposed to function as a meal initiator and has been shown to stimulate appetite in both lean and obese humans. In obese subjects, fasting ghrelin levels have been shown to be lower compared with normal weight controls and to rise following diet-induced weight loss. The expected post-prandial fall in circulating ghrelin levels is attenuated or absent in the obese[21].

Role of microRNAs in Common Forms of Obesity

In recent years, the association between microRNAs (miRNAs) and various diseases has been the subject of considerable research. miRNAs have emerged as essential modulators of physiological processes, such as intracellular energy balance and metabolic homeostasis[25]. miRNAs are a class of non-coding RNA molecules that play a central part in cell differentiation, proliferation and survival by binding specific target mRNAs. The synthesis of miRNA begins with their transcription by RNA polymerase II (Pol II) that produces a long transcript named primary miRNA (pri-miRNA), which is immediately cleaved by Drosha and transported into the cytosol where RNase III Dicer and TRBP protein cleave the terminal loop, producing a miRNA duplex. In the final step, the miRNA duplex is processed by the argonaute (AGO) family of proteins to obtain mature miRNA that can recognize a specific target[26,27]. More than 2000 different miRNAs have been described in humans, and their number is increasing[28]. miRNAs are important cell elements that primarily reduce expression of specific genes by binding to the 3' UTR of target RNA, contributing to the regulation of many biological processes[26]. Each miRNA can simultaneously regulate large groups of mRNAs, while specific mRNAs may be recognized by different miRNAs, giving rise to a complex regulatory network[29]. Although miRNAs usually only exert a weak inhibitory effect on a single target gene, they often act on several associated transcripts in a specific signaling pathway, causing significant cumulative effects. In recent years, a large number of miRNAs involved in the regulation of lipid and glucose metabolism and adipocyte differentiation have been identified. Scholars[30-32] showed that over 50 different miRNAs expressed in pancreas, adipose tissue and liver are dysregulated in patients affected by obesity or metabolic disorders. In addition, different studies suggest that miRNAs can be regulated by diet and external environmental factors and may respond to dietary changes[33]. Although miRNAs were first identified in cells, many have now been found in whole blood, serum and plasma[34]. Circulating miRNAs (cmiRNAs) have elicited great interest in the scientific community, since their expression could be used as biomarkers for several diseases[35]. Thomou et al[36] described adipose tissue as a major source of circulating miRNAs that can regulate gene expression in distant tissues, thereby acting as regulators of metabolism. In many cases, alteration of the expression of specific cmiRNAs linked to metabolic disorders can be used as a predictive marker of increased risk of disease[32]. In addition, new technologies for *in vivo* delivery of miRNAs for therapeutic purposes are developing rapidly and have been successful in the context of other multifactorial disorders[37]. Table II summarizes current knowledge on circulating miRNAs in relation to obesity and metabolic diseases[32].

Gene-Diet Interactions

Our genetic predisposition is responsible for a percentage of obesity risk that varies from person to person and explains a great part of the differential response of individuals to the same dietary treatment. Nutritional genomics is a new field of research that aims to evaluate the mechanisms by which nutrients and dietary habits interact with the genome at different levels. It is interesting that although a huge amount of scientific research has been performed in the field of obesity, many questions regarding the efficacy of various weight-loss diets remain unanswered. There has been recent interest in dietary composition and nutrient components that can reinforce weight loss[38,39]. In an interesting paper, Sacks et al[40] compared four popular diets with different fat, protein and carbohydrate composition without finding any significant differences in promoting weight loss. A recent systematic comparison of the carbohydrate/protein ratio of low-calorie diets[41] showed that high-protein diets were relatively ineffective for reduction of fat mass. On the other hand, Ajale et al[42] found that low-carbohydrate and Mediterranean diets led to greater weight loss than other kinds of diet.

Regarding the genetic basis of regulation of body weight, different independent studies in different populations have furnished reproducible evidence of interactions between genetic and dietary factors in relation to obesity[43]. Recent GWAS found that increased intake of sugar-sweetened beverages amplified the association between BMI and a group of 32 obesity-associated SNPs[44]. Notably, the same panel of SNPs showed a stronger association with BMI in individuals with high lipid intake (fried foods)[45]. This work showed clearly that unhealthy eating habits amplify the association between genetic risk score and obesity-related traits[43]. Much research has been focused on the Mediterranean diet, which is characterized

by regular intake of vegetables and reduced amounts of animal proteins[46]. Several studies showed associations with a reduced incidence of metabolic disorders and obesity. In addition, some food components of this diet have been shown to improve several metabolic biomarkers[47] associated with body weight[48], type-2 diabetes and hypertension[49,50].

GWAS for obesity have provided new insights into the genetics of this pathology and it is not surprising that identification of a single SNP often failed to have clinical utility for predicting predisposition for obesity and related disorders[43]. Several authors have tried to disentangle this issue by analyzing the genetic component of obesity associated with multiple loci, an approach that aims to identify more reliable and replicable parameters, known as genetic risk scores (GRS), based on cumulative effects of multiple risk alleles[51]. Using multi-loci GRS, San Cristobal et al[52] analyzed the effects and interactions between Mediterranean diet and genetic background in more than 1200 individuals from seven European countries. They calculated a GRS based on 14 selected risk alleles and a Mediterranean diet score (MDS) based on food intake data. A significant interaction between GRS and Mediterranean diet was observed, as expected. In addition, when the participants were classified by eating habits, those with higher MDS had significantly lower mean BMIs, waist circumference and total cholesterol, and a significantly greater decrease in total cholesterol was recorded in subjects with low GRS than in those with high GRS.

A similar approach was used to study the interaction of Mediterranean diet with *FTO* polymorphisms in relation to obesity phenotypes. GRS was calculated for each subject and this parameter was matched with relative adherence to a Mediterranean dietary pattern, expressed as Mediterranean dietary score (MDS). Individuals associated with the risk-allele for SNPs rs9939973, rs8050136, rs1781749 and rs3751812 showed less risk of obesity for higher MDS, suggesting that better adherence to the Mediterranean diet can have positive effects on metabolic biomarkers in subjects with an adverse genetic background[53].

Genetic Variation in Taste Perception and Association with Diet and Obesity

Taste perception is known to play a central role in defining food preferences and several studies have linked genetic variation in taste receptors to risk of disease. This can occur through individual differences in taste perception, which may lead to differences in food preferences and food intake, altering nutritional behavior and nutrition-related disease risk[54].

A variety of investigations have considered the influence of bitter taste perception, mediated by the *T2R38* gene, on food preferences and intake. Interestingly, an inverse relationship between bitter perception and preference for fruit and vegetable consumption has been reported[55-57]. Moreover, variations in the *T2R38* gene have also been associated with healthy eating behavior correlated with intake of fiber, vitamin B6, thiamine and folate[58]. Evidence of a correlation between taste perception and dietary habits has also been reported for other taste perceptions. It has been shown that sweet perception can influence food preferences because subjects with a lower sweet perception generally have a higher preference for sugar than more sensitive individuals[59]. From this point of view, it is not surprising that genetic variation in the *TAS1R2* gene may be associated with regular consumption of sugars by obese individuals[60]. Differences in sweet taste have also been related to alcohol intake and BMI[61,62].

Taste sensitivity to some types of fatty acids has been linked to predisposition for overweight or obesity in animals and humans. Humans hypersensitive to fatty acids proved to have lower BMIs than hyposensitive individuals; similarly, animals showing hyposensitivity to fatty acids were more likely to consume high doses of fats and become obese[63,64]. These findings, suggesting a role of the taste of fat in the diet and weight regulation, were supported by GWAS that found an association between two candidate fatty acid receptors, *KCNB1* (rs6063399) and *KCNC2* (rs7311660), and obesity[65]. Other independent studies linked the SNP rs1761667 with fatty acid perception, probably associated with alteration of *CD36* gene expression[66]. In addition, a relationship between *CD36* polymorphisms and BMI was reported by studies in different populations[67,68]. In other reports, higher free fatty acids, triglyceride levels and metabolic syndrome were associated with specific genetic variants in the *CD36* gene[69-71]. Taken together, these findings underline the way specific genetic differences may play a role in individual food preferences and intake, with important implications for nutrition and dietary habits.

Conclusions

Thanks to the raise of the scientific evidences, metabolic diseases like obesity, diabetes, metabolic syndrome or polycystic ovarian syndrome (PCOS) are coming closer and closer, generating evident overlapping areas between these pathologies. Indeed, it is becoming increasingly clear that the metabolic syndrome predisposes to the obesity and diabetes, that the obesity favours the diabetes onset and vice-versa and that PCOS could be considered to all effects as a variant of metabolic syndrome[2]. It must be said that this last disease, defined by the expert conference of Rotterdam in a misleading way as a disease characterized by at least two out of three conditions between oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, or 3) polycystic ovaries[3], actually it can be considered as a pre-diabetic state, an assertion confirmed by the effectiveness of insulin-sensitizing therapies such as the one based on the myo-inositol and d-chiro-inositol ratio 40:1, regularly used for the treatment of this gynaecological disease[5].

Considering this, data obtained in the present study, aiming to the analysis of the obesity predisposing genetic component, offer interesting ideas for the treatment not only of obesity but also of the main metabolic diseases. A further confirmation of this is the presence of some genetic factors, among those emerged in this review, known to be involved also in the genetic regulation of PCOS e.g. SNP rs9939609 in the *FTO* gene[6,7].

It emerges clearly from this review that various genetic and epigenetic factors influence body weight and BMI. Specifically, polymorphisms with high frequencies in the population (>1%) in genes involved in control of the balance between energy intake and expenditure, in taste perception and in differential expression of miRNAs that regulate those genes may have a role in the onset of common forms of obesity and related disorders, such as diabetes, PCOS and metabolic syndrome[11-74]. These factors obviously cannot cause obesity on their own. Risk factors (physical inactivity, excessive calorie intake, chronic stress) are necessary for the onset of obesity and related disorders. Study of the genetic background of obese subjects is therefore a powerful way to obtain insights into how these interactions produce different outcomes in different individuals, in terms of body weight and energy management. In examining genetic predisposition for obesity, the present work has highlighted fundamental aspects for the treatment of obesity and other metabolic diseases.

Contributorship statement

MB conceived the study; AV, SB, SK and MB collected information; AV wrote the manuscript; AV, GP, BP, IDC, SB, MD, SK, VU, MB reviewed and edited the text; MB supervised the work.

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Conflict of Interests

The authors do not have any competing interests.

References

1) Choquet H, Meyre D. Genetics of obesity: what have we learned? Curr Genomics 2011; 12: 169-179.
2) Fazleen NE, Whittaker M, Mamun A. Risk of metabolic syndrome in adolescents with polycystic ovarian syndrome: a systematic review and meta-analysis. Diabetes Metab Syndr 2018; 12: 1083-1090.
3) Azziz R. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. J Clin Endocrinol Metab 2006; 91:781-785.
4) Buysschaert M, Bergman M. Definition of prediabetes. Med Clin North Am 2011; 95: 289-297.
5) Gateva A, Unfer V, Kamenov Z. The use of inositol(s) isomers in the management of polycystic ovary syndrome: a comprehensive review. Gynecol Endocrinol 2018; 34: 545-550.
6) Mykhalchenko K, Lizneva D, Trofimova T, Walker W, Suturina L, Diamond MP, Azziz R. Genetics of polycystic ovary syndrome. Expert Rev Mol Diagn 2017; 17: 723-733.
7) Liu Y, Chen Y. Fat mass and obesity associated gene polymorphism and the risk of polycystic ovary syndrome: a meta-analysis. Iran J Public Health 2017; 46: 4-11.
8) Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997; 387: 903-908.

9) Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte JM, Basdevant A, Bougnères P, Lebouc Y, Froguel P, Guy-Grand B. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998; 392: 398-401.
10) Krude H, Biebermann H, Schnabel D, Tansek MZ, Theunissen P, Mullis PE, Grüters A. Obesity due to proopiomelanocortin deficiency: three new cases and treatment trials with thyroid hormone and ACTH4-10. J Clin Endocrinol Metab 2003; 88: 4633-4640.
11) Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: clinical approach and current treatments in 2016. Obes Facts 2016; 9: 158-173.
12) Stranger BE, Stahl EA, Raj T. Progress and promise of genome-wide association studies for human complex trait genetics. Genetics 2011; 187: 367-383.
13) Ramos-Lopez O, Milagro FI, Allayee H, Chmurzynska A, Choi MS, Curi R, De Caterina R, Ferguson LR, Goni L, Kang JX, Kohlmeier M, Marti A, Moreno LA, Pérusse L, Prasad C, Qi L, Reifen R, Riezu-Boj JI, San-Cristobal R, Santos JL, Martínez JA. Guide for current nutrigenetic, nutrigenomic, and nutriepigenetic approaches for precision nutrition involving the prevention and management of chronic diseases associated with obesity. J Nutrigenet Nutrigenomics 2017; 10: 43-62.
14) Martínez JA. Perspectives on personalized nutrition for obesity. J Nutrigenet Nutrigenomics 2014; 7: 1-3.
15) Meisel SF, Carere DA, Wardle J, Kalia SS, Moreno TA, Mountain JL, Roberts JS, Green RC, PGen Study Group. Explaining, not just predicting, drives interest in personal genomics. Genome Med 2015; 7: 74.
16) Yazdi FT, Clee SM, Meyre D. Obesity genetics in mouse and human: back and forth, and back again. Peer J 2015; 3: e856.
17) Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015; 518: 197-206.
18) Abadi A, Alyass A, Robiou du Pont S, Bolker B, Singh P, Mohan V, Diaz R, Engert JC, Yusuf S, Gerstein HC, Anand SS, Meyre D. Penetrance of polygenic obesity susceptibility loci across the body mass index distribution. Am J Hum Genet 2017; 101: 925-938.
19) Shin SY, Fauman EB, Petersen AK, Krumsiek J, Santos R, Huang J, Arnold M, Erte I, Forgetta V, Yang TP, Walter K, Menni C, Chen L, Vasquez L, Valdes AM, Hyde CL, Wang V, Ziemek D, Roberts P, Xi L, Grundberg, Multiple Tissue Human Expression Resource (MuTHER) Consortium, Waldenberger M, Richards JB, Mohney RP, Milburn MV, John SL, Trimmer J, Theis FJ, Overington JP, Suhre K, Brosnan MJ, Gieger C, Kastenmüller G, Spector TD, Soranzo N. An atlas of genetic influences on human blood metabolites. Nat Genet 2014; 46: 543-550.
20) Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004; 89: 2548-2556.
21) Perry B, Wang Y. Appetite regulation and weight control: the role of gut hormones. Nutr Diabetes 2012; 2: e26.
22) Lu P, Zhao Z. Advances on PPARγ research in the emerging era of precision medicine. Current Drug Targets 2018; 19: 663-673.
23) Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci 2013; 9: 191-200.
24) Halberg N, Wernstedt-Asterholm I, Scherer PE. The adipocyte as an endocrine cell. Endocrinol Metab Clin North Am 2008; 37: 753-768.
25) Rupaimoole R, Slack F. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov 2017; 16: 203-222.
26) Wilson RC, Doudna JA. Molecular mechanisms of RNA interference. Annu Rev Biophys 2013; 42: 217-239.
27) Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol 2014; 15: 509-524.
28) Kozomara A, Griffiths-Jones S. MiRBase: annotating high confidence microRNAs using deep sequencing data. Nucleic Acids Res 2014; 42: D68-73.
29) Ebert MS, Sharp PA. Roles for microRNAs in conferring robustness to biological processes. Cell 2012; 149: 505-524.
30) Kunej T, Skok DJ, Zorc M, Ogrinc A, Michal JJ, Kovac M, Jiang Z. Obesity gene atlas in mammals. J Genomics 2013; 1: 45-55.
31) Zhang L, Miller D, Yang Q, Wu B. MicroRNA regulatory networks as biomarkers in obesity: the emerging role. Methods Mol Biol 2017; 1617: 241-260.
32) Iacomino G, Siani A. Role of microRNAs in obesity and obesity-related diseases. Genes Nutr 2017; 12: 23.
33) Slattery ML, Herrick JS, Mullany LE, Stevens JR, Wolff RK. Diet and lifestyle factors associated with miRNA expression in colorectal tissue. Pharmgenomics Pers Med 2017; 10: 1-16.
34) Turchinovich A, Weiz L, Langheinz A, Burwinkel B. Characterization of extracellular circulating microRNA. Nucleic Acids Res 2011; 39: 7223-7233.
35) Kim YKK. Extracellular microRNAs as biomarkers in human disease. Chonnam Med J 2015; 51: 51-57.
36) Thomou T, Mori MA, Dreyfuss JM, Konishi M, Sakaguchi M, Wolfrum C, Rao TN, Winnay JN, Garcia-Martin R, Grinspoon SK, Gorden P, Kahn CR. Adipose-derived circulating miRNAs regulate gene expression in other tissues. Nature 2017; 542: 450-455.
37) Zaiou M, El Amri H, Bakillah A. The clinical potential of adipogenesis and obesity-related microRNAs. Nutr Metab Cardiovasc Dis 2018; 28: 91-111.
38) Goss AM, Goree LL, Ellis AC, Chandler-Laney PC, Casazza K, Lockhart ME, Gower BA. Effects of diet macronutrient composition on body composition and fat distribution during weight maintenance and weight loss. Obesity 2013; 21: 1133-1138.
39) Te Morenga L, Mann J. The role of high-protein diets in body weight management and health. Br J Nutr 2012; 108: S130-S138.
40) Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. Obstet Gynecol Surv 2009; 64: 460-462.

41) Wycherley TP, Moran LJ, Clifton PM, Noakes M, Brinkworth GD. Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012; 96: 1281-1298.
42) Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes1-3. Am J Clin Nutr 2013; 97: 505-516.
43) Goodarzi MO. Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications. Lancet Diabetes Endocrinol 2018; 6: 223-236.
44) Qi Q, Chu AY, Kang JH, Jensen MK, Curhan GC, Pasquale LR, Ridker PM, Hunter DJ, Willett WC, Rimm EB, Chasman DI, Hu FB, Qi L. Sugar-sweetened beverages and genetic risk of obesity. Obstet Gynecol Surv 2013; 68: 211-213.
45) Qi Q, Chu AY, Kang JH, Huang J, Rose LM, Jensen MK, Liang L, Curhan GC, Pasquale LR, Wiggs JL, De Vivo I, Chan AT, Choi HK, Tamimi RM, Ridker PM, Hunter DJ, Willett WC, Rimm EB, Chasman DI, Hu FB, Qi L. Fried food consumption, genetic risk, and body mass index: gene-diet interaction analysis in three US cohort studies. BMJ 2014; 348: g1610.
46) Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. Am J Med 2015; 128: 229-238.
47) Salas-Salvadó J, Garcia-Arellano A, Estruch R, Marquez-Sandoval F, Corella D, Fiol M, Gómez-Gracia E, Viñoles E, Arós F, Herrera C, Lahoz C, Lapetra J, Perona JS, Muñoz-Aguado D, Martínez-González MA, Ros E, PREDIMED Investigators. Components of the mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. Eur J Clin Nutr 2008; 62: 651-659.
48) Bonaccio M, Di Castelnuovo A, De Curtis A, Costanzo S, Persichillo M, Donati MB, Cerletti C, Iacoviello L, de Gaetano G, Moli-sani Project Investigators. Adherence to the mediterranean diet is associated with lower platelet and leukocyte counts: results from the Moli-sani study. Blood 2014; 123: 3037-3044.
49) Georgoulis M, Kontogianni MD, Yiannakouris N. Mediterranean diet and diabetes: prevention and treatment. Nutrients 2014; 6: 1406-1423.
50) Nissensohn M, Román-Viñas B, Sánchez-Villegas A, Piscopo S, Serra-Majem L. The effect of the mediterranean diet on hypertension: a systematic review and meta-analysis. J Nutr Educ Behav 2016; 48: 42-53.e1.
51) Walter S, Mejia-Guevara I, Estrada K, Liu SY, Glymour MM. Association of a genetic risk score with body mass index across different birth cohorts. JAMA 2016; 316: 63-69.
52) San-Cristobal R, Navas-Carretero S, Livingstone KM, Celis-Morales C, Macready AL, Fallaize R, O'Donovan CB, Lambrinou CP, Moschonis G, Marsaux CFM, Manios Y, Jarosz M, Daniel H, Gibney ER, Brennan L, Drevon CA, Gundersen TE, Gibney M, Saris WHM, Lovegrove JA, Grimaldi K, Parnell LD, Bouwman J, Van Ommen B, Mathers JC, Martinez JA. Mediterranean diet adherence and genetic background roles within a web-based nutritional intervention: the food4me study. Nutrients 2017; 9. pii: E1107.
53) Hosseini-Esfahani F, Koochakpoor G, Daneshpour MS, Sedaghati-Khayat B, Mirmiran P, Azizi F. Mediterranean dietary pattern adherence modify the association between FTO genetic variations and obesity phenotypes. Nutrients 2017; 9. pii: E1064.
54) Garcia-Bailo B, Toguri C, Eny KM, El-Sohemy A. Genetic variation in taste and its influence on food selection. Omi A J Integr Biol 2009; 13: 69-80.
55) Keller KL, Steinmann L, Nurse RJ, Tepper BJ. Genetic taste sensitivity to 6-n-propylthiouracil influences food preference and reported intake in preschool children. Appetite 2002; 38: 3-12.
56) Ullrich N V., Touger-Decker R, O'Sullivan-Maillet J, Tepper BJ. PROP taster status and self-perceived food adventurousness influence food preferences. J Am Diet Assoc 2004; 104: 543-549.
57) Tsuji M, Nakamura K, Tamai Y, Wada K, Sahashi Y, Watanabe K, Ohtsuchi S, Ando K, Nagata C. Relationship of intake of plant-based foods with 6-n-propylthiouracil sensitivity and food neophobia in japanese preschool children. Eur J Clin Nutr 2012; 66: 47-52.
58) Feeney E. The impact of bitter perception and genotypic variation of TAS2R38 on food choice. Nutr Bull 2011; 36: 20-33.
59) Looy H, Callaghan S, Weingarten HP. Hedonic response of sucrose likers and dislikers to other gustatory stimuli. Physiol Behav 1992; 52: 219-225.
60) Eny KM, Wolever TMS, Corey PN, El-Sohemy A. Genetic variation in TAS1R2 (Ile191Val) is associated with consumption of sugars in overweight and obese individuals in 2 distinct populations. Am J Clin Nutr 2010; 92: 1501-1510.
61) Mennella JA, Pepino MY, Lehmann-Castor SM, Yourshaw LM. Sweet preferences and analgesia during childhood: effects of family history of alcoholism and depression. Addiction 2010; 105: 666-675.
62) Donaldson LF, Bennett L, Baic S, Melichar JK. Taste and weight: is there a link? Am J Clin Nutr 2009; 90: 800S-803S.
63) Stewart JE, Feinle-Bisset C, Golding M, Delahunty C, Clifton PM, Keast RSJ. Oral sensitivity to fatty acids, food consumption and BMI in human subjects. Br J Nutr 2010; 104: 145-152.
64) Gilbertson TA, Liu L, York DA, Bray GA. Dietary fat preferences are inversely correlated with peripheral gustatory fatty acid sensitivity. Ann N Y Acad Sci 1998; 855: 165-168.
65) Comuzzie AG, Cole SA, Laston SL, Voruganti VS, Haack K, Gibbs RA, Butte NF. Novel genetic loci identified for the pathophysiology of childhood obesity in the hispanic population. PLoS One 2012; 7: e51954.
66) Keller KL, Liang LC, Sakimura J, May D, van Belle C, Breen C, Driggin E, Tepper BJ, Lanzano PC, Deng L, Chung WK. Common variants in the CD36 gene are associated with oral fat perception, fat preferences, and obesity in African Americans. Obesity 2012; 20: 1066-1073.
67) Bokor S, Legry V, Meirhaeghe A, Ruiz JR, Mauro B, Widhalm K, Manios Y, Amouyel P, Moreno LA, Molnàr D, Dallongeville J, HELENA Study group. Single-nucleotide polymorphism of CD36 locus and obesity in European adolescents. Obesity 2010; 18: 1398-1403.

68) Min Yun Y, Young Song E, Hoon Song S, Song J, Kim JQ. CD36 polymorphism and its relationship with body mass index and coronary artery disease in a Korean population. Clin Chem Lab Med 2007; 45: 1277-1282.
69) Farook VS, Puppala S, Schneider J, Fowler SP, Chittoor G, Dyer TD, Allayee H, Cole SA, Arya R, Black MH, Curran JE, Almasy L, Buchanan TA, Jenkinson CP, Lehman DM, Watanabe RM, Blangero J, Duggirala R. Metabolic syndrome is linked to chromosome 7q21 and associated with genetic variants in CD36 and GNAT3 in Mexican Americans. Obesity 2012; 20: 2083-2092.
70) Madden J, Carrero JJ, Brunner A, Dastur N, Shearman CP, Calder PC, Grimble RF. Polymorphisms in the CD36 gene modulate the ability of fish oil supplements to lower fasting plasma triacyl glycerol and raise HDL cholesterol concentrations in healthy middle-aged men. Prostaglandins Leukot Essent Fat Acids 2008; 78: 327-335.
71) Ma X, Bacci S, Mlynarski W, Gottardo L, Soccio T, Menzaghi C, Iori E, Lager RA, Shroff AR, Gervino EV, Nesto RW, Johnstone MT, Abumrad NA, Avogaro A, Trischitta V, Doria A. A common haplotype at the CD36 locus is associated with high free fatty acid levels and increased cardiovascular risk in Caucasians. Hum Mol Genet 2004; 13: 2197-2205.
72) Menichini D, Facchinetti F, Longo M. Interventions to reduce metabolic sequelae in rodent models of diet-induced obesity. IJMDAT 2018; 1: e160.
73) Alshammari G, Khan R, Brameld J, Amer S, Lomax MA. Gene expression of inflammatory markers in adipose tissue between obese women with polycystic ovary and normal obese women. Eur Rev Med Pharmacol Sci 2017; 21: 1099-1105.
74) Niu HM, Liu CL. The aberrant expression of Smad6 and TGF-β in obesity linked cardiac disease. Eur Rev Med Pharmacol Sci 2017; 21: 138-142.
75) Jones A, Danielson KM, Benton MC, Ziegler O, Shah R, Stubbs RS, Das S, Macartney-Coxson D. miRNA signatures of insulin resistance in obesity. Obesity 2017; 25: 1734-1744.
76) Hulsmans M, De Keyzer D, Holvoet P. MicroRNAs regulating oxidative stress and inflammation in relation to obesity and atherosclerosis. FASEB J 2011; 25: 2515-2527.
77) Heneghan HM, Miller N, McAnena OJ, O'Brien T, Kerin MJ. Differential miRNA expression in omental adipose tissue and in the circulation of obese patients identifies novel metabolic biomarkers. J Clin Endocrinol Metab 2011; 96: E846-850.
78) Carreras-Badosa G, Bonmatí A, Ortega FJ, Mercader JM, Guindo-Martínez M, Torrents D, Prats-Puig A, Martinez-Calcerrada JM, Platero-Gutierrez E1, De Zegher F1, Ibáñez L1, Fernandez-Real JM, Lopez-Bermejo A, Bassols J. Altered circulating miRNA expression profile in pregestational and gestational obesity. J Clin Endocrinol Metab 2015; 100: E1446-E1456.
79) Ortega FJ, Mercader JM, Catalán V, Moreno-Navarrete JM, Pueyo N, Sabater M, Gómez-Ambrosi J, Anglada R, Fernández-Formoso JA, Ricart W, Frühbeck G, Fernández-Real JM. Targeting the circulating microRNA signature of obesity. Clin Chem 2013; 59: 781-792.
80) Willeit P, Skroblin P, Moschen AR, Yin X, Kaudewitz D, Zampetaki A, Barwari T, Whitehead M, Ramírez CM, Goedeke L, Rotllan N, Bonora E, Hughes AD, Santer P, Fernández-Hernando C, Tilg H, Willeit J, Kiechl S, Mayr M. Circulating microRNA-122 is associated with the risk of new-onset metabolic syndrome and type 2 diabetes. Diabetes 2017; 66: 347-357.
81) Can U, Buyukinan M, Yerlikaya FH. The investigation of circulating microRNAs associated with lipid metabolism in childhood obesity. Pediatr Obes 2016; 11: 228-234.
82) Thompson MD, Cismowski MJ, Serpico M, Pusateri A, Brigstock DR. Elevation of circulating microRNA levels in obese children compared to healthy controls. Clin Obes 2017; 7: 216-221.