Nutrición Hospitalaria

Nutr Hosp 2013;28(Supl. 5):44-55
ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198
CODEN NUHOEQ
S.V.R. 318

Genetic susceptibility to obesity and metabolic syndrome in childhood

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Abstract

Obesity is one of the major public health problems worldwide. It is a chronic, complex, and multifactorial-origin disease characterised by body fat excess mainly due to an imbalance between dietary intake and energy expenditure. One of the major complications of obesity is metabolic syndrome, which comprises anthropometrical, clinical, and metabolic dysfunctions that predispose the affected individual to the development of type 2 diabetes mellitus and cardiovascular diseases. It is hypothesised that the variability in the susceptibility to obesity-mediated metabolic complications involves both environmental and genetic factors. Whereas advances in the knowledge of the variations in the human genome have led to the identification of susceptibility genes that contribute to obesity and related disorders, relatively few studies have specifically focused on the interactions between obesity and genetic polymorphisms and the development of metabolic complications. Despite these limited efforts, an increasing amount of evidence suggests that the effects of some gene variants on metabolic traits are modified by or present only in the setting of obesity. Furthermore, some of these loci may have larger effects on metabolic phenotypes in the presence of certain dietary or lifestyle factors. In the present manuscript, we reviewed the genes and their variants that have been evidenced to play a role in obesity-associated metabolic complications through genetic association studies, including candidate gene and genome-wide association approaches in adults and children.

Nutr Hosp 2013; 28 (Supl. 5):44-55

Key words: *Genes. Gene variants. Metabolic syndrome. Obesity. Single-nucleotide polymorphisms.*

SUSCEPTIBILIDAD GENÉTICA DE OBESIDAD Y SÍNDROME METABÓLICO EN LA INFANCIA

Resumen

La obesidad es uno de los principales problemas de salud pública a nivel mundial. Es una enfermedad crónica, compleja y de origen multifactorial que se caracteriza por el exceso de grasa corporal y se desarrolla, fundamentalmente, debido a un desequilibrio entre la ingesta dietética y el gasto energético. Una de las principales complicaciones de la obesidad es el síndrome metabólico, el cual comprende alteraciones antropométricas, clínicas y metabólicas que predisponen el desarrollo de diabetes *mellitus* tipo 2 y enfermedades cardiovasculares.Existe la hipótesis de que tanto factores ambientales como genéticos participan en la variabilidad a la susceptibilidad de las complicaciones metabólicas mediadas por la obesidad. Mientras que los avances en el conocimiento de las variaciones en el genoma humano, han llevado a la identificación de genes que contribuyen a la susceptibilidad de la obesidad y las enfermedades asociadas, son relativamente pocos los estudios que se han centrado específicamente en la interacción entre la obesidad y polimorfismos genéticos relacionados con el desarrollo de complicaciones metabólicas o directamente con el síndrome metabólico. Además, algunos de estos *loci* pueden tener mayor efecto en los fenotipos metabólicos cuando está modificado por la dieta u otrosfactores ambientales. En este manuscrito se revisan los genes ylas variantes con mayor evidencia de asociación con las complicaciones metabólicasrelacionadas con la obesidad descritas en estudios de asociación genética, incluyendo estudios de genes candidatos y estudios amplios del genoma humano en adultos y niños.

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Palabras clave: *Genes. Obesidad. Polimorfismos de nucleótido simple. Síndrome metabólico. Variantes génicas.*

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Abbreviations

BMI: body mass index.
CVD: cardiovascular disease.
T2DM: type 2 diabetes mellitus.
HDL-c: high-density lipoprotein-cholesterol.
IR: insulin resistance.
MetS: metabolic syndrome.
TAG: triacylglycerol.
VLDL: very-low-density lipoprotein.
GWAS: genome-wide association studies.
BP: blood pressure.
OR: odds ratio.
SNP: single nucleotide polymorphisms.
PPARG: peroxisome proliferator-activated receptor gamma.
TNF-α: tumour necrosis factor alpha.1

Introduction

Obesity, in addition to overweight, is the sixth major cause of disease risk worldwide. It has been estimated that 1 billion adults are currently overweight, and an additional 475 million adults are obese. It has also been estimated that 200 million school-aged children are either overweight or obese worldwide and that 40-50 million of these children are classified as obese.[1] The obesity epidemic, which mainly affected developed countries at the beginning, has extended to developing countries, particularly their urban areas. Childhood obesity has lead to an increase in morbidity and mortality, which in turn result in high financial burdens for health systems.

Childhood obesity is a condition in which excess body fat negatively affects the child's health and/or wellbeing. This disease has been associated with several comorbidities, such as cardiovascular events, hypertension, insulin resistance (IR), dyslipidaemia, metabolic syndrome (MetS), liver steatosis, orthopaedic problems, and sleep apnoea, which can occur in either the short or long term. Different studies have shown an association between childhood obesity and the risk of cardiovascular diseases (CVD) in adulthood,[2] the early development of atherosclerosis, changes in the BMI over time, and the prediction of lipid and lipoprotein concentrations.[3]

Of all of the complications of obesity, a cluster of anthropometric, clinical, and metabolic alterations (low levels of high-density lipoprotein-cholesterol (HDL-c), high triacylglycerols (TAG), high blood pressure (BP), and impaired glucose metabolism) form part of MetS, which predisposes the affected individuals to the development of type 2 diabetes mellitus (T2DM) and CVD.[4]

The mechanisms linking obesity to its metabolic complications are extremely complex and remain hotly debated. It is hypothesised that the variability in the susceptibility to obesity-mediated metabolic complications involves both environmental and genetic factors. Whereas advances in knowledge of the variations in the human genome have led to the identification of susceptibility genes that contribute to obesity and related disorders, relatively few studies have specifically focused on the interactions between obesity and genetic polymorphisms in the development of metabolic complications. Despite these limited efforts, an increasing amount of evidence, particularly related to adipokines and adipose tissue, suggests that the effects of some gene variants on metabolic traits are modified by or present only in the setting of obesity. Furthermore, some of these loci may have larger effects on metabolic phenotypes in the presence of certain dietary or lifestyle factors. In this chapter, we review the small number of genes and their variants that have been evidenced to have a role in obesity-associated metabolic complications.

Definition and prevalence of metabolic syndrome

The MetS diagnosis criteria are very well defined in the adult population (table I).[5] However, despite many attempts, no consensus has yet been reached for the diagnosis of MetS in children and adolescents.[6,7] Many authors, such as those cited in the study by Olza et al[6], have proposed different classifications, but methodological and physiological limitations have complicated the establishment of a definitive definition.[7] The main difficulties in the definition of the criteria are the following:

1. The measure of the adiposity excess with different parameters (body mass index [BMI] or waist circumference).

Table I
The International Diabetes Federation metabolic syndrome definition for adults

For a person to be defined as having metabolic syndrome, they must have central obesity (defined through the waist circumference* with ethnicity specific values) plus any two of the following four factors:

Increased triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL-c	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Increased blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Increased fasting plasma glucose	FPG ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define the presence of the syndrome.

*If the BMI is greater than 30 kg/m², central obesity can be assumed and the waist circumference does not need to be measured. HDL-c, high-density lipoprotein-cholesterol; BP, blood pressure; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; BMI, body mass index. Adapted from ref. 5. For ethnicity-specific waist circumference values, see this reference.

2. The extrapolation of the cut-off values from the adult population.
3. The lack of ethnicity- and sex-specific charts with separate cut-off values for the prepubertal and the pubertal populations.
4. The physiological pubertal changes that temporarily modify the plasma hormones levels have not been taken into account.
5. The measurement of the glucose metabolism dysfunction with a fasting plasma glucose test or an oral glucose tolerance test instead of IR, e.g., homeostatic model of insulin resistance (HOMA-IR).
6. Factors such as physical activity or environmental conditions that have not been taken into account.
7. The lack of inclusion of other biomarkers (e.g., proinflammatory and/or prothrombotic factors) that might contribute to the identification of the syndrome, particularly at the early onset.

Due to the abovementioned problems, it is very difficult to epidemiologically monitor MetS. The prevalence rates depend on the definition used for its classification, but, given that MetS is driven by obesity, the prevalence of the latter will strongly influence the prevalence of MetS[8]. Recently, our group showed that the percentage of MetS in Spanish prepubertal obese children varies from 7.6% to 30.8% in the same population depending on the definition used.[7] In a recent systematic review conducted by Friend et al[9], the prevalence of MetS in a paediatric population was studied (including 85 studies) using the three most used definitions (International Diabetes Federation, National Cholesterol Education Program's Adult Treatment Panel III and World Health Organisation). The results of the review showed that the median prevalence of MetS was 3.3% (range of 0% to 19.2%) in the whole population, 11.9% (range of 2.8% to 29.3%) in the overweight population, and 29.2% (range of 10.0% to 66.0%) in the obese population. These data reinforce the necessity of unifying criteria and establishing a unique definition that encompasses all of the variables involved in the development of the syndrome. In the search of a methodology to overcome this barrier, one promising approach has been the use of the measurements of the MetS components as continuous variables to obtain a sum of the z-scores of each component that can be used to quantify the risk[7]. It has been shown that the use of this cluster would better identify the at-risk paediatric population compared with the use of the most common five components in the definition of this syndrome.

Origin of metabolic syndrome

The aetiology of MetS is not completely clear; however, the evidence indicates that IR, inflammation, and obesity are the three factors that converge to cause all of the metabolic changes that intervene in the development of MetS (fig. 1). Nevertheless, other factors, such as the environment, diet, physical inactivity, genetic predisposition, age, ethnicity, and some drugs, are involved in the development of the syndrome.

Individuals with IR increase their insulin production to force glucose into the peripheral tissues. In fact, each tissue exhibits differential insulin sensitivity, but the liver appears to be where the disorder starts. The increase in the free fatty acid (FFA) flux within the liver, either by *de novo* lipogenesis or by FFA delivery via the portal vein, impairs the hepatic insulin action, which leads to an increase in the hepatic glucose output, the synthesis of proinflammatory cytokines, the TAG syn-

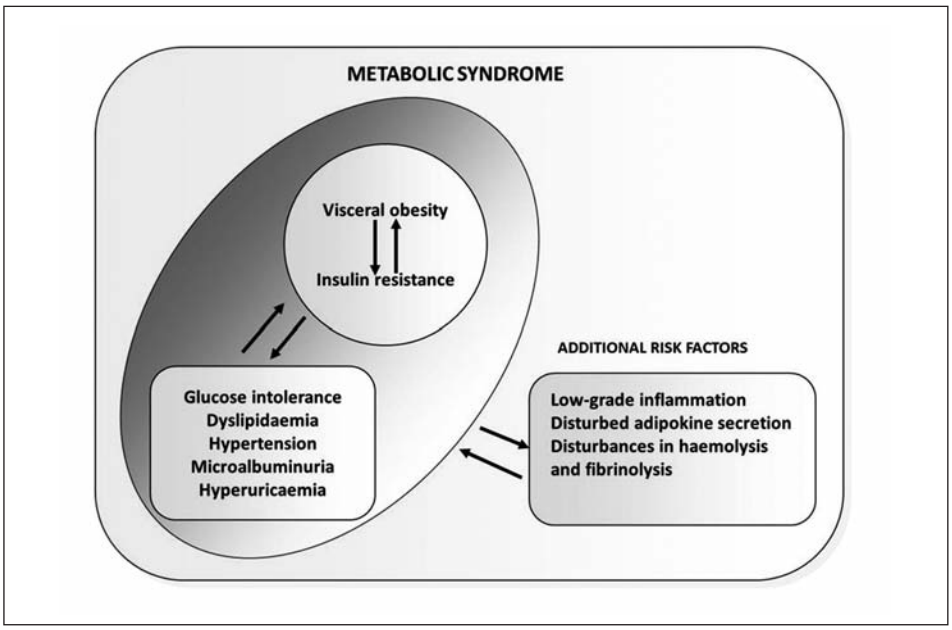

Fig. 1.—Metabolic disorders and inflammation in the metabolic syndrome.

thesis, the intrahepatic lipid deposition, and the ectopic lipid accumulation.[4] The excess TAG is released with apolipoprotein B as VLDL, the HDL-c secretion diminishes, and the number of relatively cholesterol-depleted small dense low-density lipoprotein particles increase. These changes in the lipoprotein metabolism are considered the primary cause for MetS dyslipidemia.[10]

IR in the adipose tissue is also important in the development of MS. The expanded adipose tissue increases lipolysis and releases FFA due to a reduced antilipolytic effect and the loss of inhibition of the hormone-sensitive lipase. The FFAs drain to the liver via the portal vein and increase the hepatic FFA accumulation to create a vicious circle between the liver and the adipose tissue. The changes in the expanding adipose tissue promote the transition to a metabolically dysfunctional phenotype. Whereas the macrophages in lean adipose tissue express markers of M2, the macrophages in obese tissue lead to the recruitment and accumulation of M1 and T cells, which indicates the infiltration of the tissue and the formation of crown-like structures and results in the accumulation of macrophages around dead adipocytes in inflamed adipose tissue.[11] The metabolic dysfunction also stimulates the production of large amounts of pro-inflammatory factors and cytokines as interleukins, leptin, tumour necrosis factor alpha (TNF-α), resistin and plasminogen activator inhibitor-1, that have effects in other tissues such as liver or skeletal muscle but also acts in a paracrine way.[7,11]

The skeletal muscle is an important contributor to the glucose homeostasis, and the liver IR contributes to the disruption of the glucose-fatty acid cycle and the insulin-mediated glucose uptake by skeletal muscle, which facilitates the development of hyperglycaemia. The accumulation of FFAs in the muscle worsens the IR to induce the impairment of insulin signalling.[12]

Evidence for a genetic component

Obesity is a complex trait that stems from a complicated network of contributory components, including genomic and environmental factors, the aggregations of which increase the probability of disease. Sedentary behaviours and high-calorie diets are the major environmental factors that drive the epidemic of obesity. Studies in twins, no twin siblings, and adoptees have shown that genetic components contribute from 40% to 70% to the interindividual variation in common obesity.[13] The influence of both family history and childhood obesity on the obesity risk in young adulthood was assessed by Whitaker et al,[14] who showed that the influence of having one obese parent throughout childhood and adolescence increases an individual's risk of adult obesity by 2.2- to 3.2-fold compared with someone whose parents were not obese. Having two obese parents during childhood and adolescence substantially increases the risk of being an obese adult, with ORs (odds ratios) ranging from 5 to 15.30, compared with someone who had no obese parents, with the exception of parental obesity at the age of 10 to 14 yrs. The influence of obesity during childhood and adolescence on the risk of adult obesity increases steadily with age. Whereas obesity during infancy (1-2 yrs) does not increase one's risk of being an obese adult, an obese child at the age of 10 to 14 yrs has a 22.30-fold increased risk of being an obese adult compared to someone who was not obese as a child. Therefore, without a doubt, the obese phenotype runs prevalently in families, but most of the causative genes are still undiscovered.

Furthermore, the high clustering of components in family and twin studies has implied the importance of a genetic contribution to MetS. In a seminal study of 2,508 male twin pairs, concordance for the clustering of three MetS components (hypertension, diabetes, and obesity) was found in 31.6% of the monozygotic pairs compared with 6.3% of the dizygotic pairs.[15] Similarly, among 236 female twin pairs, the heritability estimates for obesity, insulin/glucose, and dyslipidaemia were found to be 61%, 87%, and 25%, respectively, using a classical non-molecular approach. This finding indicates an important genetic contribution for each of these components.[16] Among 803 individuals from 89 Caribbean-Hispanic families in the Northern Manhattan Family Study, the heritability of MetS itself was found to be 24%, with significant heritability for the lipid/glucose/obesity (44%) and hypertension (20%) components.[17] The marked variability in the heritability between studies might be partly attributable to ethnicity. Based on these demonstrations of heritability for MetS and its components, several investigators have directly examined the genetic determinants for MetS using linkage or association studies.

Genetics of obesity and metabolic syndrome

Hundreds of candidate genes for obesity susceptibility have been identified through a variety of approaches, as revised by Rankinen et al:[18] animal studies, Mendelian syndromes, linkage studies, genetic association studies, and expression studies. Since the mid-1990s, candidate gene studies have aimed to identify obesity-susceptibility genes. Candidate gene studies are hypothesis-driven, and hundreds of genes for which there is some evidence that supports a role in the regulation of the energy balance in animal models or in extreme/monogenic forms of obesity have been tested to determine their association with obesity-related traits.[18] However, consistent associations have been reported for only a handful of these candidate genes. The main reasons for the limited success of the candidate gene approach include the small sample sizes used and thus the low statistical power, the low number of genetic variants tested per gene and thus the incomplete coverage of the common variations, and the limited biological insights that provide the basis for the gene candidacy. The advent of genome-wide association studies (GWAS) in 2005 changed the way and the speed through

which genetic loci are discovered. The completion of the Human Genome Project and the HapMap project, in conjunction with the development of high-throughput genotyping techniques and statistical and computational methods, have enabled large-scale GWAS, in which a large number of genetic variants are tested for association with the trait of interest. To adjust for the vast number of tests performed in GWAS, procedures such as multiple testing correction and replication in independent samples are undertaken to minimise the number of false discoveries. Among the strongest arguments in favour of performing GWASs is the fact that such studies are hypothesis-free, i.e., the whole genome is screened for association to a complex disease or trait without prior hypotheses about which genes or regions are likely to be associated. The results of numerous GWASs performed in recent years have justified this approach because many previously unsuspected regions have been reproducibly associated with numerous complex traits.

Nevertheless, interest remains in the analysis of candidate genes. With GWAS data now available on numerous large cohorts, it has become possible to embed candidate gene studies within GWAS to test the association of a much larger number of candidate genes than previously possible. Recent studies have examined whether those obesity candidate genes are enriched for associations with BMI compared with non-candidate genes using data from a large-scale GWAS. The authors concluded that the candidate genes are more likely to be truly associated than the non-candidate genes, at least in the obesity-susceptibility evidence that supports the enrichment of the association of candidate genes, which suggests that the candidate gene approach retains some value. However, the degree of enrichment is small despite the extensive number of candidate genes and the large sample size. Studies that focus on candidate genes have only slightly increased chances of detecting associations and are likely to miss many true effects in non-candidate genes, at least for obesity-related traits.[19]

Genome-wide association studies of obesity and metabolic syndrome

To date, GWASs have provided robust evidence for a role of some variants, particularly the *FTO*, *MC4R* and *TMEM18* loci, in the development of obesity. The vast majority of these studies have been performed in white Europeans and in adults and have identified 32 loci that reached genome-wide significance. These studies were recently revised.[19,20] Table II reports the genes that have so far been found to be associated with obesity (BMI). The search for genetic factors that specifically influence paediatric obesity-related outcomes has primarily focused on replicated candidate genes in adult studies. In a study performed by Willer et al,[21] the analysis was conducted using a study sample from the Avon Longitudinal Study of Parents and Children (ALSPAC; N = 4,951 with BMI information at age 11) and confirmed significant associations of variants in/near *FTO*, *MC4R*, *TMEM18*, *KCTD15*, and *GNPDA2* with the BMI. Successively, the data were replicated in a cohort of obese children (N = 1,038) from the United Kingdom cohort of the Severe Childhood Onset Obesity Project, and an increased risk of extreme childhood obesity was revealed for the BMI-increasing alleles near *TMEM18*, *GNPDA2*, and *NEGR1*.[22] In the European Youth Heart Study (1,252 children and 790 adolescents), the associations of 15 variants (*NEGR1*, *SEC16B*, *LYPLAL1*, *TMEM18*, *ETV5*, *GNPDA2*, *TFAP2B*, *MSRA*, *BDN*F, *MTCH2*, *BCDIN3D*, *NRXN3*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15*) with BMI were similar to those observed in adults.[23] In a meta-analysis data of 13,071 children and adolescents, significant associations with BMI were found for 9 of 13 variants, and a region near to the *TMEM18* variant had the strongest effect. The effect on the BMI tended to be more pronounced for variants in/near *SEC16*, *TMEM18*, and *KCTD15* in children and adolescents compared with adults.[24]

Several extensive and successful efforts have been made to map variants associated with the components of MetS. Studies using MetS as a binary trait and studies investigating the components using bivariate or multivariate methods have been published in the last few years. However, bivariate methods may be considered somewhat paradoxical because three or more components are used to define the syndrome. Moreover, it should be noted that a number of investigators within the scientific community do not agree that MetS is an entity in itself, but a set of risk factors for cardiometabolic disease that are useful to the biological understanding. Zabaneh and Balding[25] conducted a two-stage GWAS to identify common genetic variations that alter the risk of MetS and related phenotypes in Indian Asian men, who exhibit a high prevalence of these conditions. In stage 1, approximately 317,000 SNPs were genotyped in 2,700 individuals, and 1,500 of these SNPs were selected to be genotyped in an additional 2,300 individuals. No evidence of a common genetic basis for the MetS traits was found in this study. Another approach was used in the study performed by Kraja et al,[26] which grouped seven country-studies from the STAMPEED consortium, comprising 22,161 participants of European ancestry, who underwent bivariate genome-wide association analyses of metabolic traits. The phenotypes for MetS were combined in all possible pairwise combinations, and those individuals who exceeded the thresholds for both traits of a pair were considered affected. Twenty-eight SNPs were associated with MetS or a pair of traits. These variants were located in or near 15 genes that were associated with binary pairwise traits or with MetS *per se* at the genome-wide significance level. All but two of these bivariate associations included a lipid abnormality. The authors suggested that these results show that the genetic effects on lipid levels are more pronounced

Table II

Genetic variants associated with obesity and metabolic syndrome through genome-wide association studies (GWAS)

Nearest gene	*Full gene name*	*SNP*	*Trait*
FTO	Fat mass and obesity associated	rs1558902	BMI*
		rs1121980	BMI*
		rs9939609	BMI*
		rs8050136	BMI*
		rs17817449	BMI*
		rs12149832	BMI*
MC4R	Melanocortin 4 receptor	rs571312	BMI*
		rs12970134	BMI*
TMEM18	Transmembrane protein 18	rs2867125	BMI*
		rs6548238	BMI*
		rs7561317	BMI*
SEC16B	SEC16 homolog B	rs543874	BMI*
		rs574367	BMI
		rs516636	BMI*
BDNF	Brain-derived neurotrophic factor	rs10767664	BMI*
		rs4923461	BMI
		rs6265	BMI*
		rs2030323	BMI
GNPDA2	Glucosamine-6-phosphate deaminase 2	rs10938397	BMI*
SH2B1	SH2B adaptor protein 1	rs7359397	BMI*
		rs7498665	BMI
ETV5	Ets variant 5	rs9816226	BMI*
		rs7647305	BMI
NEGR1	Neuronal growth regulator 1	rs2815752	BMI*
		rs2568958	BMI*
TFAP2B	Transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	rs987237	BMI*
NRXN3	Neurexin	rs10150332	BMI*
FAIM2	Fas apoptotic inhibitory molecule 2	rs7138803	BMI
MTCH2	Mitochondrial carrier 2	rs3817334	BMI
		rs10838738	BMI
KCTD15	Potassium channel tetramerisation domain containing 15	rs29941	BMI*
		rs11084753	BMI
SLC39A8	Solute carrier family 39 (zinc transporter), member 8	rs13107325	BMI

Table II *(cont.)*
Genetic variants associated with obesity and metabolic syndrome through genome-wide association studies (GWAS)

Nearest gene	*Full gene name*	*SNP*	*Trait*
GPRC5B	G protein-coupled receptor, family C, group 5, member B	rs12444979	BMI
PRKD1	Protein kinase D1	rs11847697	BMI
QPCTL	Glutaminyl-peptide cyclotransferase-like	rs2287019	BMI
		rs11671664	BMI
MAP2K5	Mitogen-activated protein kinase 5	rs2241423	BMI
		rs4776970	BMI
LRRN6C	Leucine rich repeat neuronal 6C	rs10968576	BMI
FANCL	Fanconi anaemia, complementation group L	rs887912	BMI
CADM2	Cell adhesion molecule 2	rs13078807	BMI
TMEM160	Transmembrane protein 160	rs3810291	BMI
LRP1B	Low-density lipoprotein receptor-related protein 1B	rs2890652	BMI
MTIF3	Mitochondrial translational initiation factor 3	rs4771122	BMI
TNNI3K	TNNI3-interacting kinase	rs1514175	BMI
ZNF608	Zinc finger protein 608	rs4836133	BMI
PTBP2	Polypyrimidine tract-binding protein 2	rs1555543	BMI
RPL27A	Ribosomal protein L27a	rs4929949	BMI
NUDT3	Nudix (nucleoside diphosphate linked moiety X)-type motif 3	rs206936	BMI
LPL	Lipoprotein lipase	rs295	MetS
CETP	Cholesteryl ester transfer protein, plasma	rs173539	MetS
APOA5	Apolipoprotein A-V	rs2266788	MetS
ZNF259	Zinc finger protein 259	rs2075290	MetS
BUD13	BUD13 homolog (S. Cerevisiae)	rs10790162	MetS
APOC1	Apolipoprotein C-I	rs4420638	MetS
BRAP	BRCA1-associated protein	rs11065987	MetS
PLCG1	Phospholipase C, gamma 1	rs753381	MetS
APOA1/C3/A4/A5	Gene cluster region (SNP rs964184)	rs964184	MetS

* Association observed in children. BMI: body mass index. MetS: metabolic syndrome.

than for other traits. The most influential variants in the correlation among traits were in or near *LPL*, *CETP*, *APOA5*, *ZNF259*, *BUD13*, *TRIB1*, *LOC100129500*, and *LOC100128154*. The genes with variants that influence MetS *per se* included *LPL*, *CETP*, and the APOA-cluster (*APOA5*, *ZNF259*, and *BUD13*), which are known to play an important role in lipid metabolism.[26]

Another approach that combined several components of MetS in a GWAS was published by Avery et al,[27] who used data from 19,486 European Americans and 6,287 African Americans. Six phenotype domains (atherogenic dyslipidemia, vascular dysfunction, vascular inflammation, pro-thrombotic state, central obesity, and elevated plasma glucose), including 19 quantitative traits, were examined and analysed through a principal component analysis. These researchers then applied a multivariate approach that related eight principal components from the six domains. In European

Americans, these researchers identified genome-wide significant SNPs representing 15 loci. Many of these loci were associated with only one trait domain, and five of these associations were consistent with the results obtained with the cohort of African Americans. In addition, several of these associations were already known, e.g., the association of central obesity with *FTO*. However, the study identified three new loci in or near *APOC1*, *BRAP*, and *PLCG1*, which were associated with multiple phenotype domains. The strongest new pleiotropic signal in European Americans was observed for rs4420638, which is located near *APOC1* and was associated with elevated plasma, atherogenic dyslipidemia, vascular inflammation, and central obesity. A recent GWAS on MetS and its component traits in four Finnish cohorts consisting of 2,637 MetS cases and 7,927 controls (all of the individuals in both cohorts were free of diabetes) suggested that genes from the lipid metabolism pathways have a key role in the genetic background of MetS. The lipid locus at the *APOA1/C3/A4/A5* gene cluster region (SNP rs964184) was associated with MetS in all four study samples. Interestingly, the association was further supported by the results from a serum metabolite analysis, in which rs964184 was associated with various VLDL, TAG, and HDL-c metabolites. Most of these metabolites were associated with lipid phenotypes, and none of them were associated with two or more uncorrelated MetS components. A genetic risk score, which was calculated as the number of alleles in a loci associated with individual MetS traits, was strongly associated with the MetS status.[28] Nevertheless, further replication is needed, and, if these pleiotropic loci hold true, these loci may help characterise metabolic deregulation and identify targets for intervention. In addition, to the best of our knowledge, no GWAS has been performed in children; thus, this is mandatory.

Candidate gene association studies of metabolic syndrome

Because glucose metabolism, insulin signalling, adipokines, and inflammation are thought to play crucial roles in MetS pathogenesis, it may be fruitful to examine candidate genes from these areas for MetS. Table III lists the reported candidate genes associated with an increased or decreased risk for MetS. The main findings reported by candidate gene associations studies of the main metabolic pathways involved in MetS are reviewed below.

Glucose metabolism and insulin signalling

The genetic basis of T2DM, glucose homeostasis (fasting plasma glucose and insulin), and indirect measures of IR (HOMA-IR) have been demonstrated by GWAS and meta-analyses of individual case-control studies. More than 50 loci have been found to be associated with the risk of T2DM, and the strongest effect was observed with the rs7903146 in the *TCF7 L2* gene. In a meta-analysis of 21 GWAS cohorts (Meta-Analyses of Glucose and Insulin-related traits Consortium [MAGIC]),[29] robust statistical evidence for the genome-wide association with fasting glucose was observed for SNPs in eight loci (including the candidate genes *ADCY5*, *FADS1*, and *GLIS3*) and SNPs in one locus (with the candidate gene *IGF1*). Expanding upon MAGIC, a joint meta-analysis was conducted to determine whether genes involved in the IR pathways (HOMA-IR) could be discovered by accounting for differences in obesity (BMI) and interactions between the BMI and genetic variants.[30] The discovery of SNPs in six loci (including the candidate genes *COBLL1/GRB14*, *IRS1*, *PPP1R3B*, *PDGFC*, *UHRF1BP1*, and *LYPLAL1*) that were associated with fasting insulin, high TAG levels, and low HDL-c levels suggested a new series of pathways that can be studied to identify genes with contributions to multiple phenotypes.

The associations of genetic variants in insulin signalling have been reported to be associated with MetS. In a recent association study with 1,886 participants from the EPIC-NL cohort, a group of five SNPs were found to be related with IR (*IRS1* rs2943634, *PPARG* rs1801282, *GCKR* rs780094, *GCK* rs1799884, and *IGF1* rs35767), and the *IRS1* SNP was the only one that was significantly associated with MetS and the MetS score. This SNP was also associated with HbA1C, TAG, and HDL-c.[31] Several studies have indicated that *INPPL1* gene polymorphisms may be associated with the MetS and/or T2DM. In a British cohort, three SNPs in the *INPPL1* gene were significantly associated with components of MetS, such as hypertension, obesity, and T2DM, although the findings could not be replicated in French subjects.[32] In a recent cross-sectional study with 1,328 participants with MetS and 1,074 controls without MetS, two SNPs of *INPPL1*, rs2276048 (silent mutation) and rs2276047 (intronic) were found to be associated with MetS in men.[33]

Lipid metabolism

Genes related to lipid metabolism have been described to be strongly associated with MetS. The determinants of the plasma TAG metabolism might be determinants of MetS, and genetic variants have been revised by Joy et al.[34] Apolipoprotein C-III is present in TAG-rich lipoproteins and inhibits lipoprotein lipase, thereby delaying the catabolism of TAG. A case-control study consisting of whites, South Asians, and blacks demonstrated that the *APOC3* promoter polymorphisms –482C > T and –455 T> C were associated with MetS. Among 1,788 Japanese individuals, of whom 1,017 had MetS and 771 were controls, the *APOA5* –1131T > C polymorphism was strongly associated with MetS prevalence, and the C allele was signifi-

Table III

Genetic variants associated with obesity and metabolic syndrome through genome-wide association studies (GWAS)

Nearest gene	*Full gene name*	*Trait*
ADCY5	Adenylate cyclase 5	Increased fasting glucose
ADIPOQ	Adiponectin	Decreased risk of obesity, MetS, and T2DM and high adiponectin
APOA5	Apolipoprotein A-V	Increased TAG and decreased HDL-c
APOC3	Apolipoprotein C-III	Increased TAG and decreased HDL-c
COBLL1/GRB14	Cordon-bleu WH2 repeat protein-like 1 growth factor receptor-bound protein 14	Increased fasting insulin and TAG and decreased HDL-c
FABP4	Fatty acid binding protein 4	Increased HOMA-IR and FABP4 levels in children
FADS1	Fatty acid desaturase 1	Increased fasting glucose
ENPP1	Nucleotide pyrophosphatase/phosphodiesterase-1	Increased fasting insulin and risk of MetS in children
GLIS3	GLIS family zinc finger 3	Increased fasting glucose
IGF1	Insulin-like growth factor 1 (somatomedin C)	Increased fasting glucose
IL6	Interleukin 6	Increased risk of MetS
INPPL1	Inositol polyphosphate phosphatase-like 1	Increased systolic and diastolic blood pressure, obesity, and T2DM
IRS1	Insulin receptor substrate 1	Increased fasting insulin and TAG and decreased HDL-c
INS VNTR	Insulin variable number of tandem repeats	Increased fasting insulin and risk of MetS in children
LPL	Lipoprotein lipase	Decreased fasting HDL-c
LYPLAL1	Lysophospholipase-like 1	Increased fasting insulin and TAG and decreased HDL-c
MCP1	Monocyte chemoattractant protein 1	Increased risk of MetS
PDGFC	Platelet derived growth factor C	Increased fasting insulin and TAG and decreased HDL-c
PLIN4	Perilipin 4	Increased risk of MetS in children and adolescents
PPARG	Peroxisome proliferator-activated receptor gamma	Increased abdominal circumference and TAG and decreased HDL-c
PPP1R3B	Protein phosphatase 1, regulatory subunit 3B	Increased fasting insulin and TAG and decreased HDL-c
RSTN	Resistin	Increased TAG, BMI, and systolic and diastolic blood pressure
SR-BI	Scavenger receptor class B type I	Decreased fasting HDL-c and increased risk of MetS in children
TCF7 L2	Transcription factor 7-like 2	Increased fasting glucose
TNFA	Tumour necrosis factor a	Increased systolic blood pressure and obesity in adults and children
UHRF1BP1	UHRF1-binding protein 1	Increased fasting insulin and TAG and decreased HDL-c
ZFP36	ZFP36 ring finger protein	Increased fasting glucose and LDL-c

TAG: triacylglycerides. HDL-c: high-density lipoprotein-cholesterol. LDL-c: low-density lipoprotein-cholesterol. MetS: metabolic syndrome. T2DM: type 2 diabetes mellitus.

cantly related to increased TAG and decreased HDL-c levels. In contrast, a study of 3,124 white individuals from Germany and Austria did not find an association between the *APOA5* –1131T > C polymorphism and MetS, but did discover that the *APOA5*56C > G variant conferred an increased risk of MetS. These varied results in genetic associations are likely due to ethnic differences. In addition, the *lipoprotein lipase S447X* variant has been associated with MetS in Turkish women. In particular, this study showed that females with the more common SS genotype had a significantly increased likelihood for MetS and low HDL-c levels.

Interestingly, in a recent systematic review, the 56C > G (*APOA5*), –1131T > C (*APOA5*), –482C > T (*APOC3*), and –455T > C (*APOC3*) polymorphisms were more prevalent in subjects with MetS.[31] Thus, genetic variations affecting TAG metabolism might be associated with the composite MetS phenotype.

In addition to genes involved in the TAG metabolism, peroxisome proliferator-activated receptor gamma (PPARG), which is a nuclear receptor involved in glucose and fatty acid metabolism, has been associated with obesity and MetS. The Pro12Ala (rs1801282) polymorphism of the *PPARG* gene has been consistently associated with T2DM. However, although 16 studies have investigated the association between Pro12Ala (rs1801282) and MetS, as discussed in a systematic review,[35] most of these showed no effect. Interestingly, although the 12Pro allele is associated with an increased risk of T2DM and IR independent of BMI, the meta-analysis demonstrates that 12Ala is the risk allele if any effect on MetS exists. The association between C1431T (rs3856806), which is another well-known *PPARG* polymorphism, and MetS has been investigated in six cross-sectional studies, which are included in the same meta-analysis, and no association was found between this SNP and MetS. Although both the 12Ala and the C1431T alleles do not appear to significantly increase the MetS risk, a haplotype containing the same alleles was associated with an increased prevalence of MetS in a cross-sectional study of 1,115 French subjects.[36] Other SNPs in the *PPAR* family of genes have been studied. A study of French-Canadian men revealed no association between the *PPARA* L162 V polymorphism and MetS despite the higher frequency of this polymorphism in men exhibiting increased abdominal circumference, high TAG levels, and low HDL-c levels. The *PPARD* –87T>C polymorphism in French-Canadian men and women conferred protection from the MetS phenotype, and this protection was further enhanced if the carriers consumed less than 34.4% calories from fat, which suggests a gene-environment interaction.[37]

Adipokines

In humans, several polymorphisms in leptin (*LEP*), leptin receptor (*LEPR*), resistin (*RETN*), adiponectin (*ADIPOQ*), adiponectin receptor 1 (*ADIPOR1*), and adiponectin receptor 2 (*ADIPOR2)* have been found to be associated with obesity and MetS phenotypes. A recent metanalysis that included 21 polymorphisms in seven genes that were significantly associated with obesity suggested that only polymorphisms in *ADIPOQ* decreased the risk of obesity, whereas polymorphisms in the *LEP, LEPR*, and *RETN* genes were not related to the development of obesity.[38] Interestingly, some of these genetic variants have been associated with MetS. Among 1,438 Taiwanese individuals, the G allele of the *ADIPOQ* SNPrs1501299 in intron 2 was associated with decreased risk of obesity, MetS, and T2DM.[39] The examination of the –420C>G SNP in the *RSTN* gene revealed that G/G homozygotes had an increased prevalence of MetS and elevated TAG, BMI, and systolic and diastolic BP values compared with the other genotypes. In a follow-up case control study, the *RSTN* –420C > G SNP was associated with an increased MetS prevalence but did not influence the MetS prevalence among individuals at high cardiovascular risk.[40] Recently, 64 tagging SNPs in *ADIPOQ, ADIPOR1*, and *ADIPOR2* were genotyped in two general population cohorts consisting of 2,355 subjects and one cohort of 967 subjects with T2DM. A genetic variation in *ADIPOQ*, but not in its receptors, was associated with altered serum adiponectin. However, genetic variations in *ADIPOQ* and its receptors do not appear to contribute to the risk of IR or MetS.[41]

Inflammation

Proinflammatory cytokines, such as interleukin-6, TNF-α, and monocyte chemoattractant protein-1 (MCP1), are postulated to have a role in the MetS pathogenesis and represent candidate genes. The main finding in adults was revised by Joy et al.[34] Among 6,916 Danes, the AGC/GGG haplotype of three common *IL6* promoter polymorphisms were more common among the adults with MetS compared with the controls without MetS. The examination of the *IL6* –174G > C promoter polymorphism in 571 whites revealed a higher MetS prevalence among those individuals with the CC genotype. Conversely, a population-based sample of 1,630 Germans revealed that none of the seven SNPs of the proinflammatory cytokine *MCP1 g*ene were associated with MetS. In addition, although a meta-analysis of 31 studies revealed that the *TNFA* –308G>A polymorphism conferred a risk of 1.23 for obesity and an increase in the systolic BP of 3.5 mm Hg, the relationship of this polymorphism with MetS was not examined. Zinc finger protein 36 (*ZFP36*), which is involved in TNF-α regulation, has been proposed as a candidate gene for MetS based on its position on the long arm of chromosome 19, which is a region linked with MetS that exhibits significant differential expression (4.6-fold higher) among obese individuals without MetS compared with those with MetS. In the same study, the *ZFP36* rs251864 polymorphism was associated with a lower body weight among women and the T allele was associated with glucose levels in men. Furthermore, the *ZFP36* haplotype was associated with plasma low-density lipoprotein in men and women. Thus, future studies might replicate the *ZFP36* association with MetS.

Association studies of metabolic syndrome in children

Candidate gene association studies that search for factors that specifically influence paediatric obesity

and metabolic-related outcomes are limited and scarce in the scientific literature. The main limit is the sample size, most likely due to the abovementioned difficulty associated with the epidemiological monitoring of MetS depending on the definition used for its classification. Those studies that investigated genes involved in glucose metabolism, insulin signalling, adipokines, and inflammation in at least 100 obese children are briefly summarised below.

The T allele of the rs997509*ENPP1* (nucleotide pyrophosphatase/phosphodiesterase-1) gene has been found to predispose obese children to MetS and IR in 409 obese children compared with 400 lean controls.[42] The insulin variable number of tandem repeats (VNTR) polymorphism located in the insulin gene promoter (*INS VNTR*) has been associated with the insulin levels in obese children and was found predispose 320 obese children to develop the MetS[43] Several genes involved in lipid metabolism have been associated with childhood MetS risk. The rs5888 in the *scavenger receptor class B type I* (*SR-BI*) gene, which plays a role in cholesteryl esters-HDL metabolism, was associated with MetS in 39 children diagnosed with the syndrome compared with 124 children with simple obesity.[44] The presence of selective SNPs in the *FABP4* gene increased HOMA-IR and FABP4 levels in 309 children aged 5-7 years, although the MetS classification was not considered in this study.[45] The minor A allele in *PLIN4* was associated with a higher risk of MetS in 234 obese children and adolescents.[46] In addition, two inflammation genes associated with MetS in adults have also been studied in children. The TNFA –308G > A polymorphism was more common in 124 children with simple obesity; however, it did not appear to be associated with the degree of obesity, insulin resistance, lipid profile, leptin levels, or the incidence of MetS in obese children.[47] The IL6 –174G > C promoter polymorphism did not appear to be associated with obesity or with the incidence of MetS in 124 obese children.[48]

Conclusion

MetS represents a complex phenotypic trait consisting of several clinical factors associated with an increased risk of T2DM and CVD. Genetic studies in adults and children have provided conflicting associations of genes and gene variants rather than consistently reproducible associations and linkages. Nonetheless, the hope remains that understanding the genetic determinants of MetS will lead to early detection of new cases and possible preventive strategies based on the important caveats for genetic studies of complex traits. Thus, although genetics likely plays a crucial role in MetS development, the elucidation of the exact genes involved has been hindered by the lack of a consistent MetS definition, the varying combination of phenotypes even within a single definition, ethnic disparities, and gender influences. Furthermore, the lifestyle determinants for MetS development should not be ignored, and these determinants are also likely under genetic control. In short, MetS development represents an intricate interaction between genetic susceptibilities and environmental influences, and genetic studies increase our appreciation of this complexity.

Acknowledgements

This work was supported by Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica (I+D+I) of the Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (PI020826, PI051968), Consejería de Innovación y Ciencia of the Junta de Andalucía (P06-CTS 2203), and Ministerio de Universidades y Tecnología of the Instituto de Salud Carlos III, Fondo de Investigaciones Sanitarias, RETIC (Red SAMID RD08/0072/0028).

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