The Metabolic Syndrome: A Crossroad for Genotype-Phenotype Associations in Atherosclerosis

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The metabolic syndrome comprises a set of metabolic and physiologic risk factors associated with elevated cardiovascular disease risk. The expression of each one of its major factors (hypertriglyceridemia, low high-density lipoprotein cholesterol levels, hypertension, abdominal obesity, and insulin resistance) has been found to be the result of complex interactions between genetic and environmental factors. Moreover, obesity may play a major role in triggering the metabolic syndrome by interacting with genetic variants at candidate genes for dyslipidemia, hypertension, and insulin resistance. In support of this hypothesis, several studies at multiple candidate genes have already demonstrated the significance of these interactions; however, the data and their reliability are still very limited, and in many cases replication studies are still lacking in the literature. Therefore, more studies with better epidemiologic design and standardized adiposity measures are needed to estimate the contribution of body weight and fat distribution to the genetic predisposition to the metabolic syndrome, which is the most common cardiovascular disease risk factor in industrialized societies.

Introduction

Cardiovascular diseases (CVD) are the result of complex interactions between both environmental and genetic factors. Unlike the rare and severe genetic defects that cause monogenic diseases, the genetic factors that modulate the individual susceptibility to CVD in the general population are, most likely, common polymorphisms having modest effects at the individual level; however, because of their high allele frequencies, these polymorphisms may have an associated significant population-attributable risk. For over two decades, researchers have been using the candidate gene approach for identifying genes contributing to CVD. The goal behind this effort is the identification of genes and their variants involved in the multiple pathophysiologic pathways leading to CVD. By doing this, we should be able to increase our understanding of the mechanisms of the disease. Moreover, this knowledge should give us the tools to identify individual susceptibilities and specific therapeutic interventions targeted to more personalized prevention and clinical management.

The progress of this endeavor will be facilitated by sequence data available for the human genome. Moreover, our increased capacity for sequencing is allowing the resequencing of hundreds of candidate genes, which will yield reliable and reproducible data on the nucleotide sequence diversity in different populations throughout candidate regions of the human genome. The other key element for our progress will be provided by genetic and molecular epidemiology involving large-scale population studies requiring close integration of genetics with more traditional epidemiologic research. This is essential for a disease in which environmental factors mediate the phenotypic expression of the susceptibility genes. In fact, most of the susceptibility genes for common diseases in general and CVD in particular do not have a primary etiologic role in the development of the disease, but rather act as response modifiers to exogenous factors such as stress, environment, disease, and drug intake. In the words of Olden and Wilson [1], "The relation between genes and the environment can be compared to a loaded gun and its trigger. A loaded gun by itself causes no harm; it is only when the trigger is pulled that the potential for harm is released." Obviously, the loaded gun represents our genes and the trigger the environment. Therefore, a better characterization of the interactions between environmental and genetic factors constitutes a key issue in the understanding of the pathogenesis of CVD and our ability to use the knowledge on its prevention and therapy.

The Metabolic Syndrome: Components, Prevalence, and Therapies

Hypertension, hyperlipidemia, impaired glucose tolerance, and obesity are well established traditional CVD risk

factors. When these risk factors cluster in one individual, CVD risk dramatically increases. This clustering of risk factors is not a rare event but the most common cause of CVD in the modern society. This combined phenotype has been known since the late 1980s as the "metabolic syndrome" [3], but prior to this (since the 1930s) it had been described as the syndrome X, the insulin resistance syndrome, and the deadly quartet. More recently, some authors have suggested the use of "dysmetabolic syndrome" to capture better the concept of metabolic abnormality or dysfunction [3].

The precise definition of the metabolic syndrome has shifted slightly from time to time, and there have been a number of attempts to develop standardized criteria for its diagnosis. One of the most commonly used today is the definition developed by the World Health Organization (WHO) in 1998 [4] and revised in 1999, which establishes that the human metabolic syndrome requires at least one of the following: type 2 diabetes mellitus or impaired glucose tolerance or insulin resistance. It also requires at least two of the following: hypertension (blood pressure ≥ 140/90 mm Hg), obesity (body mass index [BMI] ≥ 30 kg/m^2, or waist to hip ratio > 0.90 for male subjects or > 0.85 for female subjects), dyslipidemia (low high-density lipoprotein [HDL] cholesterol [< 0.9 mmol/L]) and/or hypertriglyceridemia (≥ 1.7 mmol/L), or microalbuminuria (urinary albumin excretion rate > 20 μg/min). In 2001, the Third Report of the National Cholesterol Education Program (NCEP) of the Adult Treatment Panel III (ATP III) [5] outlined the importance of the primary prevention of CVD in persons with multiple risk factors and provided for the first time a working definition of the metabolic syndrome. Five diagnostic traits were listed, and the presence of any three of these factors is considered sufficient for diagnosis. These traits are hypertension (blood pressure ≥ 130/85 mm Hg or medication), obesity (waist circumference > 102 cm in men or > 88 cm in women), hypertriglyceridemia (≥ 1.7 mmol/L), low HDL cholesterol (< 1.04 mmol/L in men or < 1.29 mmol/L in women), or high fasting glucose (≥ 6.1 mmol/L). Although estimates of prevalence in different populations are highly dependent on the definition of the metabolic syndrome, the reality is that the current estimates are appalling and the future perspective is even more alarming. Thus, age-adjusted estimates from the National Health and Nutrition Examination Survey III (NHANES III) [6] from 1988 to 1994 revealed that 24% of adult Americans (aged 20 years or older) had this syndrome. Prevalence of this syndrome clearly increases with age (from 6.7% among NHANES III participants aged 20 to 29 years to 43.0% for participants aged 60 years or older). Although gender has been considered another important trait that modulates gene expression and genetic susceptibility to this syndrome [3], the global prevalence of the metabolic syndrome among adult Americans differed little in men (24.0%) and women (23.4%). However, substantial differences of gender prevalence depending on the ethnic group were observed. Moreover, the overall prevalence of this syndrome was highest among Mexican-Americans (31.9%) and lowest in blacks (21.6%) [6]. It has been pointed out that differences in prevalence by gender or by ethnic group may be largely attributed to the definition used to diagnose the syndrome and that central obesity is the key factor. Nowadays, this remains controversial and different results have been reported. For example, Bonora *et al*. [7] in the Bruneck study in Italy reported a prevalence of 34.1% of the metabolic syndrome according to the WHO criteria, and 17.8% according to the NECP-ATPIII criteria. Conversely, Meigs *et al*. [8] did not find differences in prevalence depending on the definition used. Thus, among Framingham subjects who were white, the age-adjusted prevalence of the metabolic syndrome was 24% by both ATP III and WHO criteria; among San Antonio Heart Study (SAHS) non-Hispanic white subjects, the age-adjusted prevalence of the metabolic syndrome was 23% and 21%, respectively; and among SAHS Mexican-American subjects, the age-adjusted prevalence of the metabolic syndrome was 31% and 30%, respectively. By any criteria, subjects with the metabolic syndrome in this study were at higher risk of CVD [8]. Limited data exist on the syndrome's association with CVD morbidity and mortality. Recently, it has been estimated that in the NHANES III [9], the metabolic syndrome was associated with a higher risk of nonfatal myocardial infarction (odds ratio of 2.01; 95% CI, 1.53 to 2.64) and stroke (odds ratio of 2.16; 95% CI, 1.48 to 3.16). Prospectively, Lakka *et al*. [10] reported a higher risk of coronary mortality associated with the metabolic syndrome (hazard ratio of 4.16; 95% CI, 1.60 to 10.8). Therefore, a major effort should be placed on its detection, prevention, and therapy. In terms of the treatment, we have the therapeutic tools to successfully deal with some of the individual components. Thus, we have efficient drugs to lower blood pressure; likewise, several drugs are being used to improve insulin sensitivity, and the dyslipidemia can be treated with fibrates and even with statins. However, such therapeutic success has not been shared by the other major component of the metabolic syndrome (*ie*, obesity, and more specifically central obesity), which may be a key etiologic factor in the development of the underlying insulin resistance. It may be the "trigger for the loaded gun" of its genetic predisposition. Therefore, obesity may be at the root of the metabolic syndrome, with the aggravated situation of being an unresolved and fast growing problem all over the world. This review focuses on the current evidence supporting the idea that many of the common genetic variants found in candidate genes for each of the individual components of the metabolic syndrome (hypertension, insulin resistance/diabetes, and dyslipidemia) are associated with higher-risk phenotypes and thus with increased disease risk, primarily when overweight and/or obesity is concurrently present.

Multiple Candidate Genes and Environmental Factors Driving the Metabolic Syndrome

The metabolic syndrome is a complex disease characterized by clustering of several of the components described previously. Twin and familial aggregation studies have shown a high heritability for each of the individual components [3]; however, its genetic basis as a composite phenotype has not been systematically investigated.

The "thrifty genotype" hypothesis has been postulated to justify the sudden and dramatic rise of the metabolic syndrome. The concept is simple and logical. In order to ensure survival during the frequent periods of famine that characterized the lives of our ancestors, certain genes evolved to regulate efficient intake and utilization of fuel stores. Nowadays, in those societies characterized by food abundance and physical inactivity, some forms of these genes confer a greater risk of obesity and related metabolic disorders. Such genes were termed "thrifty genes" in 1962 by Neel [11]. An alternative explanation of the metabolic syndrome uses the concept of "thrifty phenotype" [12]. According to this hypothesis, factors in the intra-uterine environment (mainly malnutrition) would lead to intrauterine growth retardation and low birth weight, with subsequent increased risk of the metabolic syndrome later in life. Results from animal studies add evidence to this hypothesis, and there are already several epidemiologic studies showing a significant association between low birth weight and impaired insulin sensitivity, type 2 diabetes mellitus, hypertension, and CVD risk [13]. In relation to this, we know about the classic association between short stature and higher CVD risk [14]. However, stature also reflects the postnatal nurture as well as the genetic background of the individual, adding complexity to a phenotype that deserves more investigation as a modulating variable in the metabolic syndrome. In this regard, Turner *et al*. [15], in a study that examined the context-dependent associations of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism with blood pressure, found that height modified the effect of this polymorphism. Therefore, stature, in addition to obesity, acts as a modulating factor, and simultaneously supports a role for both the "thrifty phenotype" and the "thrifty genotype" in the etiology of the metabolic syndrome and atherosclerosis. In a recent work, Hypponen *et al*. [16] evaluated how the risk of diabetes associated with low birth weight was affected by accumulation of body mass from childhood to adulthood. Their data indicate that excessive postnatal weight gain was required for the manifestation of diabetes among those with small weight at birth. Phenotype and genotype are also examined in the work from Eriksson *et al*. [17], which showed that the associations of the peroxisome proliferator activated receptor (PPAR) γ2 Pro12Ala polymorphism with glucose and insulin metabolism in adult life depend on body size at birth.

In the past 10 years, hundred of genetic variants have been examined in epidemiologic studies as candidate genes for the development of the different features of the metabolic syndrome; however, the modulating role of obesity in such associations has not been given the proper protagonism. The best characterized genes and common genetic variants associated with each of the individual components of the metabolic syndrome are summarized below.

Hypertension

Despite the large body of research about the genetics of hypertension, no common genetic variants with large effects have been identified for human hypertension. It is conceivable that blood pressure depends on a mosaic of multiple loci, each one with small influence that may be increased by certain conditions such as age, gender, obesity, salt intake, and so forth. Despite the lack of a major genetic influence, a number of polymorphisms in candidate genes, including those involving the renin-angiotensin-aldosterone system (RAAS), sodium epithelial channel, catecholaminergic/adrenergic function, renal kallikrein system, and alpha-adducin, and others involving lipoprotein metabolism, hormone receptors, and growth factors, have significantly been associated with differences in blood pressure [18]. The most intensely examined have been the polymorphisms in the RAAS, with most studies focusing on the ACE I/D polymorphism. Initial studies reported an association between the D allele and increased plasma ACE activity as well as with diastolic blood pressure. However, subsequent studies reported either no association or associations that were highly context dependent, primarily from age and gender [15]. Angiotensin II is the principal effector of the RAAS and most of its effects are mediated by the angiotensin II type 1 receptor (AGTR1R). A modulation by gender of the A1166C polymorphism in the AGTR1R gene has also been reported, with the C allele related to higher blood pressure in men but not in women [19]. The M235T polymorphism in the angiotensinogen (AGT) gene has also been the subject of extensive research, and a recent meta-analysis including 127 publications concluded that the T allele was associated with a statistically significant but weak risk of hypertension, with some differences in magnitude among ethnic groups [20].

Within the growing numbers of candidate genes for hypertension, we should also cite endothelin-1 (ET-1), a vasoconstrictor peptide [21•]. This gene has a common polymorphism, K198N(G/T), which has been found by some to be a promising hypertension marker. This is also the case for the β2-adrenergic receptor gene (ADRβ2), traditionally associated with lipolysis and obesity, but also emerging as a potentially important mediator of vasodilatation. Two variants (Arg16Gly and Gln27Glu) have been found by some to be associated with hypertension and/or obesity; however, the results have been contradictory [22].

Dyslipidemia

The dyslipidemia associated with the metabolic syndrome is characterized by elevated triglycerides and low HDL cholesterol concentrations. Plasma low-density lipoprotein (LDL) cholesterol concentrations are often normal, but there is a relative increase of small, dense, atherogenic particles. One of the new potential candidate genes is the scavenger receptor class B type I (SR-BI or SCARB1) gene. SCARB1, a cell-surface glycoprotein, was the first HDL receptor to be defined and characterized in vitro and in animal studies. Osgood *et al.* [24] described three common variants (at exon 1 [G→A], exon 8 [C→T], and intron 5 [C→T]), which were associated with HDL cholesterol, triglycerides, and BMI, suggesting that SCARB1 might be involved in determining some features of the metabolic syndrome [23]. Moreover, Osgood *et al.* [24] have demonstrated that type 2 diabetes interacts with the exon 1 polymorphism in the SCARB1 gene in determining HDL cholesterol concentrations and LDL particle size in the Framingham Heart Study participants. Another promising locus is the ATP-binding cassette A1 (ABCA1) transporter, which is involved in the cholesterol efflux from macrophages to HDL. In addition to Tangier disease, a defective ABCA1 gene has been associated with lower HDL cholesterol and higher CVD risk. Recent evidence suggests additional associations with insulin resistance, as demonstrated by the relation between ABCA1 gene expression and fasting glucose concentration in vivo [25]. Moreover, a differential effect of the R219K polymorphism between blacks and whites has been reported [26], suggesting that adiposity may be a crucial determinant of the effects of this polymorphism. PPARs have become the subject of intense interest for both pharmacologic and genetic studies. These transcription factors enhance ABCA1 expression by inducing the liver X receptor (LXR). PPARs have four isoforms (alpha, beta, gamma, and delta) that play key roles in the regulation of lipid and glucose metabolism. PPARγ, a regulator of lipogenic genes, has a common Pro12Ala polymorphism that has been associated with HDL cholesterol, triglycerides, glucose, and obesity in some studies but not in others [27].

The cholesteryl ester transfer protein (CETP) is a key protein that facilitates the transfer of esterified cholesterol from HDL to very low-density lipoprotein (VLDL) cholesterol. The TaqIB polymorphism in this locus has shown remarkably consistent results in its association with plasma HDL cholesterol concentrations. In terms of the relations between HDL and triglyceride-rich lipoproteins, the lipase gene family (hepatic lipase [LIPC], lipoprotein lipase [LPL], endothelial lipase [LIPG], and pancreatic lipase [PL]) represents a growing and promising superfamily in which common variations had repeatedly been related with HDL cholesterol and triglycerides, but also sporadically with blood pressure, obesity, and insulin resistance. The LPL gene has been studied the most. LPL is a multifunctional protein that hydrolyses core triglycerides from circulating chylomicrons and VLDL that are then either degraded by the liver or converted to LDL particles by hepatic lipase. Numerous sequence variants within the LPL gene have been identified (*ie*, HindIII, S447X, D9N, and N291S), and they have been widely associated with HDL cholesterol and triglycerides concentrations; however, some differences among studies and populations suggest the presence of interactions with additional factors [28]. Numerous polymorphisms have also been analyzed in the LIPC gene coding for hepatic lipase. Four single nucleotide polymorphisms (SNPs) in the promoter region (-250G/A, -514C/T, -710T/C, and -763A/G) are in strong linkage disequilibrium, and they have been associated with HDL cholesterol and triglyceride levels, with important differences among studies depending on the ethnic, anthropometric, and dietary characteristics of the populations [29]. Finally, several variants of the APOA1/C3/A4/A5 and APOE/C1/C2 gene clusters have been consistently associated with the characteristic dyslipemia of the metabolic syndrome [30].

Obesity

The genetic architecture of obesity is still a matter of debate. In addition to the important influence of environmental factors, two main hypotheses are being considered: 1) obesity is the result of a small number of common variants, and 2) the genetic predisposition to obesity may instead result from multiple rare variants in a large number of genes. Several studies have indicated that some of the genes involved in pathways regulating energy expenditure and food intake may play a prominent role in the predisposition to obesity. Among them, variations in the adrenergic receptors (ADR), uncoupling proteins (UCPs), PPARs, leptin (LEP), and the leptin receptor (LEPR) genes are of particular interest. ADRs are genes involved in the regulation of catecholamine-stimulated lipolysis. A missense mutation in the ADRB3 (Trp64Arg) has been considered a prime candidate for obesity. However, although it has been associated with obesity-related phenotypes in various initial studies, subsequent investigations have reported conflicting results. Additional gene-gender interactions, as well as a modulation by the HindIII-LPL polymorphism, have been reported to explain these results [31]. The UCPs are proton channel proteins on the inner mitochondrial membrane that play a pivotal role in adaptive thermogenic responses. Five UCPs genes (UCP-1, UCP-2, UCP-3, UCP-4, and UCP-5) have been described in humans. Experimental studies have linked the UCPs with basal metabolic rate, proton transport activity, energy homeostasis, and, therefore, with obesity [32]. In humans, a promoter variant, -3826 A/G, of the UCP-1 has been associated with BMI and weight gain with inconsistent results [33]. UCP-2 and UCP-3 actions can be modulated by transcriptional upregulation mediated by fatty acids via PPARs, cytokines, leptin signaling via hypothalamic pathway, and by thyroid and β2 adrenergic stimulation,

suggesting very complex interaction in the genetics of obesity [32]. LEP, the obese gene product discovered in 1995, may play a key role in the feedback system between adipose tissue and the ventromedial nucleus of the hypothalamus. A few common polymorphisms have been found in the LEP gene that have controversial associations with obesity. However, a defective LEP signaling to the brain may be due to receptor and postreceptor defects, and promising investigations are in progress on this topic.

Insulin resistance

Insulin resistance is a fundamental dysregulation that precedes the development of type 2 diabetes. Tumor necrosis factor α (TNF-α), a cytokine highly expressed in the adipose tissue, is implicated in its induction. The most studied polymorphism has been the -308G/A [33]. However, the results are inconsistent. TNF-α can induce insulin resistance by inhibition of tyrosine phosphorylation of the insulin receptor β chain and insulin receptor substrate-1 (IRS-1). Insulin resistance is characterized by a decrease in the insulin effect on glucose transport in muscle and adipose tissue. Tyrosine phosphorylation of IRS-1 and its binding to phosphoinositide 3-kinase are critical events in the insulin signaling cascade, leading to insulin-stimulated glucose transport. A Gly972Arg polymorphism in the IRS-1 gene has been associated with metabolic risk markers with inconsistent results [34]. Several other insulin receptor substrates (IRS-2, IRS-3, and IRS-4) have been found with promising results [35]. In addition, adipocytes secrete a number of factors that might modulate insulin sensitivity. One of these factors is adiponectin. Some polymorphisms in the adiponectin gene have been associated with blood glucose, obesity, and plasma lipids [36]. Another recently discovered adipocyte-specific secretory factor is resistin. Three common polymorphisms in the human resistin gene have been associated with insulin resistance and type 2 diabetes in whites [37].

In the past 2 years, some authors have pointed out the finding of genetic variants associated with the so-called multiple risk factor syndromes as a new area of research. Iwai *et al.* [38] have described a common polymorphism (A/G in intron 12) of the SAH gene, an acyl coenzyme A synthetase gene that was related to the multiple features of the metabolic syndrome. Thus, the G allele was associated with obesity, hypertriglyceridemia, hypertension, and hypercholesterolemia. Moreover, the recent ATP III definition of the metabolic syndrome [5] has facilitated the genetic investigation of the clustering of risk factors by classifying patients as having or not having the metabolic syndrome. This is the case of the recent work of Dallongeville *et al.* [39], in which they studied 276 patients with metabolic syndrome (ATP III criteria) and 872 control subjects. They found that the Arg16Gly polymorphism in the ADRB2 gene was statistically associated with the metabolic syndrome in men, with carriers of the 16Gly allele having a higher risk. Nowadays, in addition to this combined investigation, a more prominent role of obesity in the research of the metabolic syndrome is needed. The goals of this research should reach beyond the intrinsic role of obesity as a major determinant of the metabolic syndrome and investigate the modulation by obesity of the genetic susceptibility for other traits of the metabolic syndrome.

Obesity As a Modulating Phenotype of the Effect of the Genetic Variants

Considering the central role of obesity as well as the lack of consistency usually observed in association studies, we propose that obesity significantly affects the association between candidate genes and metabolic syndrome-related phenotypes. According to this notion, association studies should stratify their analyses by obesity-related phenotypes. This hypothesis and suggestion is largely based on the growing body of emerging evidence. In an exhaustive search of the bibliography, we have found more than 30 reports supporting the modulating effect of obesity on the different features of this syndrome (hypertension, dyslipidemia, and glucose intolerance), and they are summarized in Table 1. One of the limitations in comparing the results is the lack of standardization in the definition of obesity. The majority of studies focus on BMI; however, BMI is only an incomplete surrogate of body fat mass. In addition, this heterogeneity persists in the criteria for defining obesity between the WHO and the ATP III. In the ATP III criteria [5], obesity has been considered in terms of sex-specific waist circumference, whereas in the WHO definition [4], an individual is classified as obese if their BMI is 30 kg/m^2 or higher. The rationale for the use of waist criteria arises from data showing that measures of BMI are relatively insensitive indicators for CVD risk as compared with measures of abdominal obesity. However, more investigation is needed and the incorporation of the novel anthropometric and biochemical measures of adipose mass and function into large epidemiologic studies is required. Another subject of debate is the different cut-off point to define obesity depending on ethnicity. Such is the case of Asian populations, for which the WHO universal cut-off point of 30 kg/m^2 for obesity and 25 kg/m^2 for overweight have been considered very high (a reduction of 2 points has been proposed) [40]. Finally, a methodologic issue appears as another difficulty for replication, which is the treatment of the obesity variable in the statistical analysis: should it be a continuous variable, a categoric one based on international criteria, or based on the characteristics of the population.

In conclusion, a higher standardization for defining and analyzing obesity in the metabolic syndrome is needed in order to obtain results that are more consistent. Most of the studies reported so far fall short of using experimental designs that provide the best scientific

Table 1. Summary of studies analyzing gene*obesity interactions in the different features of the metabolic syndrome

Gene	Population	Variable and cut-off point	Results	Study
Adiponectin (APM1) [+276G>T]	642 diabetic and 995 control patients in the Nurses' Health Study	Obesity	The +276 genotype was significantly associated with diabetes risk among obese subjects	Hu *et al.* [50]
APM1 (T45G; [Gly15Gly]) and IVS2 + G62T	96 unrelated female patients with severe obesity and 96 non-obese control patients from the Swedish Obese Subjects cohort	Obesity	The T45G was associated with TC and waist circumference (P = 0.023 and 0.043, respectively) in obese subjects only. Glucose was highest in GG obese subjects for the IVS2 + G62T	Ukkola *et al.* [36]
Angiotensin-converting enzyme (ACE) insertion/deletion (I/D)	1875 non-Hispanic white individuals (988 female and 887 male subjects) from the general population of Rochester	Logistic regression models	The influence of variation in the ACE gene on interindividual variation in blood pressure is dependent on contexts that are indexed by gender, age, and measures of body size	Turner *et al.* [15]
ACE (I/D)	959 adult men, 25–75 years of age in Italy	Obesity (BMI ≥ 30)	DD was associated with larger increases in body weight and blood pressure	NCEP ATP III [5]
ACE (I/D)	205 community-dwelling healthy subjects in Japan	Regression model	The age*ACE genotype interaction was significantly associated with IMT	Tabara *et al.* [52]
Angiotensinogen (AGT) M235T	205 community-dwelling healthy subjects in Japan	Regression model	The SBP*AGT genotype interaction was significantly associated with IMT	Tabara *et al.* [52]
Apolipoprotein E (apoE) genotypes	2929 individuals participants in the Framingham Heart Study	Obesity (BMI ≥ 30)	Obesity modulates the association between APOE and fasting insulin and glucose in men	Elosua *et al.* [53•]
Apolipoprotein E (apoE) genotypes	205 community-dwelling healthy subjects in Japan	BMI	BMI by APOE interaction was significantly associated with IMT	Tabara *et al.* [52]
ATP binding cassette A1 (ABCA1) (R219K)	Community-based sample of 887 white and 390 black young adults aged 20–38 years; BMI of 26.4 in whites and 28.8 in blacks	Linear regression model	The K219 allele differs between blacks and whites, and modulates the association between age and HDL cholesterol, body fat, and triglycerides only in whites	Srinivasan *et al.* [26]
β2-adrenergic receptor (ADRB2) [ADRB2/Arg16Gly and Gln27Glu]	Quebec Family Study (QFS) cohort	Obesity (BMI ≥ 35)	There were interactions between markers within the β2-ADR gene affecting plasma TG concentrations and subcutaneous abdominal fat	Ukkola *et al.* [54]
ADRB2 (ADRB2/Arg16Gly)	1576 subjects (men and women) randomly selected in Brazil	BMI and WHR	Interaction between this polymorphism and BMI (P = 0.036) and WHR (P = 0.003) in SBP	Pereira *et al.* [22]
ADRB3 (Trp64Arg)	476 men and 587 women randomly selected from Spain	BMI and obesity	The Trp64Arg interacted with the LPL-HindIII polymorphism in determining obesity	Corella *et al.* [31]
ADRB3 (Trp64Arg)	271 unrelated individuals of Turkish origin	BMI < 25 and > 30	Frequency of the Arg allele decreases as BMI increases only in men	Proenza *et al.* [33]
Calpain 10 (CAPN10)	700 members of 63 families in America of European descent	Obesity	The effect on fasting insulin was most marked among obese individuals (P = 0.0061)	Elbein *et al.* [55]
CETP (TaqIB and D442G)	718 Chinese (392 male and 326 female patients); mean age of 55.4 y	Obesity (BMI ≥ 26)	For obese subjects, the TaqIB2 or D442G allele was not associated with increased HDL cholesterol	Hsu *et al.* [56]
CETP (TaqIB)	Healthy Scottish population (220 men and women)	BMI tertiles	In obese subjects, the difference between B1B1 and B2B2 individuals was diminished.	Freeman *et al.* [57]

BMI—body mass index; BP—blood pressure; HDL—high-density lipoprotein; IMT—intima-medial thickness; TC—total cholesterol; TG—triglyceride; WHR—waist to hip ratio.

Table 1. Summary of studies analyzing gene*obesity interactions in the different features of the metabolic syndrome *(Continued)*

Gene	Population	Variable and cut-off point	Results	Study
CETP (TaqIB)	245 women (41 with type 2 diabetes); BMI > 25; mean BMI of 33.5	Obesity	B2B2 genotype associated with elevated HDL cholesterol in obese women with low fasting insulin	Heilbronn *et al.* [58]
CETP (TaqIB)	187 sedentary men free from metabolic disorders in Canada	BMI	The association between the TaqIB polymorphism and HDL cholesterol was altered in obese subjects	Vohl *et al.* [59]
Endothelin-1(EDN1) (Lys198Asn)	General Japanese population (n = 1250); age > 40 y	Obesity (BMI ≥ 25)	Only obese subjects' diastolic BPs were significantly associated with the polymorphism of EDN1	Asai *et al.* [42•]
EDN1 (Lys198Asn)	Men and women in two large Japanese populations	Obesity (BMI ≥ 25)	Interaction between the K198N (G/T) polymorphism and BMI in hypertension (P = 0.027)	Jin *et al.* [21•]
EDN1 (Lys198Asn)	ECTIM study (648 cases/760 controls) and the Glasgow Heart Scan Study	Obesity (BMI ≥ 26)	Interaction between the T allele and BMI was observed on blood pressure	Tiret *et al.* [41]
HSL (C-60G)	Adult white and black subjects (HERITAGE study)	BMI	The effect of the C-60G polymorphism is sex, race, and insulin dependent	Garenc *et al.* [60]
Insulin receptor substrate-1 (IRS-1, Gly972Arg)	3684 subjects selected from a large, population-based cohort (Dutch); mean age of 53 y	BMI groups	The IRS-1 Gly972Arg polymorphism relates to higher fasting insulin levels and lower TG levels	Jellema *et al.* [34]
IRS-2 (Gly1057Asp)	193 Italian patients with type 2 diabetes and 206 control subjects	BMI < 27	Overweight modifies the effect of this polymorphism toward a higher risk of diabetes	Mammarella *et al.* [61]
IRS-2 (Gly1057Asp)	Pima Indians (n = 998); mean age of 29 y; BMI of 36	Linear regressions	The association of this allele with type 2 diabetes is mediated by interaction with obesity	Stefan *et al.* [35]
LIPC (-514C/T)	235 French-Canadian men; mean age of 42 y; BMI of 30	Adipose tissue	The effect of the T allele on HDL(2) cholesterol was abolished in visceral obesity	St. Pierre *et al.* [62]
Lipoprotein lipase (LPL) (D9N)	ECTIM; 1474 subjects in Europe; 662 MI cases and 812 control subjects	BMI ≥ 26	Interaction of the LPL-N9 mutation with obesity in determining an atherogenic lipid profile. The interaction BMIxLPL for TG is significant, especially in Belfast.	Mailly *et al.* [43]
LPL (HindIII)	339 Chinese (82 cases with HTG and 257 control subjects)	Obesity (BMI ≥ 26)	Interaction between obesity and this polymorphims on the risk of high TG	Ko *et al.* [44]
LPL (HindIII)	952 Chinese subjects (men and women) including 482 diabetic patients	BMI ≥ 25	The H+ allele was associated with higher TG and lower HDL cholesterol levels in obese subjects	Ma *et al.* [45]
LPL (HindIII)	156 women; age range 25–93 y	WHR	A statistically significant interaction between WHR and genotype for HDL cholesterol (P = 0. 027)	Senti *et al.* [46]
LPL (HindIII)	52 white men; mean age of 36 y	BMI (25 and 27)	This polymorphism may modulate the dyslipidemic state associated with visceral obesity	Vohl *et al.* [47]
LPL (N291S, D9N, and Ser447X)	632 patients with coronary angiography and 91 control subjects in Italy	BMI split 25	The favorable effect of the LPL S447X variant was even more pronounced in lean subjects and in those with low insulin levels	Arca *et al.* [48]
LPL (P207L, D9N, -93T/G)	206 (109 men and 97 women) heterozygous carriers of the D9N mutation (n = 118) or the P207L mutation (n = 88) in Canada	BMI 30 and waist	Abdominal obesity, more so than overall obesity, is an important determinant of variations in LDL and HDL particle size among heterozygous carriers of mutations in the LPL gene	Ruel *et al.* [49]

BMI—body mass index; BP—blood pressure; HDL—high-density lipoprotein; IMT—intima-medial thickness; TC—total cholesterol; TG—triglyceride; WHR—waist to hip ratio.

Table 1. Summary of studies analyzing gene*obesity interactions in the different features of the metabolic syndrome *(Continued)*

Gene	Population	Variable and cut-off point	Results	Study
LPL PvuII	273 unrelated individuals of Turkish origin; 186 men and 85 women	BMI < 25 and > 30	The P- allele was associated with lower TG in obese subjects only	Proenza *et al.* [33]
Microsomal triglyceride transfer protein (MTP) (-493G/T)	227 men	Adipose tissue	Visceral obesity and hyperinsulinemia modulate the impact of this polymorphism on cholesterol and LDL-apoB levels, as well as on LDL peak particle diameter	St. Pierre *et al.* [63]
Peroxisome proliferator activated receptor γ (PPARγ)	A sample of 820 men and women living in northern France	BMI (30)	Obese subjects bearing at least one T allele had higher plasma leptin levels than subjects who did not	Meirhaeghe *et al.* [64]
Resistin (RETN) (several SNPS)	44 T2DM/20 control subjects (Northern European descent)	BMI (35)	Noncoding SNPs may influence insulin sensitivity in interaction with obesity	Wang *et al.* [65]
Scavenger receptor class B1 (SCARB1)	2463 nondiabetic (49% men) and 187 diabetic (64% men) participants in the Framingham Study	Diabetes	SR-BI gene variation modulates the lipid profile, particularly in type 2 diabetes, contributing to the metabolic abnormalities in these subjects	Osgood *et al.* [24]
Tumor necrosis factor α (TNF-α) (308 G/A)	148 MI cases with severe CAD and 148 matched controls in Brazil	Obesity (BMI 30 / 27.5)	Obesity increases the risk of myocardial infarction in A carriers: odds ratio of 14.5 (95% CI, 1.8–113)	Padovani *et al.* [66]
TNF-α (308 G/A)	129 healthy subjects in Finland	BMI (26)	Interaction of the polymorphism with obesity	Pihlajamaki *et al.* [67]
Uncoupling protein 1 (A/G-3286)	272 unrelated individuals of Turkish origin (186 men and 85 women)	BMI < 25 and > 30	The G allele associated with increased plasma cholesterol levels only in obese subjects	Proenza *et al.* [33]

BMI—body mass index; BP—blood pressure; HDL—high-density lipoprotein; IMT—intima-medial thickness; TC—total cholesterol; TG—triglyceride; WHR—waist to hip ratio.

evidence about the modulating effect of obesity on the features of the metabolic syndrome. Nevertheless, they are enticing, and some of the reports in Table 1 merit specific comment. This is the case of the endothelin-1 Lys198Asn polymorphism and blood pressure. There are three studies in different populations (whites and Japanese) showing that obesity increases the effect of the 198Asn allele on blood pressure and hypertension [21•,41,42•], supporting additional research to elucidate the molecular basis for this interaction. Likewise, highly consistent results have also been obtained for the LPL locus. Thus, Mailly *et al*. [43] have reported that carriers of the D9N polymorphism have a predisposition to developing an atherogenic lipid profile if they are obese. Ko *et al*. [44] and Ma *et al*. [45] have described that in Chinese subjects, the H+ allele of the HindIII polymorphism was associated with higher triglycerides and lower HDL cholesterol only in obese patients. Some other studies [46–49] analyzing different polymorphisms or studying other anthropometric measures to define obesity have found additional evidence supporting that the effect of LPL variants on plasma lipids is strongly modulated by adiposity. Several other candidate genes among those listed in the previous section are beginning to show similar interactions with anthropometric measures [50–52,53•,54–67]; however, in most cases, there has not been yet replication of the findings, and given the experimental design they should be considered as hypothesis-generating studies that need to be confirmed by subsequent investigations.

Conclusions

In the metabolic syndrome, obesity seems to play a major role in "triggering the loaded gun." Several studies support the presence of significant interactions between obesity and genetic variants at multiple candidate genes for the metabolic syndrome. However, the information and its reliability are still very limited, and more studies with better epidemiologic design and standardized adiposity measures are needed to estimate the contribution of body weight and fat distribution on this highly prevalent syndrome.

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