REVIEW / SYNTHÈSE

Genetics of the metabolic syndrome

Margarita Terán-García and Claude Bouchard

Abstract: The concept of a metabolic syndrome (MetS), a cluster of pre-clinical metabolic alterations commonly associated with obesity, is the object of much debate. Genetic studies have the potential to contribute to some of the key questions, including the true nature of the cluster of pre-clinical features and whether it is associated with human genetic variation. This review summarizes the evidence for the presence of familial aggregation for the individual components of MetS and their heritability levels. It also provides an overview of the studies that have dealt with candidate genes for MetS. Potential leads from genome-wide linkage scans are also discussed. The assumption is made that obesity, ectopic fat deposition and abnormal adipose tissue metabolism are responsible for alterations in lipid metabolism, which in turn generates the commonly observed pre-clinical shifts in glucose tolerance, lipids and lipoprotein profile, blood pressure, inflammatory markers, endothelial function, and a prothrombotic state. Progress in the understanding of the genetic basis of MetS should occur as soon as a consensus is reached on the true nature of MetS, its components and diagnostic criteria.

Key words: metabolic syndrome, genetics, genetic epidemiology.

Résumé : Le concept du syndrome métabolique (MetS), déterminé par un ensemble de troubles précliniques généralement associés à l'obésité, suscite bien des débats. Les études sur l'hérédité peuvent répondre à des questions de premier plan telles que les caractéristiques fondamentales des troubles précliniques et leurs associations à la variabilité génétique chez l'humain. Cet article-synthèse présente des preuves de la présence d'agrégation familiale des constituants du MetS et leur niveau d'héritabilité et donne un aperçu des gènes candidats à la base du MetS. Nous analysons aussi les pistes potentielles issues des criblages génomiques. Nous proposons le postulat suivant : l'obésité, les dépôts ectopiques de gras et le trouble du métabolisme du tissu adipeux sont la cause d'anomalies du métabolisme lipidique, entraînant comme conséquence des observations courantes du déplacement préclinique de la courbe de tolérance au glucose et des modifications des profils lipidiques et lipoprotéiques, de la pression sanguine, des marqueurs de l'inflammation, de la fonction des endothéliums et de l'état prothrombotique. Notre connaissance des bases génétiques du MetS avancera dès qu'on s'entendra sur les caractéristiques fondamentales du MetS et ses constituants et sur les critères de diagnostic.

Mots clés : syndrome métabolique, génétique, l'épidémiologie génétique.

[Traduit par la Rédaction]

Introduction

There is an ongoing debate regarding the nature of metabolic syndrome (MetS) and whether it exists at all. This debate is largely fueled by two differing schools of thought, one promoting an ''insulin–glucocentric'', the other a ''cardio–lipocentric'' approach to the MetS concept. Is MetS a separate entity? Does it add anything to the collection of individual factors that are typically used in its clinical definition? Should the concept be abandoned?

Syndrome, from the Greek, means ''concurrence''. A syndrome is therefore a cluster of co-occurring symptoms, usually three or more (Jablonski 1991). The term MetS was likely adopted originally in the spirit that over time its nature and usefulness would be clarified, that a more precise designation would replace it, or that it would be abandoned. None of this has materialized yet, but a commonly held view among many leaders in the area is that MetS is neither a true syndrome nor a disease as such.

This review focuses on the genetics of MetS. How can we address the genetic determinants of MetS while its existence and definition is still a matter of debate? We will assume that the most common definitions of MetS have some validity and will not discuss the merit of the basic concept or its usefulness. We assume that there are multiple presentations of MetS, and that it depends on the interactive effects of many genes and environmental factors, including physical inactivity and poor diet (Bouchard 1995).

Historical notes

Numerous scientists and laboratories have contributed to the early phases of the evolution of the MetS concept. It is

Received 10 August 2006. Accepted 14 November 2006. Published on the NRC Research Press Web site at http://apnm.nrc.ca on 7 February 2007.

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impossible to recognize them all here, but the following are highlighted: Despres (1993), Hanefeld and Willms (1996), Jahnke et al. (1969), Kissebah and Peiris (1989), Vague (1956), and Williams et al. (1988). However, the impetus for the development of the MetS definition as we know it today came from Reaven (1988) in his Banting Lecture. In his influential paper, Reaven emphasized the metabolic anomalies associated with insulin resistance and hyperinsulinemia. He referred to the cluster as "Syndrome X". Since then, the clustering of cardiovascular disease and diabetes risk factors has been referred to as MetS (Björntorp 1992), insulin-resistance syndrome (DeFronzo and Ferrannini 1991), deadly quartet (Kaplan 1989), and plurimetabolic syndrome (Crepaldi et al. 1993).

Of particular importance is the contribution of Per Björntorp. He suggested that hormonal abnormalities, mainly consisting of hypercortisolemia and deficiencies of sex steroid hormones, are important in the pathogenesis of insulin resistance (Björntorp 1992). He proposed that these hormonal defects, combined with an insufficiency of growth hormone secretion, favor triglyceride (TG) deposition in adipose tissues. Björntorp suggested that, as a consequence of neuroendocrine derangement, visceral fat accumulation may amplify the manifestations of MetS.

Since then, a vigorous debate has taken place regarding how MetS should be defined. In brief, the World Health Organization (WHO) proposed a definition of MetS in 1998 (Alberti and Zimmet 1998). The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults provided a working definition (the NCEP III definition) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001) that was seen as more suitable for clinical practice. In 2002, the term MetS was used by the National Library of Medicine to define a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus (T2DM). More recently, the International Diabetes Federation proposed yet another version of MetS (Alberti et al. 2005).

The apparent lack of consensus on what MetS truly is and the tendency to lower the threshold for the presence of MetS prompted a series of critical appraisals and statements by members of the American Diabetes Association and the European Association for the Study of Diabetes (Kahn et al. 2005), as well as from the American Heart Association and the National Heart, Lung, and Blood Institute (Grundy et al. 2005). The existence of MetS has been challenged even by those who played a key role in the development of the concept (Reaven 2005) and by several others as well (Gale 2005; Kahn et al. 2005; Laakso and Kovanen 2006).

It is evident that MetS has evolved in the direction of lower thresholds for all the components deemed relevant for inclusion in the evolution of the syndrome. The situation is such that by now all components are defined as present using frank preclinical values often bordering on commonly accepted normal values. This does not facilitate the conduct of genetic studies and the situation may deteriorate further if growing numbers of adults are declared "affected" simply by the fact that the bar has been lowered.

The biology underlying the clustering of risk factors

A large amount of stored lipids and (or) abnormal adipose tissue metabolism seems to play a central role in the events leading to the development of a cluster of metabolic anomalies. A dysfunctional lipid physiology underlies or is commonly present in obesity, insulin and glucose abnormalities, endothelial dysfunction, hypertension, inflammation, atherogenic dyslipidemia, and prothrombotic state (Fig. 1). For practical purposes, one can recognize at least four components of lipid storage and adipose tissue metabolism that are relevant to the clustering of metabolic abnormalities. These four components include abnormal adipose tissue biology, excess fat mass, high level of abdominal fat, and ectopic fat deposition.

Abnormal adipose tissue biology

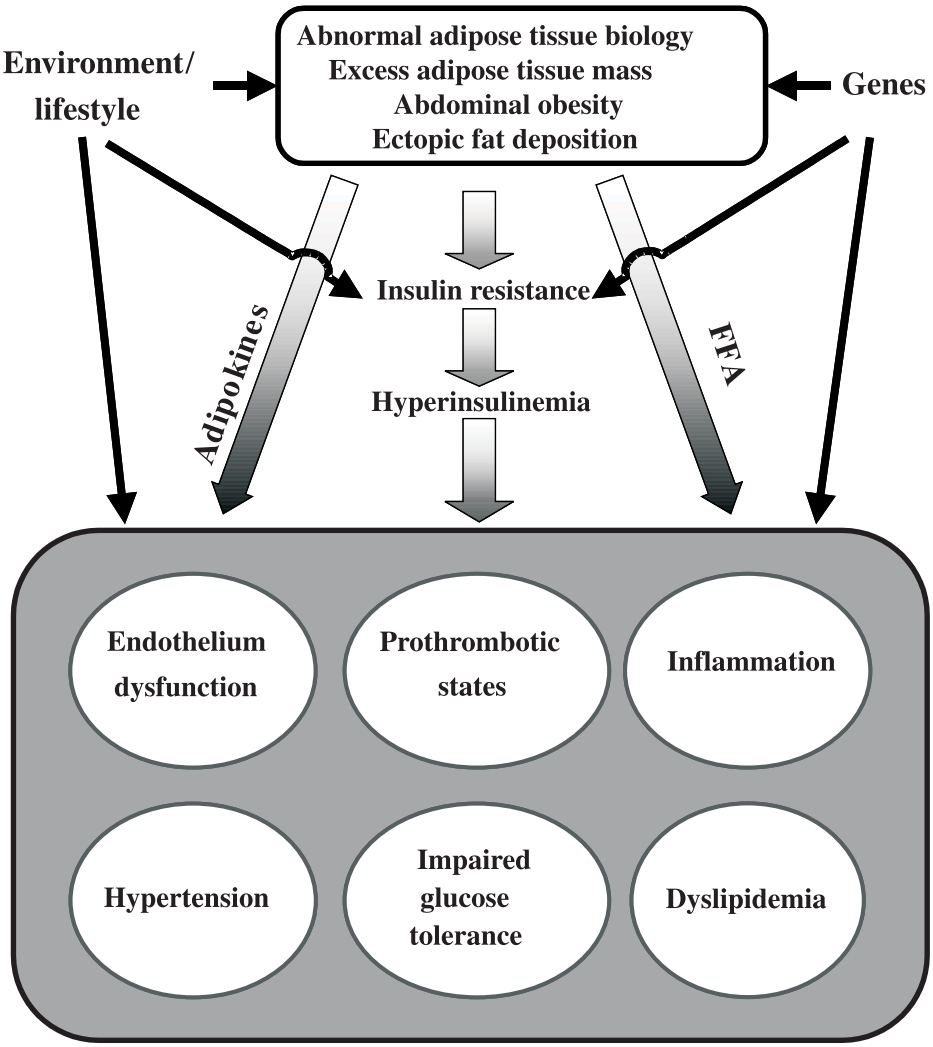
Adipose tissue is composed of mature adipocytes (50%–70%), preadipocytes and (or) stromal cells (20%–40%), endothelial cells (1%–10%), and macrophages or inflammatory cells (1%–30%), along with other cell types such as vascular and sympathetic nerve fibers (Ailhaud and Hauner 2004). The adipocyte produces and secretes hormones, cytokines or adipokines, and other bioactive substances such as free fatty acids (FFAs), prostaglandins, and angiotensinogen.

Preadipocytes differentiate into adipocytes that grow, replicate, and die through a regulated interplay of transcription factors and signaling mechanisms. Transcription factors include members of the CAAT–enhancer binding proteins (CEBP) and the peroxisomal proliferator-activated receptor (PPAR) (MacDougald and Lane 1995; Rosen and Spiegelman 2000) families. Key differentiation factors include CEBP-α (CEBPA), peroxisome proliferative activated receptor γ2 (PPARγ2), and sterol regulatory element binding protein-1 (SREBP1). Endocrine and paracrine signals from hormones and cytokines such as insulin, glucagon, glucocorticoids, retinoids, prostacyclin, and tumor necrosis factor α (TNFα), among others, coordinate a cascade of events with transcription factors to regulate expression of genes that differentiate and sustain the adipocyte phenotype. For example, expression of insulin-responsive genes such as the glucose transporter (*SLC2A4*), fatty acid synthase (*FASN*), stearoyl CoA desaturase 1 (*SCD*), leptin (*LEP*), and the fatty-acid binding protein (*FABP4*) characterize differentiated, mature adipocytes.

Impaired regulation of adipose tissue biology is typically observed in obese individuals, but is also common in normal-weight people. Such dysregulation may promote insulin resistance, increased lipolysis, endothelial dysfunction, and secretion of proinflammatory adipokines. Their effects on blood vessels contribute to the physiopathology of hypertension and atherosclerosis.

Adipocytokines and other adipocyte products have been implicated as biomarkers for MetS-related traits in a number of studies. These adipocyte biomarkers include leptin (Considine et al. 1996; Leyva et al. 1998; Montague et al. 1997), adiponectin (Guo et al. 2006; Kumada et al. 2003; Lara-Castro et al. 2006; Pollin et al. 2005; Yang and Chuang 2006), resistin (McTernan et al. 2002; Menzaghi et al. 2006), and other factors such as FFA and lipase activity (Perusse et al. 1997). Novel adipocyte biomarkers include circulating concentrations of retinol-binding protein 4 (RBP4) (Graham et

Fig. 1. Schematic representation of the hierarchical relations among putative causes and manifestations of MetS. Causally related to the cluster of cardiovascular disease and T2DM risk factors are excess adipose tissue mass, abdominal obesity, abnormal adipose tissue metabolism favoring production of free fatty acids (FFAs), and poorly regulated adipose tissue hormones and cytokines, as well as ectopic fat deposition, particularly in liver and skeletal muscle but also in the pancreas and other organs. These conditions favor the development of insulin resistance and hyperinsulinemia in the presence of a genetic predisposition and an unhealthy lifestyle (sedentarism, smoking, high fat diet, high sugar diet, etc.).



al. 2006) and fatty-acid binding protein (FABP) (Xu et al. 2006). The relationships between these adipocyte biomarkers with cardiovascular risk factors and their link with obesity, insulin resistance, and T2DM raise the hypothesis that they play a role in the etiology of MetS. Altered production and secretion of adipokines has physiological and metabolic consequences that tend to promote MetS. However, not all studies replicate these observations (Considine et al. 1996; Graham et al. 2006; Kumada et al. 2003; Langenberg et al. 2006; Singhal et al. 2002; Xu et al. 2006).

Excess fat mass

Another hypothesis is that most of the metabolic effects of obesity result from the increased fat mass. Larger adipocytes exhibit generally greater rates of TG synthesis, lipolysis, and transmembrane fatty acid flux. For example, increased fat cell size has been associated with insulin resistance and the development of diabetes (Paolisso et al. 1995; Weyer et al. 2001). As adipose tissue increases in size, the systemic concentrations of cytokines and polypeptides secreted by the adipose tissue are affected. This is the case for leptin, resistin, adiponectin, TNFα, angiotensinogen, interleukin 6 (IL-6), C-reactive peptide (CRP) and plasminogen activator inhibitor-1 (PAI1) to name but a few.

On average, reducing adipose tissue mass decreases secretion of proinflammatory adipokine factors and chemokines (i.e., TNFα, IL-6) but increases anti-inflammatory factors (i.e., adiponectin). In contrast, on average, enlarged fat mass produces more proinflammatory adipokines that influence hepatic lipoprotein metabolism and endothelial functions. Enlarged adipocytes tend to be more dysfunctional, as they progressively lose their ability to store fat, but contribute to higher circulating FFAs levels. Excess fat mass is likely to be the single-most important cause of the metabolic anoma-

lies associated with MetS as suggested by the concordance between the increase in obesity prevalence and the morbidities that bear a relation to obesity.

Excess abdominal fat

Abdominal fat consists of subcutaneous and deep adipose tissue depots. Deep-fat depots consist of intraperitoneal or visceral fat (mainly omental and mesenteric) and retroperitoneal fat.

A body of data supports the hypothesis that high amounts of abdominal adipose tissue are associated with insulin resistance, glucose intolerance, and cardiovascular risk factors. Large omental adipocytes exhibit high lipolytic activity and their FFA products drain into the hepatic portal venous system. The ''portal hypothesis'', as described by Björntorp (1990), specifies that increased visceral fat results in altered hepatic functions affecting insulin clearance and hepatic glucose and very low density lipoprotein (VLDL) TG production.

However, other studies have indicated that subcutaneous abdominal adipose tissue is also a strong contributor to the same metabolic alterations (Kelley et al. 2000; Miles and Jensen 2005; Smith et al. 2001). Visceral fat has been shown to be not as important as originally thought in supplying FFAs to the liver; the contribution of visceral fat accounted for only 5 to 20% of the FFAs delivered to the portal circulation in lean or obese individuals (Nielsen et al. 2004). Therefore, most of the FFAs that pass through the liver are lipolytic products of subcutaneous fat that flow through the portal vein (80%) or the hepatic artery (20%). FFAs from non-visceral fat depot sources are more likely to reach peripheral tissues such as skeletal muscle than are those derived from visceral fat. Expression and secretion of angiotensinogen, IL-6, IL-8, 11-β-hydroxysteroid dehydrogenase (11-β-HSD), resistin, PPARG, vascular endothelial growth factor, and PAI1 are relatively higher in visceral adipose tissue, whereas cholesterol ester protein (CETP), adipsin, acylation stimulating protein, leptin, and adiponectin are higher in subcutaneous fat depots (Schaffler et al. 2005). There are also specific receptor expression patterns that influence the responses to afferent signals. For example, higher expression of angiotensin receptor 1, β3-adrenergic receptor (ADRB3), glucocorticoid receptor, and androgen receptor is observed in visceral compared with subcutaneous adipose tissue (Fain et al. 2004).

The abdominal adipose tissue depot seems to play an important role in the etiology of MetS and may increase the risk of being affected beyond the major contribution of total fat mass. However, the specific contribution of visceral and subcutaneous depots to the risk of MetS remains to be clarified.

Ectopic fat deposition

One other potential pathway to consider in the etiology of MetS is that of fat deposition in non-adipose tissue (Unger 1995). Lipid deposition in non-adipose tissues (liver, skeletal muscle, pancreas) has been shown to affect insulin sensitivity (Krssak et al. 1999; Lee et al. 1994; Seppala-Lindroos et al. 2002). At a given level of lipid storage, which is variable among people, the adipocyte becomes insulin resistant and its lipolytic rates increase along with the release of FFA into circulation, while the uptake of glucose and fatty acids decreases. The fatty acid excess tends to be stored as lipids in pancreas, liver, skeletal muscle, heart, and possibly other tissues (Krssak et al. 1999; Lee et al. 1994; Seppala-Lindroos et al. 2002), generating what has been referred to as a ''lipotoxic'' effect. This scenario may explain how the excess calories, which cannot be stored by the adipocytes, are deposited as ectopic fat mainly in liver and muscle, impairing insulin sensitivity and promoting the development of T2DM (Krssak et al. 1999; Lee et al. 1994) among other metabolic consequences.

Intramyocellular lipid content and hepatic lipid infiltration, as assessed by nuclear magnetic resonance spectroscopy, are associated with strong determinants of insulin resistance in humans, independently of obesity (Krssak et al. 1999; Seppala-Lindroos et al. 2002). These observations are compatible with the insulin resistance commonly seen in lipodystrophic syndromes in humans and mouse models. For example, segmental lipodystrophy syndromes result in altered fat distribution, diabetes, and hyperlipidemia. Evidence of impaired muscle fatty acid metabolism in the obese state suggests that differences in muscle fatty acid oxidative capacity might play a role in the pathogenesis of obesity (Kelley et al. 1999). Disturbed muscle fat oxidative capacity results in accumulation of lipid intermediates such as diacylglycerol and fatty acid acyl coenzyme A, which may interfere with insulin signaling and inhibit insulin-mediated glucose uptake (Ruderman et al. 1999). The term ''non-alcoholic fatty liver disease'' describes a type of ectopic fat accumulation within the liver, characterized by increased hepatic de novo lipogenesis and associated with impairment of insulin-stimulated glucose metabolism, suppression of endogenous glucose production, and whole-body lipolysis (Donnelly et al. 2005; Marchesini et al. 2001).

The ''lipotoxic'' theory requires consideration in parallel with the ''glucotoxic'' theory. Chronic high glucose influences cellular lipid metabolism via substrate availability, changes in the activity and expression of enzymes of glucose and lipid metabolism, and modifications in the expression level of key transcription factors. It has been suggested that pancreatic β-cell ''glucotoxicity'' is partly caused by ''lipotoxicity'', and that β-cell abnormalities become apparent when both glucose and circulating fatty acids are high (Prentki et al. 2002). This ''glucolipotoxicity'' could explain how an excess of glucose and fatty acids synergize to cause toxicity in multiple tissues, including pancreatic islets, a process that may be instrumental in the development of MetS.

Genetic epidemiologic studies and the clustering of risk factors

Individual components of MetS

The question of whether there is a genetic basis to MetS continues to be debated. One tool to estimate the genetic effect is the heritability coefficient, which quantitatively estimates how much of the phenotypic variance is compatible with a genetic transmission across generations. It is important to recognize that there may be ethnic differences in the heritability of MetS or its components. Table 1 lists the range of commonly reported heritability values from family and twin studies that have dealt with individual components of MetS. The common features of MetS are all individually characterized by significant heritability levels.

Table 1. Commonly reported heritability estimates for components of MetS.

Phenotype	Estimated heritability (%)
Body composition	
BMI	25–60
Body fat	25–40
Abdominal obesity	40–55
Insulin/glucose	
Fasting glucose	10–75
Fasting insulin	20–55
Insulin resistance or T2DM	46–90
Lipids	
Triglycerides	25–60
LDL-cholesterol	25–60
HDL-cholesterol	30–80
Total cholesterol	50–60
Blood pressure	
Systolic BP	20–70
Diastolic BP	10–50
Hypertension	50
Hemostasis-related traits	20–60
Microalbuminuria	30

Note: The range of heritability estimates is derived from (Argyropoulos et al. 2005). Additional references can be found in (Forsblom et al. 1999; Hong et al. 2001*b*; Lin et al. 2005; Ring et al. 2005; Warren et al. 2005). Heritability data include twin and family studies.

Total body fatness has heritability levels that range from 25% to 40%. The heritability for abdominal fat adjusted for total adiposity reaches about 50% (Bouchard 1995). Heritability varies from 20% to 55% (Burke et al. 1991; Manson et al. 1991; Sarlund et al. 1992) for fasting insulin, from 10% to 63% (Hong et al. 2001*b*; Li et al. 2006; Santos et al. 2006; Watanabe et al. 1999) for fasting glucose, and from 46% to 90% for insulin resistance or T2DM.

The heritability estimates for lipoprotein traits range from 25% to 60% for TG, 50% to 60% for total cholesterol, 30% to 80% for high-density lipoprotein (HDL) cholesterol, and 26% to 60% for low-density lipoprotein (LDL) cholesterol (Perusse et al. 1997; Wu et al. 2002). The genetic components are also significant for systolic blood pressure (30%), diastolic blood pressure (10%–30%), and hypertension (50%) (Bouchard 1995; Lin et al. 2005; Wu et al. 2002). It has been estimated that about 50% of the total variability in fibrinogen levels could be explained by genetic factors (Voetsch and Loscalzo 2004). Among 16 hemostasis-related traits moderate to high heritabilities (20 to 60%) were reported; the Von Willebrand factor, thrombin-activatable fibrinolysis inhibitor, activated protein C ratio, factor V, and prothrombin time all had heritability coefficients greater than 50% (Warren et al. 2005).

The heritability of albumin excretion reaches about 30% (Forsblom et al. 1999). Variations in sex hormone concentrations have been associated with obesity and T2DM (Ding et al. 2006; Zumoff et al. 1990) and have been shown to be partly heritable with values for testosterone, serum hormone binding globulin (SHBG), and estradiol reaching about 57%–69%, 68%–70%, and 25%, respectively (Hong et al. 2001*a*; Ring et al. 2005).

Indicators of the MetS cluster

In recent years, the search for genetic determinants of MetS has been conducted using either the MetS NCEP definition (affected vs. unaffected) or weighted components of MetS resulting from a number of factor analysis approaches (Kraja et al. 2005*a*). In brief, the heritability of the NCEP-defined MetS has been estimated to be about 30%. In contrast, heritability varies from 11% to 37% for blood pressure, 47% to 66% for obesity and insulin, and 43% to 54% for lipid and insulin traits, as defined by principal component or factor analysis procedures (Kraja et al. 2005*b*).

The fact that most factor analysis and principal component studies have identified several factors has been used as an argument against a "common ground" or a single MetS hypothesis. For example, studies have found that MetS is best defined by two (Chen et al. 1999; Lin et al. 2005; Loos et al. 2003), three (Arya et al. 2002; Austin et al. 2004; Edwards et al. 2001; Meigs et al. 1997), or four (Hanson et al. 2002; Lakka et al. 2002; Ninomiya et al. 2004) principal components or factors. In general, insulin-related variables correlate with determinations of glucose and obesity, and lipid traits are frequently included in one factor, whereas measures related to blood pressure fall in a separate factor.

Another factorial analysis strategy is to test whether a constellation of traits is best described by a single underlying factor. A few studies have used this approach (Novak et al. 2003; Pladevall et al. 2006; Shen et al. 2003), and two have provided support for this hypothesis (Pladevall et al. 2006; Shen et al. 2003). However, overall, there is little evidence for the presence of a single underlying heritable factor that would lead to the MetS cluster.

Mendelian monogenic forms

Monogenic obesity and lipodystrophic disorders are instructive not only for our understanding of the pathophysiology of MetS, but also because they can shed light on candidate pathways and genes for MetS. The Online Mendelian Inheritance in Man (OMIM) is the most comprehensive source of information on inherited monogenic disorders (Hamosh et al. 2000) and can be accessed on-line at http://www.ncbi.nlm.nih.gov/entrez.

Lipodystrophic diseases

Lipodystrophy is characterized by an absolute or relative decrease in adipose tissue mass that is accompanied by ectopic fat storage. Lipodystrophies can result from either genetic or acquired causes and are reviewed in detail elsewhere (Agarwal and Garg 2006). Congenital lipodystrophic syndromes described in Table 2 are included here to highlight the fact that meager amounts of adipose tissue could lead to metabolic anomalies just as an abundance of adipose tissue does. Lipodystrophy triggers lipotoxicity as a consequence of ectopic deposition of TG and acyl CoA in insulin-sensitive tissues such as liver and muscle. Lipotoxicity is exacerbated by leptin deficiency, given the limited amount of adipocytes. Thus, in individuals with total or par-

Table 2. Key lipodystrophic syndromes associated with MetS phenotypes.

Disease	OMIM No.	Phenotype	Associated gene(s)	Molecular mechanisms or pathogenesis
Autosomal dominant familial partial lipodystrophy (FPLD)				
FPLD2 or Dunnigan-type	151660	Onset at or near puberty, is characterized by loss of subcutaneous fat from the limbs, gluteal, and truncal regions, resulting in a muscular appearance with prominent superficial veins. Simultaneously, adipose tissue accumulates on the face and neck, causing a cushingoid facade. Patients are insulin resistant, have dyslipidemia with elevated triglycerides and low HDL.	Lamin A/C (*LMNA*)	*LMNA* gene encodes nuclear proteins (lamin A and C), important for adipocyte differentiation and survival. Lamin A interacts with transcription factor SREBP1a and 1c. Disrupted nuclear function might result in adipocyte apoptosis. LMNA mutations are found in ~50% of families with FPLD.
FPLD3 associated with *PPARG* mutations	604367	Characterized by loss of subcutaneous fat, with preservation of visceral and subcutaneous abdominal fat and some gluteal fat, facial fat is normal or mildly decreased. Symptoms of insulin resistance and hypertension are more severe than in FPLD2.	*PPARG*	PPARγ is a nuclear receptor essential to induce transcription of genes involved in insulin sensitivity, inflammation, and adipogenesis. Still unknown why lipodystrophy is restricted to distinct regional depots.
FPLD associated with AKT2	164731	Described in a family with insulin resistance, T2DM, and hypertension. There was partial lipodystrophy in the proband.	*AKT2*	AKT2, is also known as PKB (protein kinase B), belongs to the phosphoinositide-dependent serine (threonine) protein kinases. Expressed predominantly in insulin sensitive tissues, involved in postreceptor signaling. Probable mechanisms include reduced adipocyte differentiation and defects in postreceptor insulin signaling.
FPLD1 or Kobberling type	608600	Characterized by loss of adipose tissue confined to the extremities, with normal or increased distribution of fat on the face, neck, and trunk. Other features included hypertension, coronary artery disease, and T2DM.	None of the patients had mutations in the *LMNA* or *PPARG* genes.	Unknown
Congenital generalized lipodystrophy (CGL)				
CGL1 Berardinelli–Seip syndrome	608594	Extreme lack of adipose tissue since birth, with extreme insulin resistance, hypertriglyceridemia, hepatic steatosis and early onset of diabetes.	*AGPAT2* (acyl glycerol-3-phosphate *O*-acetyltransferase).	AGPAT2 is essential for triglyceride and phospholipid biosynthesis. Mainly expressed in adipose tissues, disrupted function might reduce triglyceride synthesis.
CGL2	269700	CGL manifests at birth as a complete absence of adipose tissue, hepatomegaly, and severe non-ketotic insulin-resistant diabetes. Other features include acanthosis nigricans, muscular hypertrophy, hepatomegaly, altered glucose tolerance or T2DM, and hypertriglyceridemia.	*BSCL2* (seipin, homolog of mouse guanine nucleotide-binding protein γ3-linked gene)	Gene function unknown, possible central nervous system defect.

tial lipodystrophy, leptin deficiency leads to hyperphagia and possibly loss of direct peripheral actions of leptin (Semple et al. 2006). Hepatic steatosis is a clinical phenotype distinctive of familial partial lipodystrophy syndromes (FPLDs) (Ludtke et al. 2005). FPLD syndromes have become useful monogenic models in studying MetS (Berger et al. 2002; Herbst et al. 2003; Peters et al. 1998; Simha and Garg 2003; Speckman et al. 2000).

Another conceivable genetic model for MetS is Launois–Bensaude syndrome (LBS), known as benign symmetric lipomatosis, a rare disorder of unknown origin characterized by ectopic deposition of fatty tissue in shoulders, arms, thighs, and abdominal region. It is believed to be a disease of disturbed lipogenesis induced by catecholamines, but its pathophysiology is unknown. LBS patients often display MetS features such as T2DM, hyperlipidemia, hypertension, and hyperuricemia, besides a characteristic polyneuropathy (Harsch et al. 2002).

Other monogenic disorders related to MetS

Some obesity-related syndromes have been associated with MetS-related traits. The reader is referred to OMIM for a more detailed description and discussion of them. Many of the rare syndromic obesities are characterized by defects in the regulation of food intake or energy balance, and lead to the development of diabetes or MetS-related traits. Single-gene mutations causing obesity include those in *LEP* (OMIM No. 164160) and its receptor (*LEPR*, OMIM No. 601007), melanocortin 3 receptor (*MC3R*, OMIM No. 601665), melanocortin 4 receptor (*MC4R*, OMIM No. 155541), proopiomelanocortin (*POMC*, OMIM No. 176830), and proprotein convertase subtilisin/kexin type 1 (*PCSK1*, OMIM No. 162150). Other relevant Mendelian disorders (and their associated genes) include digenic syndromes such as severe insulin resistance with obesity *(PPARG* and *PPP1R3A*, OMIM No. 600917) and cortisone reductase deficiency (*H6PD*, OMIM No. 138090, and *HSD11B1*, OMIM No. 604931). As we progressively identify more genes involved in Mendelian defects with clinical obesity and MetS-related traits, our knowledge of the physiopathological events surrounding MetS development will likely be enhanced.

The contribution of specific genes

Association studies aim to detect relationships between one or more genetic polymorphisms and a quantitative or qualitative trait. The list of genes in which DNA sequence alterations cause full-blown MetS is still rather short. However, the evidence is quite promising for 14 candidate genes that have been associated with at least two traits of MetS, which are reviewed here. Figure 2 displays the chromosomal location of these genes plus the 38 quantitative trait loci (QTLs) to be defined in the next section.

11-β-hydroxysteroid dehydrogenase (*HSD11B1*, *HSD11B2*)

The 11-β-HSD enzymes convert cortisol into inactive cortisone and vice versa. There are two isoforms of 11-β-HSD-encoded enzymes: 11-β-HSD-1 (mainly localized in the liver), which acts bidirectionally to potentially restore cortisone into active cortisol, and 11-β-HSD-2 (mainly localized in the kidney), which inactivates cortisol unidirectionally (Vogeser et al. 2002). Renal 11-β-HSD-2 inactivates 11-hydroxysteroids in the kidney, thus protecting the non-selective mineralocorticoid receptor from occupation by glucocorticoids (Ferrari and Krozowski 2000).

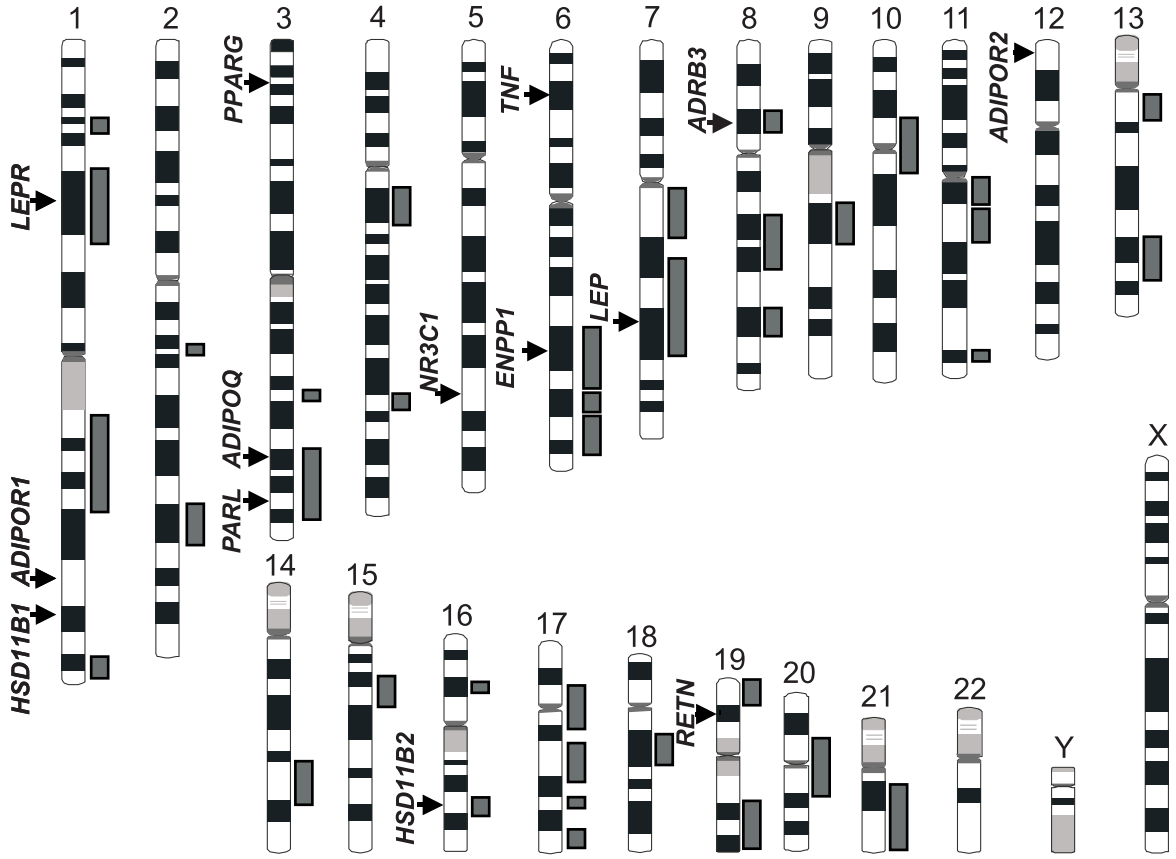
HSD11B1 has been proposed as a candidate gene to explain the MetS-related cluster, but it is not clear whether increased 11-β-HSD-1 activity is a cause or a consequence of obesity or MetS-related phenotypes. A mouse model overexpressing *Hsd11b1* in adipose tissue became a model for MetS. It was characterized by increased visceral fat mass, glucose intolerance, insulin resistance, dyslipidemia, and hypertension (Seckl et al. 2004). Cross-sectional studies have reported associations between genetic variability in the *HSD11B1* gene and enzyme activity with obesity, glucose intolerance, T2DM, or hypertension (Draper et al. 2002; Franks et al. 2004; Lindsay et al. 2003; Nair et al. 2004).

Hepatic transcription of *HSD11B1* is regulated by members of the CEBP family of transcription factors providing a mechanism of crosstalk between CEBP and the glucocorticoid signaling pathway (Williams et al. 2000). 11-β-HSD is highly expressed in all sodium-transporting epithelia, and mutations in the gene cause a rare monogenic juvenile hypertensive syndrome called apparent mineralocorticoid excess (AME) (Ferrari and Krozowski 2000). Recent studies have shown a prolonged half-life of cortisol and an increased ratio of urinary cortisol to cortisone metabolites in some patients with essential hypertension, similar to the effects of a CA-repeat polymorphism in the first intron, although there was no correlation between this marker and blood pressure (Ferrari and Krozowski 2000). The same CA repeat, however, was associated with a mean arterial pressure difference between sodium-loaded and sodium-depleted states (Agarwal et al. 2000; White et al. 2000). In another study, a proband with AME was homozygous for a mutation (Ala328→Val) resulting in a protein devoid of activity (Li et al. 1997), whereas a different individual with AME was homozygous for a Pro227→Leu mutation (Wilson et al. 1998). In other cases, the Arg213→Cys SNP was strongly associated with AME (Rogoff et al. 1998), whereas two other mutations (Lys179→Arg, Arg208→His) resulted in a protein devoid of activity (Nunez et al. 1999).

In French-Canadians, three intronic sequence variants identified in the *HSD11B1* gene were investigated for associations with MetS: two SNPs in intron 3 (g.4478T → G) and intron 4 (g.10733G → C) and one insertion in intron 3 (g.4437 → 4438insA). The rare allele frequency was 19.6%, 22.1%, and 19.6% for the g.4478G, g.10733C, and g.4438insA alleles, respectively. None of these variants were associated with components of MetS, except for plasma apolipoprotein B levels (Robitaille et al. 2004).

Given the hypothesis that 11-β-HSD-1 deficiency may protect against obesity and its metabolic consequences because of impaired regeneration of cortisol in adipose tissue, a functional polymorphism associated with low 11-β-HSD-1 activity was investigated in polycystic ovary syndrome (PCOS) women with and without obesity (Gambineri et al. 2006). The G all*ele* of the rs12086634 polymorphism, located in the 3rd intron of the *HSD11B1* gene was significantly related to PCOS status (p = 0.041), and this

Fig. 2. Chromosomal location of 14 MetS-related genes and 38 QTLs. The names of genes associated with MetS are on the left side of the chromosome. Boxes on the right side of chromosomes represent the quantitative trait loci (QTLs) that have been implicated by genome-wide scans.



association was mainly attributable to lean (p = 0.025), rather than obese (p = 0.424) PCOS patients. The G allele was associated with lower plasma cortisol ($p < 0.001$) and higher cortisol response ($p < 0.001$) in all women with PCOS, and with higher DHEA-S levels ($p < 0.001$), greater suppression of DHEA-S by dexamethasone ($p < 0.001$), and lower fasting plasma LDL cholesterol (p = 0.002) levels in lean PCOS women. Genetic variation in *HSD11B1* contributes to enhanced cortisol clearance and compensatory adrenal hyperandrogenism in lean patients with PCOS, but may be protective against obesity and some features of MetS (Gambineri et al. 2006).

Other polymorphisms, in *HSD11B2*, have also been associated with essential hypertension (Odermatt et al. 2001; Poch et al. 2001; Sugiyama et al. 2001). From these data, we conclude that the *HSD11B2* gene plays a significant role in essential hypertension and therefore may contribute to the development or the severity of MetS. Its mode of action may be independent of adipose tissue or insulin-signaling pathways.

Adiponectin and adiponectin receptors (*ADIPOQ, ADIPOR1, ADIPOR2*)

Adiponectin, encoded on chromosome 3q27 (*ADIPOQ*), is a secretory and collagen-like plasma protein, synthesized mainly by adipose tissue that participates in the regulation of energy homeostasis and glucose and lipid metabolism. It is variously known as adipocyte complement-related protein-30 (ACRP30), adipose most abundant transcript (AMP1), gelatin-binding protein 28 kD (GBP28), and adipocyte C1Q and collagen domain containing (ACDC) protein (Berg et al. 2002; Berg et al. 2001; Fruebis et al. 2001). Its secretion is enhanced by insulin, and it is a significant factor in energy homeostasis, food intake, and energy metabolism (Hsueh et al. 2001).

Associations of the *ADIPOQ* gene with parameters of MetS are inconsistent. A study based on fine-mapped *ADIPOQ* SNPs was recently conducted in a healthy population of 1727 Caucasians (Heid et al. 2006). A total of 53 SNPs (average spacing of 0.7 kb) were genotyped and two blocks of linkage disequilibrium (LD) were found, which enabled a selection of tag SNPs. Strong associations with adiponectin concentrations for 11 of 15 tag SNPs were found in this cohort. Haplotype analysis provided further information on adiponectin concentrations, with 9 of 17 haplotypes showing significant associations. However, no significant association was found for any SNP with MetS parameters (Heid et al. 2006).

Genes for two adiponectin receptors have been identified, *ADIPOR1* and *ADIPOR2*, located on chromosomes 1q32.1 and 12p13.33, respectively. Adiponectic receptors 1 and 2 serve as receptors for globular and full-length adiponectin and mediate several adiponectin functions such as increase in AMP-activated protein kinase, PPARA ligand activities, and glucose uptake and fatty-acid oxidation. In humans,

ADIPOR1 is ubiquitously expressed, with the highest levels in skeletal muscle, but it is also expressed in liver and pancreas and binds the globular form of adiponectin with high affinity (Yamauchi et al. 2003). Adiponectic receptor 2 is predominantly expressed in skeletal muscle and liver and is an intermediate-affinity receptor for both globular and full-length adiponectin, and seems to be primarily responsible for the hepatic effects of adiponectin (Yamauchi et al. 2003).

Expression of these two receptors is lower in obese individuals (Kern et al. 2003) and in normal glucose-tolerant subjects with a family history of T2DM (Civitarese et al. 2004). Sequence variations in or near both *ADIPOR* genes have been investigated for their effects on MetS-related phenotypes (Damcott et al. 2005; Jang et al. 2006; Kantartzis et al. 2006; Vaxillaire et al. 2006; Wang et al. 2004). The data from these studies are not consistent. For example, from 22 SNPs investigated in Caucasian and African-American subjects, none were associated with T2DM, insulin sensitivity, or insulin secretion (Wang et al. 2004). However, the two alleles of a SNP in the 3′ untranslated region were expressed unequally, and *ADIPOR1* mRNA levels were significantly lower in transformed lymphocytes from diabetic African-Americans than in control cell lines. This altered gene expression was proposed to play a role in MetS (Wang et al. 2004). Data supporting this hypothesis emerged recently from the association of the A allele at the –8503 G→A SNP in the *ADIPOR1* gene with insulin resistance in obese but not in lean individuals (Kantartzis et al. 2006).

Multiple polymorphisms in both *ADIPOR1* and *ADIPOR2* were significantly associated with T2DM and related traits in the Old Order Amish, suggesting that genetic variation in the receptors, particularly *ADIPOR2*, plays a role in T2DM susceptibility (Damcott et al. 2005). No associations with other MetS-related phenotypes were found in this study.

A haplotype of three *ADIPOR2* variants (+795G→A (rs16928751), +870C→A (Ile290Ile), and +963C→T (rs9805042)) was associated with high plasma adiponectin levels and low fasting TG, VLDL TG, and VLDL cholesterol levels. However, this *ADIPOR2* haplotype was not associated with glucose metabolism phenotypes (Broedl et al. 2006).

In conclusion, genetic variations in adiponectin and its receptors could play an important role in the development of MetS. As recently documented, individuals with T2DM exhibited reduced adiponectin levels and decreased adiponectin receptor expression prior to the onset of hyperglycemia, which was related to adiponectin regulation of mitochondrial number and function (Civitarese et al. 2006).

Adrenergic receptor β-3 (*ADRB3*)

The cloning of the human *ADRB3* produced excitement in the field of obesity because of its thermogenic, anti-obesity, and antidiabetic activities in animal models (Emorine et al. 1989). The *ADRB3* gene maps to 8p12–p11.2 (Wilkie et al. 1993). Structurally, human *ADRB3* consists of two coding exons, and pharmacological properties of the full-length cDNA differ somewhat from those of the truncated receptor (Granneman et al. 1993). The human *ADRB3* gene is expressed predominantly in infant peripheral brown adipose tissue (which also expresses the thermogenic mitochondrial uncoupling protein UCP1). In adults, it is expressed at low levels in deep fat, such as perirenal and omental, and at much lower levels in subcutaneous fat (Krief et al. 1993). It is also highly expressed in the gallbladder, but to a lower extent in the colon, suggesting a potential minor role in lipid metabolism and TG storage and mobilization in adipose tissues (Krief et al. 1993; Lafontan 1994). However, doubts about its therapeutic potential were raised after finding that *ADRB3* is also expressed in human heart where agonists for this receptor induce a negative inotropic effect, whereas in blood vessels, stimulation of *ADRB3* produces vasodilation (Balligand 2000). Transcriptionally, *ADRB3* is regulated by CEBPα through a binding site in an enhancer *cis*-acting element at position –3306 (Dixon et al. 2001).

The Trp64→Arg SNP was found to contribute significantly to multiple risk factors in male subjects with hyperuricemia (Walston et al. 1995). Pharmacological associations with the Trp64→Arg polymorphism include the modulation of β blocker effects on TG and HDL cholesterol concentrations (Hayashi et al. 1998; Manraj et al. 2001) and increased sensitivity to the vasopressor effect of noradrenaline (Rissanen et al. 1997; Strazzullo et al. 2001). The associations between *ADRB3* sequence variants and MetS phenotypes are population-specific. Associations between the Trp64→Arg variant allele and insulin resistance have been described in Japanese-Americans with impaired glucose tolerance (Kawamura et al. 1999). In Japanese men, the Trp64→Arg mutation is associated with visceral obesity but with lower serum TG (Kim-Motoyama et al. 1997). It has been suggested that the mutation may identify a subset of subjects characterized by decreased lipolysis in visceral adipose tissue (Kim-Motoyama et al. 1997). In Chinese subjects, no support for the involvement of the Trp64→Arg polymorphism in the development of T2DM, hypertension, or dyslipidemia has been found, but the data suggest a relationship with obesity (Thomas et al. 2000). The inconsistent associations of the Trp64→Arg polymorphism with MetS could be explained by population differences, sample sizes, and, potentially, also by variations in diet, exercise, and other behaviors.

Ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*)

ENPP1, also known as plasma cell membrane glycoprotein-1, inhibits insulin receptor (IR) tyrosine kinase activity (Maddux and Goldfine 2000). IR kinase activity is impaired in muscle, fibroblasts, and other tissues of many patients with T2DM, but abnormalities in the insulin receptor gene are not the cause of this decreased kinase activity. Plasma ENPP1 of 19 ng/mL or less identified a cluster of insulin resistance-related alterations (Frittitta et al. 1998; Frittitta et al. 1999). In addition, women with gestational diabetes or T2DM have an increased ENPP1 content, which could contribute to lower phosphorylation levels of insulin receptor substrate-1 (IRS-1). These post-receptor defects in the insulin-signaling pathway are greater in the latter two groups of women than in women with normal pregnancies (Tomazic et al. 2002).

An *ENPP1* SNP (transversion A → C in codon 121) that resulted in an amino acid substitution, Lys121→Gln, was strongly associated with insulin resistance (Pizzuti et al.

1999). This SNP was also associated with higher fasting plasma glucose and insulin levels and higher systolic blood pressure in both diabetics and normal individuals. This SNP was not associated with T2DM among Danish Caucasians (Rasmussen et al. 2000*b*). A haplotype of three SNPs in the 3′ UTR of *ENPP1* (G2897A, G2906C, C2948T) was associated with increased ENPP1 protein content and insulin resistance in Caucasians from Sicily (Frittitta et al. 2001). *ENPP1* maps to a region on chromosome 6q22–q23 that has generated linkage peaks with body mass index (BMI) and insulin resistance-related phenotypes in Caucasians of the Framingham Study (Atwood et al. 2002), non-diabetic Mexican-Americans (Duggirala et al. 2001), and French Caucasians (Meyre et al. 2005). It has been suggested that ENPP1 could play a role in the etiology of MetS (Duggirala et al. 2001). Recent analysis of a QTL on chromosome 6q16.3–q24.2 that is associated with childhood obesity and includes a 2.4 Mb region common to eight genome scans for T2DM or obesity identified *ENPP1* as a candidate (Meyre et al. 2005). This study included 6147 subjects and showed associations between a three allele haplotype (K121Q, IVS20delT-11, and A → G+1044TGA; QdelTG) and childhood obesity (odds ratio (OR) = 1.69, $p = 0.0006$), morbid or moderate obesity in adults (OR = 1.50, $p = 0.006$ or OR = 1.37, $p = 0.02$, respectively)m and T2D (OR = 1.56, $p = 0.00002$) (Meyre et al. 2005). The molecular mechanism by which *ENPP1* exerts its effects is not clear, but may involve an interaction with other genes that contribute to the etiology of obesity and hypertension rather than inhibiting insulin-signaling pathways.

Leptin (*LEP*) and the leptin receptor (*LEPR*)

The discovery of leptin in 1994 represents a landmark that played a major role in changing our view of adipose tissue from a passive fuel-storage organ to a complex endocrine gland (Zhang et al. 1994). The *LEP* gene is the human homolog of the *ob* gene mutant in the mouse "obese" phenotype and maps to human chromosome 7q31.3 (Green et al. 1995). Leptin participates in the regulation of body mass by inhibiting food intake and stimulating energy expenditure (Frederich et al. 1995). However, the initial view of leptin as an anti-obesity hormone evolved rapidly after the realization that it was also involved in the regulation of hematopoiesis, angiogenesis, wound healing, and immune and inflammatory responses (Fantuzzi and Faggioni 2000). *LEP* consists of one 5′ non-coding region, two coding exons, and 2 introns spanning over 33 Mb of genomic sequence and encoding a 16 kDa protein (Karvonen et al. 1998). Leptin is produced at many sites in addition to white adipose tissue, but the amount of body fat is the main determinant of the circulating levels of this hormone. For example, small amounts of leptin are produced by non-adipose tissues such as placenta, gastric mucosa, bone marrow, mammary epithelium, skeletal muscle, pituitary, hypothalamus, and bone (Fruhbeck 2006). Insulin and cortisol are the major regulators of leptin production by the adipose tissue. Serum leptin levels follow a circadian rhythm, which seems to be related to insulin and cortisol changes (Licinio et al. 1997). Compared with males, females have higher leptin levels for a given level of adiposity (Martin et al. 2002).

Leptin acts through the leptin receptor (*LEPR*, encoded on chromosome 1p31), a single transmembrane-domain receptor of the cytokine receptor family, which is found in many tissues in several alternatively spliced forms. Leptin is involved in signal transduction by the selective activation of its receptor and the signal transducer and activator of transcription-3 (STAT3). Other signaling pathways used by Leptin include Janus-activated kinase (JAK)/STAT, MAPK, and SOCS3 (Fruhbeck 2006). Leptin down-regulates the expression of some orexigenic neuropeptides, such as neuropeptide Y, orexins, and agouti-related peptide. Leptin up-regulates anorexigenic neuropeptides such as α-melanocyte-stimulating hormone (α-MSH), which acts on MC4R, cocaine- and amphetamine-regulated transcripts, and corticotropin-releasing-hormone (Marsh et al. 1999).

Despite the physiological data indicating that Leptin might play a significant role in the development of obesity or other phenotypes of MetS, the literature is mixed regarding the relevance of mutations or SNPs in *LEP* and *LEPR* genes, and only a handful of those mutations have been functionally validated. A recent meta-analyses found no evidence of association between genes involved in leptin regulation and obesity (Paracchini et al. 2005). Still, some genetic variants in the *LEP* gene are associated with MetS-related traits independently of obesity (Shintani et al. 2002), as well as with T2DM (Lakka et al. 2000). It has been suggested that DNA sequence variations in the *LEP* and *LEPR* genes induce a mild dysfunction in the leptin-mediated signaling pathway and impair the peripheral effects of leptin (Seufert et al. 1999).

Nuclear receptors, ligand-activated transcription factors (*NR3C1, PPARG*)

The nuclear receptor superfamily of ligand-dependent transcription factors is one of the most abundant classes of transcriptional regulators. Nuclear receptors modulate gene expression in response to the signaling effects of diverse ligands in coordination with co-activators and (or) co-repressors. In general, nuclear receptors have been separated into two classes. The first class includes those that bind as homodimers to DNA sites, generally palindromic sequences, and undergo nuclear translocation upon ligand activation. Their DNA-binding site, known as the hormone response element, includes estrogen, androgen, glucocorticoid, mineralocorticoid, and progesterone receptors. The second class incorporates those that usually bind as heterodimers with the retinoid X receptor (RXR) transcription factor and to DNA elements called direct repeats (DRs). The binding specificity of these transcription factors depends upon precise sequences and spacing of the DR motifs. Some locate in the target cell nucleus, regardless of the presence of ligand, such as the thyroid hormone or retinoic acid receptors. Others undergo nuclear translocation upon ligand activation, like the PPAR subtypes (α, β/*δ*, and γ, or PPARα, PPARδ and PPARγ, respectively) and prefer a 1 bp space between DRs, whereas some prefer a 4 bp space, like the liver X receptors (LXR). The functions and molecular mechanisms of these nuclear receptor and (or) transcription factors have been reviewed in detail (Beaven and Tontonoz 2006). Our attention focuses on two genes that have been implicated in MetS in humans.

*Glucocorticoid receptor (*NR3C1*)*

The glucocorticoid receptor is a member of the steroid family of receptors that requires the binding of a ligand to become transcriptionally active. The gene is encoded on chromosome 5q31, contains 10 exons, and produces a 777 amino acid protein. There are two isoforms of *NR3C1* (producing NR3C1α and NR3C1β), which are products of alternate splicing. Only NR3C1α has functional properties given its hormone-binding ability (Rosmond 2002). *NR3C1* could function with the basal transcriptional machinery to enhance or repress transcription (Rosmond 2002). Several mutations in *NR3C1* have been associated with MetS (Rosmond 2002; van Rossum and Lamberts 2004). They have been associated with hyperactivity or abnormal regulation of the hypothalamic–pituitary–adrenal axis (Björntorp and Rosmond 2000; DeRijk et al. 2002).

Of the more than 50 genetic polymorphisms identified in the *NR3C1* gene, at least 3 seem to be associated with altered glucocorticoid sensitivity and changes in body composition and metabolic parameters (van Rossum and Lamberts 2004). These three polymorphisms are the two linked point mutations ER22/23EK, the Asn363→Ser, and the previously described *Bcl*I restriction fragment length polymorphism (RFLP) recently identified as a C → G nucleotide change. The two linked point mutations ER22/23EK identified by Koper et al. (1997) includes a G → A silent transition in codon 22, with both GAG and GAA coding for glutamic acid (E), and a change from arginine (R) to lysine (K) (AGG → AAG) in codon 23.

Carriers of the ER22/23EK allele have been associated with a relative resistance to glucocorticoids. The ER22/23EK carriers had lower total cholesterol and LDL cholesterol levels, as well as lower fasting insulin concentrations and better insulin sensitivity compared with the non-carriers (van Rossum et al. 2002). CRP levels were lower in those with the ER22/23EK genotype. There was a healthier metabolic profile in the ER22/23EK allele carriers, along with better survival in that population over a 4 year follow-up period. Male ER22/23EK allele carriers were taller, stronger, and had more muscle mass compared with the non carriers. The ER22/23EK allele female carriers from the same age group had a tendency towards smaller waist and hip circumferences along with lower body mass (van Rossum and Lamberts 2004).

The Asn363→Ser polymorphism has been associated with increased sensitivity to glucocorticoids, increased insulin response to dexamethasone, a tendency towards lower bone mineral density, and increased BMI (Lin et al. 1999; Rosmond et al. 2001). However, other reports found no associations with BMI or altered sensitivity to glucocorticoids (Huizenga et al. 1998). Another study reports an association of the Ser363 allele of the Asn363→Ser SNP with increased waist–hip ratio (WHR) in males, but no association with blood pressure, BMI, serum cholesterol, TG, LDL, or glucose-tolerance status (Dobson et al. 2001).

The G allele at the *Bcl*I RFLP has been associated with increased sensitivity to glucocorticoids. In middle-aged subjects, the G allele was associated with increased abdominal obesity, whereas in older individuals, a lower BMI was found, accompanied by a tendency towards a lower lean body mass (van Rossum and Lamberts 2004). This polymorphism has been studied by several groups and appears to be associated with several subphenotypes of MetS. In a study on the effects of *NR3C1* in response to overfeeding, 2.3/2.3 kb homozygotes (CC) for the *Bcl*I RFLP experienced greater increases in body mass, blood pressure, cholesterol levels, and visceral fat than 4.5/2.3 kb (GC) subjects (Ukkola et al. 2001). In the Quebec Family Study, the 4.5 kb fragment, the G allele, of the *NR3C1 Bcl*I RFLP was associated with a higher amount of abdominal visceral fat independent of the levels of total body fat (Buemann et al. 1997; Ukkola et al. 2001). The G allele was also associated with elevated BMI, WHR, abdominal sagittal diameter, leptin, and a borderline association with elevated systolic blood pressure (Rosmond et al. 2000). The NR3C1 *Bcl*I RFLP has also been associated with indices of glucose metabolism in obesity, where GG homozygotes had elevated fasting insulin and insulin resistance (Weaver et al. 1992).

The 3.8 kb homozygotes of another RFLP in the 5′ flanking region of the *NR3C1* gene were associated with elevated total and evening cortisol levels in a cohort of randomly selected middle-aged men (Rosmond et al. 2000). *NR3C1* mutations in patients with primary cortisol resistance have been reported and were associated with lack or reduction of transactivation capacity (Arg477→His and Gly679→Ser, respectively) (Ruiz et al. 2001). Other *NR3C1* mutations in the promoter (–22C → A) and 3′ UTR exon 9β (A → G in an AUUUA motif) have been reported (Ikeda et al. 2001; Schaaf and Cidlowski 2002) in *NR3C1*, but they were not associated with phenotypes of MetS.

Overall, the evidence suggests that the *NR3C1* gene may contribute to the observed variability in glucocorticoid sensitivity. Because DNA sequence variations in *NR3C1* are associated with variation in body composition and metabolic factors associated with MetS, it is possible that DNA sequence heterogeneity in *NR3C1* plays a role in the etiology of MetS. However, conflicting results make it difficult to determine exactly what effect *NR3C1* variants have on MetS incidence and progression.

*Peroxisome proliferative activated receptor γ (*PPARG*)*

The *PPARG* gene encoded on chromosome 3 (3p25) is a member of the nuclear hormone receptor subfamily of transcription factors and produces two proteins, PPARγ1 and PPARγ2. PPARγ2 is considered more specific to adipose tissue and its differentiation. The *PPARG* gene has been considered a strong candidate for MetS with concomitant effects on adipocyte differentiation, obesity, dyslipidemia, and insulin resistance (Yen et al. 1997). Predominantly expressed in the intestine and adipose tissue, its products trigger adipocyte differentiation and promote lipid storage (Bocher et al. 2002). PPARγ regulates the transcriptional activation of several adipose tissue-specific genes. PPARγ and its agonists are the subject of intense investigations as therapeutic agents for obesity, insulin resistance, and MetS (Olefsky and Saltiel 2000).

One common *PPARG* polymorphism, Pro12→Ala, has been associated with increased adiposity and insulin resistance (Gonzalez Sanchez et al. 2002), but oddly enough is also associated with decreased risk of MetS (Frederiksen et al. 2002). Although early studies of T2DM were inconsistent, a meta-analysis confirmed a modest (1.25 fold) but significant (p = 0.002) increase in T2DM risk associated

with the Pro allele (Altshuler et al. 2000). In a more recent meta-analysis, the same Pro12→Ala polymorphism increased the T2DM risk by 1.21 fold (range 1.08–1.37) (Lohmueller et al. 2003). We still do not understand the mechanism whereby this polymorphism affects glucose and lipid homeostasis. It has been suggested that there is enhanced suppression of lipolysis in Ala carriers, but not all studies have found differences in fasting FFAs or in FFA response to an oral lipid load (Semple et al. 2006). Thus, *PPARG* appears to be an important "diabetogene", but lately it has also been associated with the full MetS cluster. A recent haplotype analysis in a French population (n = 1195, 279 of them with MetS), reportedly showed a significant enrichment of the GTGC haplotype frequency (corresponding to P3 –681C → G, P2 –689C → T, Pro12→Ala (C→G), and 1431C → T polymorphisms) among those with MetS compared with control subjects. Compared with the most common CCCC haplotype, bearers of the GTGC haplotype had a 2.37 increased risk of the MetS (1.42–3.95; p = 0.002) (Meirhaeghe et al. 2005). Although the GTGC haplotype frequency was higher in subjects with MetS (5%, n = 14) compared with controls (2.2%), this data awaits replication in other populations.

Agarwal and Garg described a C to T mutation at nucleotide 1273 in exon 6 of the *PPARG* gene with heterozygotes exhibiting lipodystrophy (Agarwal and Garg 2002). Although rare, this mutation is instructive in the sense that the metabolic sequelae are almost identical to those seen in the "common" forms of obesity. Recently, several pedigrees have been described with severe insulin resistance, diabetes, and peripheral fat wasting. The clinical manifestations of this inherited partial lipodystrophy syndrome are quite similar to MetS, except that these patients do not respond to anti-diabetic thiazolidinediones. These families were found to have mutations in the *PPARG* gene at the ligand-binding pocket (Barroso et al. 1999). Known as PPARγ ligand resistance syndrome (PLRS), subjects without apparent lipodystrophy are either prepubertal or physically fit with low total-body adiposity, situations in which a relatively low level of adiposity in some depots may be difficult to discern. The majority of PLRS subjects have severe insulin resistance and early-onset T2DM (mean age of diagnosis 31 y), with PCOS seen in female subjects, as observed in other types of congenital generalized lipodystrophic syndromes. Most subjects have marked, sometimes extreme, dyslipidemia characterized by high TG and low HDL cholesterol levels (Semple et al. 2006).

Presenilin-associated rhomboid-like (*PARL*)

The PARL protein was identified through a search for new candidate genes to account for the diabetes phenotype in the *Psammomys obesus* under a high-energy diet (Walder et al. 2005). The *PARL* gene encodes a mitochondrial integral membrane protein that has been implicated in signal transduction, since a proteolytic processing of PARL forms a small peptide (Pβ) that translocates to the nucleus (Sik et al. 2004). It has been found that the expression of PARL was reduced in diabetic animals but increased when obese and diabetic *P. obesus* were exercise trained for 3 weeks (Walder et al. 2005). In addition, PARL expression was shown to be correlated with the expression of citrate synthase and insulin sensitivity in human skeletal muscle. The *PARL* gene is located on human chromosome 3q27, a region found to be linked to both T2DM and obesity in several genomic scans (Francke et al. 2001; Vionnet et al. 2000). In a cohort of 1031 individuals, genetic variation in *PARL* was associated with T2DM phenotypes. The PARL amino-acid substitution (Leu262→Val) interacted strongly with age and accounted for 5% of the variation in plasma insulin in elderly subjects and decreased the risk of MetS (Walder et al. 2005). Because PARL is involved in the maintenance of mitochondrial structural integrity and function, it has been considered a therapeutic target for insulin resistance and T2DM management. To date, no other reports have evaluated the relevance of this gene, if any, for the development of MetS.

Resistin (*RETN*)

Resistin, also called adipose tissue-specific secretory factor (ADSF) or found in inflammatory zone (FIZZ3), is encoded on chromosome 19p13.2. The *RETN* gene encodes a cysteine-rich 12.5 kDa polypeptide secreted by adipose tissue cells in rodents but not in humans. In humans, resistin is mainly expressed in macrophages that commonly infiltrate adipose tissue in obesity (Curat et al. 2006; Patel et al. 2003) and has been linked to insulin resistance (Steppan et al. 2001). Compared with rodents, the biology of resistin in human obesity and insulin resistance is more complex (Arner 2005). Whereas some studies report higher levels of circulating resistin in obese individuals (Degawa-Yamauchi et al. 2003; Silha et al. 2003; Valsamakis et al. 2004), others do not (Gerber et al. 2005; Heilbronn et al. 2004; Lee et al. 2003). Likewise, positive correlations of circulating resistin and insulin resistance (Azuma et al. 2003) could not be confirmed in other studies (Lee et al. 2003; Utzschneider et al. 2005). Although *RETN* mRNA expression is similar in both abdominal subcutaneous and omental fat depots, resistin expression is about 4-fold higher in abdominal fat than in thigh fat (McTernan et al. 2002). Therefore, resistin has been proposed as a mediator of insulin resistance in humans, participating in the increased risk of T2DM associated with abdominal obesity. The effects of resistin in the development of MetS are still under evaluation. Recently, resistin has been linked to inflammatory processes and atherosclerosis (Bokarewa et al. 2005; Burnett et al. 2005; Reilly et al. 2005; Silswal et al. 2005; Skilton et al. 2005).

The heritability of serum resistin levels reaches about 70% (Menzaghi et al. 2006). Several SNPs have been identified in human *RETN* and were reported as associated with insulin resistance, obesity, and T2DM (Azuma et al. 2004; Ma et al. 2002; Osawa et al. 2004; Pizzuti et al. 2002; Savage et al. 2001; Sentinelli et al. 2002). One of these sequence variants, –420C → G, is located in the 5′ flanking region of the gene and affects RETN transcriptional activity given the specific recognition of –420G by Sp1/3, which increases its promoter activity (Osawa et al. 2004). The GG genotype at the –420C → G SNP was associated with T2DM with an adjusted OR of 1.97 and was reported to accelerate the onset of T2DM by 4.9 years. Linkage disequilibrium analysis revealed that the GG genotype itself was a primary variant in determining T2DM susceptibility (Osawa et al. 2004). This –420C → G variant leads to enhanced serum resistin levels (Azuma et al. 2004; Menzaghi et al. 2006; Osawa et al. 2004) and has been

associated with increased *RETN* mRNA levels in abdominal fat (Osawa et al. 2002). A study (Engert et al. 2002) that combined population data from the Quebec Family Study and the Saguenay – Lac St-Jean region of Quebec found two promoter SNPs (–537A → C and –420C → G) associated with high BMI. In contrast, the same study reported that their result was not replicated in a population from Scandinavia (Engert et al. 2002). A trinucleotide (ATG) repeat at the 3′ UTR of the gene was, on the other hand, associated with a decreased risk of insulin resistance (Pizzuti et al. 2002). Lately, Menzaghi and collaborators found that resistin levels were significantly ($p < 0.01$) correlated with adiposity, blood pressure, CRP, and a MetS score (Menzaghi et al. 2006). This group investigated several polymorphisms of the *RETN* gene in a cohort of 264 nondiabetic Caucasian families. The SNPs included the promoter SNP –420C → G (rs1862513), IVS2 + 181G → A (rs3745367), and a trinucleotide repeat $(GAT)_n$. The G → A variation at position IVS2 + 181 of the *RETN* gene explained a small (1.5%), but significant ($p = 0.004$), proportion of the serum resistin variance.

Tumor necrosis factor α (*TNF*)

TNFα is a proinflammatory cytokine, with effects on lipid metabolism, coagulation, insulin resistance, and endothelial function. It is produced by macrophages, monocytes, endothelial cells, neutrophils, smooth muscle cells, activated lymphocytes, astrocytes, and adipocytes (Carswell et al. 1975). TNFα is a glycoprotein with a variety of functions, including mediating expression of growth factors, cytokines, transcription factors, and receptor genes. TNFα adipose tissue expression is proportional to the degree of adiposity.

TNFα is synthesized as a 26 kDa cell-membrane-bound protein that is cleaved from the cell surface and released as a 17 kDa soluble molecule. The gene maps to 6p21.3 (Xu et al. 2002). Given TNFα's inhibitory effects on lipoprotein lipase (LPL) activity, glucose homeostasis, and leptin, it has been suggested that the gene participates in the etiology of obesity. There are positive correlations between TNFα expression, BMI and leptin, and negative correlations between TNFα and LPL activity. It is possible that TNFα participates in a hemostatic mechanism that prevents further fat deposition by regulating LPL activity and leptin production (Bullo et al. 2002). High plasma levels of TNFα are also associated with insulin resistance, high BMI, high fasting glucose, and LDL cholesterol levels (Nilsson et al. 1998). TNFα has been proposed to link obesity with insulin resistance, with serine phosphorylation of the IRS-1 cited as a prominent mechanism for TNFα-induced insulin resistance (Sykiotis and Papavassiliou 2001). Physiologically, TNFα could affect several metabolic functions (likely involving the adipose tissue), but its mode of action could be indirect, possibly requiring the development of insulin resistance for its effects to become evident.

In terms of genetic variants in the *TNF* gene, most publications have centered on two promoter variants: –308G → A and –238G → A. There are inconsistent associations of *TNF* DNA sequence variants and MetS. There are negative data from several studies (da Sliva et al. 2000; Day et al. 1998; Furuta et al. 2002; Lee et al. 2000; Rasmussen et al. 2000*a*; Romeo et al. 2001; Valenti et al. 2002). However, these results are counterbalanced by other studies that support the contribution of these promoter variants to the etiology of insulin resistance, obesity, or T2DM (Brand et al. 2001; Dalziel et al. 2002; Fernandez-Real et al. 1997; Herrmann et al. 1998; Hoffstedt et al. 2000; Nicaud et al. 2002; Padovani et al. 2000). A linkage between obesity and a marker (dinucleotide repeat) near the *TNF* locus in the Pima Indians has also been reported (Norman et al. 1995). There are higher frequencies of TT homozygotes at a promoter SNP (–857C → T) in obese patients with T2DM compared with lean subjects (Kamizono et al. 2000). *TNF* sequence variation may play a role in the development of MetS but the association studies are somewhat inconclusive.

Evidence from genomic scans

Linkage studies aim to define the chromosomal location of a gene or genes associated with the phenotype of interest. Whole-genome scans (a type of linkage study) generally explore the whole genome, but sometimes only the autosomes, for the presence of QTLs. A typical QTL spans several million base pairs and contains many genes. The underlying principle of linkage studies is the cosegregation of two loci. A logarithm of the odds (LOD) score measures the likelihood that two loci located near each other on a chromosome are inherited together. It is expressed as the logarithm of the odds that an observed data set is due to linkage at a specific map distance rather than to independent assortment on nonlinked genes.

A number of genome-wide linkage scan explorations for MetS have been reported (Fig. 2). These studies have been performed on some of the MetS components or on linear combinations of phenotypes derived from principal component or factor analysis explorations (Arya et al. 2002; DeWan et al. 2001; Duggirala et al. 2001; Kissebah et al. 2000; Kraja et al. 2005*a*, 2005*b*; Lehman et al. 2005; Loos et al. 2003; Ng et al. 2004). The results from such studies are summarized in Table 3. Only those QTLs with an LOD score equal to or greater than 2 have been retained.

Kissebah and colleagues reported two QTLs for MetS (Kissebah et al. 2000). Using a 10 cM map in 2209 individuals from 507 nuclear Caucasian families, a QTL was found on 3q27 (D3S2427–D3S2398) with linkage to six putative obesity and glucose/insulin markers of MetS. This QTL was in epistatic interaction with a QTL on 17p12 strongly linked to plasma leptin levels (Kissebah et al. 2000). Evidence for linkage at the 3q27 region was also reported for hypertension and obesity in the HyperGEN study (DeWan et al. 2001).

A significant LOD score (LOD = 3.5) was identified on chromosome 6q22–q23 (D6S403–D6S264), for fasting glucose, insulin values, and other insulin resistance related phenotypes with strong pleiotropic effects with obesity-related phenotypes in non-diabetic Mexican Americans (Duggirala et al. 2001). Arya and collaborators used phenotypic data from 261 non-diabetic subjects from 27 low-income Mexican-American extended families and principal components) derived from eight phenotypes: fasting glucose and insulin, BMI, systolic and diastolic blood pressure, HDL cholesterol, TG, and leptin (Arya et al. 2002). Their analysis yielded three principal components: PC1 (BMI, leptin, and insulin), PC2 (DBP and SBP), and PC3 (HDL and TG). In their mul-

Table 3. Inventory of QTLs associated with MetS based on genome-wide linkage scans.

Marker	Location	Phenotype	LOD score	Reference
D1S305	1q22	PC with positive loadings for BMI, fasting specific insulin, and leptin (cohort: SAFADS)	2.6	Arya et al. 2002[b]
D1S1653	1q21–q25	MetS definition (3 out of 5 risk factors, NCEP III definition) (cohort: Hong Kong Family Diabetes Study)	4.51	Ng et al. 2004[a]
D1S193	1p34.1	PC with positive loadings for % body fat and HDL, and negative loading for TG (cohort: HERITAGE Family study, blacks)	2.03	Loos et al. 2003[b]
D1S1609	1q43–44	Joint phenotype obesity-fasting insulin (cohort: HyperGEN whites)	2.07	Kraja et al. 2005*a*[b]*
D2S1328	2q14.2	Joint phenotype lipids-fasting insulin (cohort: HyperGEN whites)	2.00	Kraja et al. 2005*b*[a]
D2S1649	2q32	Joint phenotype obesity-fasting insulin (cohort: HyperGEN whites)	2.40	Kraja et al. 2005*b*[a]
D3S2387	3p26	Joint phenotype obesity-fasting insulin (cohort: HyperGEN whites)	2.42	Kraja et al. 2005*a*[b]
D3S1764	3q23	Joint phenotype central-obesity, waist and waist hip ratio (cohort: SAPPHIRe Japanese)	2.61	Kraja et al. 2005*b*[a]
D3S2432	3p24.2	Joint phenotype lipids-fasting insulin (cohort: HyperGEN whites)	2.02	Kraja et al. 2005*b*[a]
D3S2427–D3S2398	3q27	Six phenotypes components of MetS: BMI, hip and waist circumferences, body weight, insulin and insulin/glucose ratio (cohort: TOPS)	2.3–3.54	Kissebah et al. 2000[b]
D3S2398–D3S2418	3q27	Hypertension and obesity (cohort: HyperGEN study)	3.61	DeWan et al. 2001[a]
D4S3248	4q22	Joint phenotype obesity-fasting insulin (cohort: GENOA whites)	2.00	Kraja et al. 2005*b*[a]
D4S1625	4q31.1	Joint phenotype lipids-fasting insulin (cohort: SAPPHIRe Chinese)	2.07	Kraja et al. 2005*b*[a]
SE30	6p25.1	Joint phenotype central-obesity (cohort: SAPPHIRe Japanese)	2.07	Kraja et al. 2005*b*[a]
D6S403–D6S264	6q22–q23	Fasting glucose, fasting specific insulin, and other insulin resistance related phenotypes with obesity-related phenotypes (cohort: SAFADS)	3.5	Duggirala et al. 2001[b]
D6S403	6q24.1–q24.2	PC with positive loadings for BMI, fasting specific insulin, and leptin (cohort: SAFADS)	4.2	Arya et al. 2002[b]
D6S264	6q25.2–q26	PC with positive loadings for BMI, fasting specific insulin, and leptin (cohort: SAFADS)	4.9	Arya et al. 2002[b]
D7S653	7q11.23	Joint HDL and In split proinsulin	4.5	Lehman et al. 2005[b]
D7S820	7q21	Joint phenotype obesity – fasting insulin (cohort: HyperGEN blacks)	2.11	Kraja et al. 2005*a*[b]
D7S479–D7S471	7q21.3–7q31.1	PC with positive loading for HDL and negative loading for TG (cohort: SAFADS)	3.2	Arya et al. 2002[b]
D8S1477	8p12	Joint phenotype obesity – fasting insulin (cohort: GENOA whites)	2.01	Kraja et al. 2005*b*[a]
D8S136	8p21	Joint phenotype obesity – fasting insulin (cohort: GENOA whites)	2.39	Kraja et al. 2005*b*[a]
D8S264	8p23	Joint phenotype lipids – fasting insulin (cohort: HyperGEN whites)	2.43	Kraja et al. 2005*b*[a]
D8S264	8p23	Joint phenotype lipids – fasting insulin (cohort: HyperGEN whites)	2.31	Kraja et al. 2005*a*[b]

Table 3 (*continued*).

Marker	Location	Phenotype	LOD score	Reference
D9S301	9q21	PC with positive loadings for BMI, fasting specific insulin, and leptin (cohort: SA-FADS)	2.8	Arya et al. 2002[b]
D10S208	10p11.2	PC with positive loadings for glucose, in-	2.53	Loos et al. 2003[b]
D10S1768		sulin, %BF, AVF, TG, and MAP, and negative loading for HDL (cohort: HERI-TAGE Family study, whites)	2.20	
D11S1985	11q12.2	Joint phenotype obesity – fasting insulin (cohort: SAPPHIRe Chinese)	2.03	Kraja et al. 2005*b*[a]
D11S2002	11q13	Joint phenotype central obesity (cohort: GENOA whites)	2.19	Kraja et al. 2005*b*[a]
D11S912	11q24	Joint phenotype lipids – fasting insulin (cohort: HyperGEN blacks)	2.63	Kraja et al. 2005*a*[b]
D13S787	13p12	Joint phenotype obesity – fasting insulin (cohort: HyperGEN blacks)	2.77	Kraja et al. 2005*a*[b]
D13S793	13q31–q32	Joint phenotype central obesity (BMI and waist) (cohort: GENOA whites)	2.17	Kraja et al. 2005*b*[a]
ATA26D07	13q32.3	Joint phenotype central obesity (cohort: BMI and waist) (cohort: GENOA blacks)	2.67	Kraja et al. 2005*b*[a]
D14S617	14q24	Joint phenotype obesity – fasting insulin (cohort: HyperGEN whites)	2.44	Kraja et al. 2005*a*[b]
D15S659–D15S103	15q14	PC with positive loadings for systolic and diastolic blood pressure (cohort: SA-FADS)	2.0	Arya et al. 2002[b]
D15S1507	15q15	Systolic and diastolic BP factor (cohort: HyperGEN whites)	3.19	Kraja et al. 2005*a*[b]
D16S2620	16q12	Joint phenotype obesity –fasting insulin (cohort: GENOA whites)	2.33	Kraja et al. 2005*b*[a]
D16S2624	16q22	Joint phenotype obesity –fasting insulin (cohort: GENOA whites)	2.59	Kraja et al. 2005*b*[a]
D17S1293	17p11.2	Joint phenotype obesity –fasting insulin (cohort: GENOA whites)	2.21	Kraja et al. 2005*b*[a]
D17S1294	17q11.2	Joint phenotype obesity – fasting insulin (cohort: GENOA whites)	2.35	Kraja et al. 2005*b*[a]
D17S2196	17q11.2	Joint phenotype obesity – fasting insulin (cohort: GENOA whites)	2.27	Kraja et al. 2005*b*[a]
D17S2193	17q23	Systolic and diastolic BP factor (cohort: GENOA hispanics)	2.78	Kraja et al. 2005*b*[a]
D17S1290	17q23.1	Systolic and diastolic BP factor (cohort: GENOA hispanics)	3.22	Kraja et al. 2005*b*[a]
D17S784	17q25	Joint phenotype obesity – fasting insulin (cohort: SAPPHIRe Chinese)	2.48	Kraja et al. 2005*b*[a]
D17S928	17q25	Joint phenotype obesity-fasting insulin (cohort: SAPPHIRe Chinese)	2.36	Kraja et al. 2005*b*[a]
D17S2180	17q21	Joint phenotype obesity – fasting insulin (cohort: GENOA whites)	2.09	Kraja et al. 2005*b*[a]
D18S535	18q12	Joint phenotype obesity – fasting insulin (cohort: GENOA blacks)	2.08	Kraja et al. 2005*b*[a]
D18S542	18q12	Joint phenotype obesity – fasting insulin (cohort: GENOA blacks)	3.94	Kraja et al. 2005*b*[a]
D18S877	18q12.1	Joint phenotype obesity-fasting insulin (cohort: GENOA blacks)	3.44	Kraja et al. 2005*b*[a]
D18S851	18q12.3	Joint phenotype obesity – fasting insulin (cohort: GENOA blacks)	2.40	Kraja et al. 2005*b*[a]
D19S1166	19p13.3	Joint phenotype lipids – fasting insulin (cohort: HyperGEN blacks)	2.19	Kraja et al. 2005*b*[a]
D19S589	19q13.4	PC with positive loadings for %BF and HDL, and negative loading for TG. (cohort: HERITAGE Family study, whites)	2.11	Loos et al. 2003[b]

Table 3 (*concluded*).

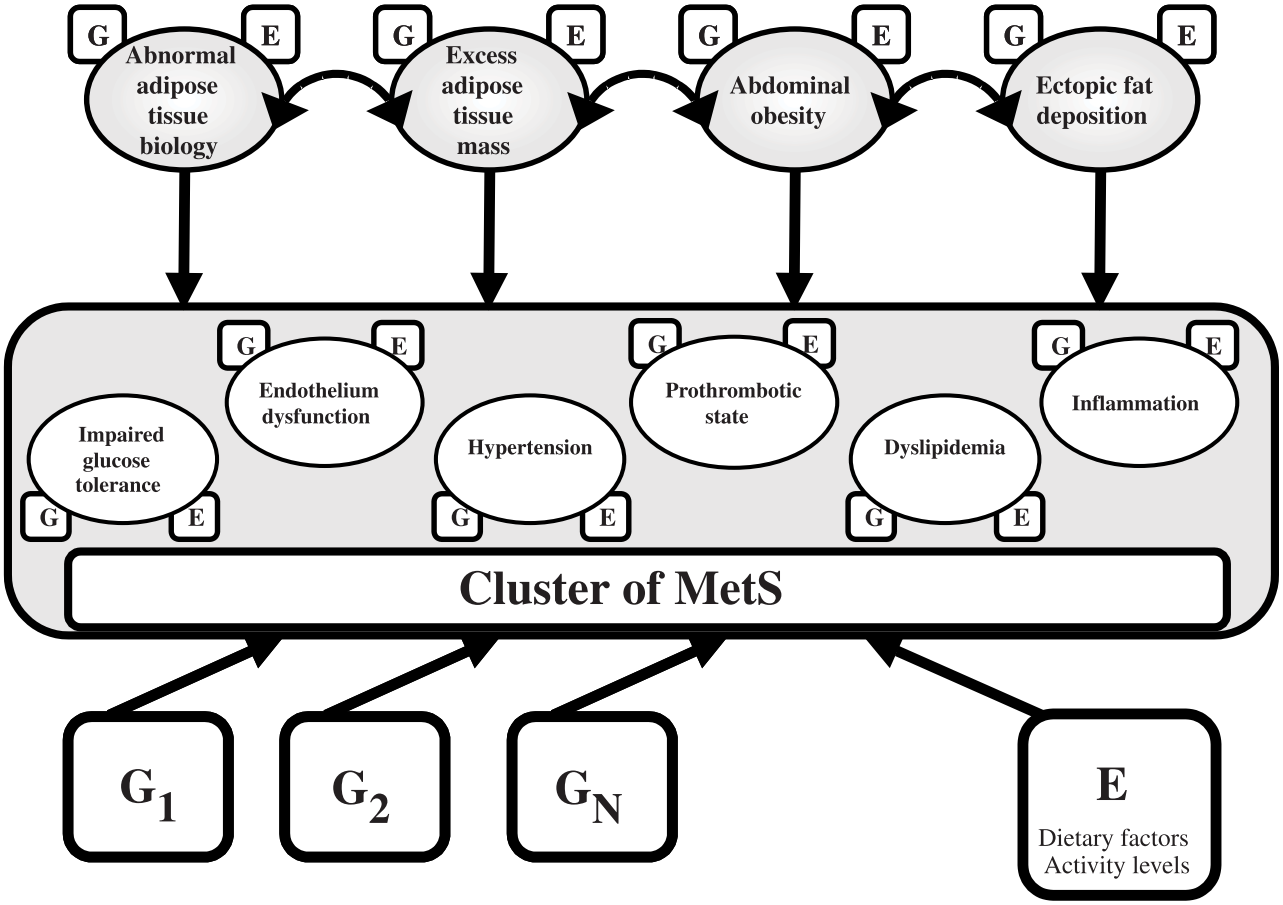
Marker	Location	Phenotype	LOD score	Reference
D19S246	19q13	PC with positive loadings for BMI, fasting specific insulin, and leptin (cohort: SA-FADS)	2.6	Arya et al. 2002[b]
D20S604	20q11	Joint phenotype central obesity (cohort: HyperGEN blacks)	2.46	Kraja et al. 2005*b*[a]
GATA11C12	21q21	Joint phenotype obesity – fasting insulin (cohort: GENOA whites)	2.15	Kraja et al. 2005*b*[a]
GATA129D11	21q21	Joint phenotype central – obesity (cohort: GENOA whites)	2.13	Kraja et al. 2005*b*[a]
D21S1440	21q22.13–q22.2	Joint phenotype central – obesity (cohort: BMI and waist) (cohort: GENOA whites)	2.13	Kraja et al. 2005*b*[a]

Note: Marker names were converted from Marshfield identifications, when possible, to the D numbering system for consistency. Adapted from an online data supplement (http://hyper.ahajournals.org/cgi/content/full/01.HYP.0000184249.20016.bb/DC1).

[a]Families and (or) sib-pair studies with a proband for at least one MetS component.

[b]Non-affected and (or) randomly selected families.

Fig. 3. This figure provides a simple scheme of the role of genetic (G) and environmental (E) factors on putative causes of MetS and related traits. Genetic and environmental effects have an impact on lipid and adipose tissue related traits that in turn influence individual risk factors and the MetS cluster. In addition, all individual components of MetS are regulated by both genetic and environmental factors. Even though the evidence is very weak at this stage, there may be DNA sequence variants in genes yet to be identified that play a role in the clustering of sub-clinical manifestations currently defined as components of MetS. Environmental and lifestyle factors such as diet and activity levels may also play a role in the development of MetS (see text for detail).



tipoint variance component linkage analyses with SOLAR, they found significant evidence of linkage for PC1 on chromosome 6 with markers D6S403 (LOD = 4.2) and D6S264 (LOD = 4.9). There was also strong evidence of linkage for PC3 (HDL and TG) on chromosome 7 (7q21.3–31.1) between markers D7S479 and D7S471 (LOD = 3.2).

Loos and colleagues performed a genome-wide search on two principal components obtained from 456 white and 217 black individuals from the HERITAGE Family Study (Loos et al. 2003). Principal component analysis was carried out on seven MetS-related phenotypes that included percent body fat, visceral fat, mean arterial blood pressure, and plasma HDL cholesterol, TG, glucose, and insulin concentrations. They found linkages with LOD scores above 2 on 10p11.2 (D10S208, D10S1768) for PC1 and on 19q13.4 (D19S589) for PC2 in whites. In blacks, linkage was found for PC2 on 1p34.1 (D1S193) (Loos et al. 2003). Ng and coworkers conducted a genome-wide scan in the Hong Kong Family Diabetes Study for non-parametric linkage analysis on MetS, using the NCEP III definition. There was suggestive linkage for MetS on 1q21–q25 (D1S1653) (LOD = 4.50) (Ng et al. 2004).

Results from a genome-wide linkage scan for the GENOA, HyperGEN, and SAPPHIRe networks were recently published (Kraja et al. 2005*b*). The study was based on 10 phenotypes, and an exploratory factor analysis procedure yielded four factors, which were defined as the combined phenotypes of obesity–insulin, lipids–insulin, systolic and diastolic blood pressure, and two measures of central obesity. These four related MetS factors were tested for linkage with 400 microsatellite markers in four different ethnic groups (blacks, whites, Hispanics, Asians). Evidence of linkage at LOD >2 was found on chromosomes 13q31.3–13q32.2 (D13S793), 20p12.2, and 20p12.1 in blacks; on chromosomes 11q13.3 (D11S2002) and 21q21 (GATA11C12 and GATA129D11) in whites; and on chromosomes 3q22.1, 5q35.2, 6p25.1 (SE30), 6p23, and 8p23.3 in Asians. No evidence of linkage was found in Hispanics (Kraja et al. 2005*b*).

A bivariate linkage analysis of MetS-related phenotypes (BMI, waist circumference (WC), lipids, and insulin) was performed in 440 subjects from 27 Mexican-American pedigrees (Lehman et al. 2005). There were linkages for most of the bivariate traits (BMI–lipids, BMI–insulin, WC–lipids, WC–insulin, BMI–WC; max LOD scores = 4.5) in a 6 cM region near marker D7S653. The maximum bivariate LOD score was found at 7q11.23 (near D7S653) for the joint trait of HDLC and split proinsulin (LOD = 4.51) (Lehman et al. 2005).

Overall, there is little concordance among the QTLs identified by genome-wide linkage scans. This should not be surprising, given the heterogeneity in the MetS phenotypes on which these scans are based. Other sources for the lack of concordance include differences in study populations as well as the nature, number and methodological aspects of the variables used to define MetS and the number of factors extracted. Nonetheless, these studies have generated a number of useful findings that are worth pursuing in terms of fine mapping and candidate genes.

Conclusions

The cardinal features of MetS include obesity, abnormal adipose tissue metabolism, ectopic fat deposition, insulin resistance, hyperinsulinemia, dyslipidemia, and hypertension. The present review has highlighted findings from genetic epidemiology, Mendelian diseases, candidate genes and genomic scans that are relevant to MetS in some fashion. The genetic basis for each component of MetS is under intense investigation. Genes of interest for these QTLs include *ADIPOQ*, *PARL*, and *LEP*. Those genes have been investigated but results are thus far inconclusive. The field would benefit from mining combined sets of informative cohorts and from the development of longitudinal data on large populations over decades of life.

Figure 3 displays a simplified rendering of the factors that may be causally related to MetS. The stage for MetS is set by lipid and adipose tissue traits that are each affected by genetic and lifestyle factors. The individual components of MetS are likewise influenced by genes, diet, physical activity and other behaviors. Finally, the MetS clustering, if it occurs, may in turn depend on genes yet to be identified and behavioral factors. One of the challenges is early identification of individuals or populations at risk for developing the full spectrum of diseases that are related to MetS, such as T2DM and cardiovascular disease.

Progress in understanding of the genetics of MetS will likely be hampered by the obvious lack of consensus on the MetS concept, its components, and diagnostic criteria. Productive genetic studies of MetS are not likely to become a common occurrence until these fundamental issues are resolved. However, one cannot exclude the possibility that genetic studies may shed light on the fundamental debate, particularly if genes and informative sequence variants were shown to play a key role in the clustering of pre-clinical metabolic deviations.

Acknowledgements

Thanks are expressed to Nina Laidlaw for her editorial support.

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