Series Editor: A. Maziar Zafari, MD, PhD

Genetics of the Metabolic Syndrome

Qing Song, MD, PhD
Shaoshan S. Wang, MD, PhD
A. Maziar Zafari, MD, PhD

Metabolic syndrome is one of the fastest growing health problems worldwide. It is a major risk factor for both diabetes mellitus[1] and cardiovascular disease (CVD).[2] The etiology is complex, determined by the interplay of both genetic and environmental factors (**Figure**).[3] It is characterized by the clustering of multiple metabolic abnormalities, including abdominal obesity, hypertension, dyslipidemia, insulin resistance, and impaired glucose tolerance.[4] This clustering has been referred to as *syndrome X, the deadly quartet*, and the *insulin resistance syndrome*. The term *insulin resistance syndrome* was widely used until 1998, when the World Health Organization proposed a unifying definition for the syndrome and chose to call it *metabolic syndrome*.

In the United States, approximately 25% of the adult population (age > 20 years) and up to 45% of those older than 50 years meet the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III) diagnostic criteria for the metabolic syndrome.[5] Metabolic syndrome has a higher prevalence in men. Prevalence varies substantially among ethnic groups, with the highest rate in Mexican-American women.[6] Due to the increasing prevalence of obesity, the prevalence of metabolic syndrome continues to increase.

An apparent paradox has been observed in African Americans. Although African Americans have a higher prevalence of obesity and hypertension compared to whites, they have a lower prevalence of metabolic syndrome.[6] Compared with whites, African-American men have a lower incidence of large waist circumference, high triglyceride levels, and low high-density lipoprotein (HDL) cholesterol levels, and a higher incidence of hypertension and diabetes[6]; African-American women have a higher frequency of large waist circumference, diabetes, hypertension, and hyperglycemia and a lower frequency of high triglyceride levels. The net result is that by the NCEP/ATP III criteria, the prevalence of metabolic syndrome in African-American men is half that observed in white men, and in African-American women the prevalence is 30% less than that of white women. These differences persist even after adjusting for contributing factors, such as age, body mass index (BMI), smoking and drinking habits, socioeconomic status, and physical inactivity as well as menopausal status among women. The ethnic differences strongly suggest a genetic component in the pathogenesis of metabolic syndrome. This manual, the seventh part in a series on the metabolic syndrome, reviews candidate genes involved in metabolic syndrome and discusses genetic approaches to understanding the genotype/phenotype interactions in this syndrome.

TAKE HOME POINTS

- Metabolic syndrome is determined by the interplay of genetic and environmental factors.
- All components of the metabolic syndrome are strongly inherited.
- The *thrifty genotype hypothesis* proposes that energy-conserving genotypes selected by a harsh environment are associated with a survival disadvantage when there is an abundance of food.
- The *thrifty phenotype hypothesis* suggests that intrauterine malnutrition leads to low birth weight and increased risk of metabolic syndrome later in life.
- Genome scans have identified strong links between certain chromosomal regions and metabolic syndrome.
- Candidate gene studies have identified linkage between metabolic syndrome and a number of genes, such as PPARγ, adiponectin, CD36, and β receptors.

Dr. Song is an assistant professor, Cardiovascular Research Institute, Morehouse School of Medicine, Atlanta, GA. Dr. Wang is a fellow, Divsion of Cardiology, and Dr. Zafari is an associate professor and director, Cardiovascular Training Program, Division of Cardiology; both are at the Emory University School of Medicine, Atlanta, GA.

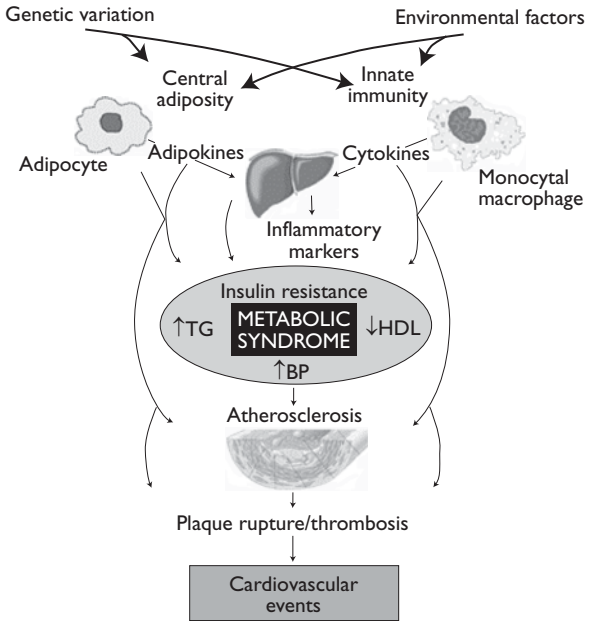

Figure. Pathophysiology of atherosclerotic cardiovascular disease in the metabolic syndrome. Common genetic variants and environmental factors may impact the development of atherosclerosis at multiple levels by affecting central adiposity, innate immunity, glucose and lipoprotein metabolism, and vascular function. BP = blood pressure; HDL= high-density lipoprotein; TG = triglycerides. (Adapted with permission from Reilly MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? Circulation 2003;108:1549.)

RELATIONSHIP AMONG THE INDIVIDUAL COMPONENTS OF THE METABOLIC SYNDROME

Although it is currently unknown which components of metabolic syndrome are primary and which are secondary, visceral obesity is believed to be a driving factor for the syndrome.[7] Visceral obesity can lead to insulin resistance with the development of impaired glucose tolerance, hyperglycemia, and type 2 diabetes. The importance of controlling obesity in the treatment of diabetes has been widely acknowledged. Visceral obesity is associated with many pathophysiologic changes, including sodium retention and volume expansion, increased sympathetic nervous activity, and stimulation of the renin-angiotensin system.[8] Adipose tissue is also an active endocrine organ that secretes a variety of molecules known as adipocytokines into the circulation; these have profound effects on the vasculature and metabolism.[9] There is an intimate association between obesity and inflammatory markers, such as C-reactive protein (CRP), which has been repeatedly associated with increased risk of CVD.[10] The proinflammatory state that is associated with obesity appears to mediate the progression to diabetes and CVD.

Insulin resistance may cause hypertension; however, not all patients with hypertension have metabolic abnormalities, nor does hypertension occur in all patients with hyperinsulinemia. In healthy individuals, infusions of insulin that produce plasma insulin concentrations in the physiologic range, given with sufficient glucose to prevent hypoglycemia, cause vasodilation but not increased blood pressure (BP).[11] Furthermore, BP falls when the dose of insulin is decreased in obese hypertensive patients with type 2 diabetes[12] and increases when insulin treatment is begun in diabetic patients whose plasma glucose concentrations are poorly controlled with oral agents.[13]

Despite the clustering of these individual metabolic syndrome components, there is substantial heterogeneity of CVD risk among individuals with increased adiposity. Insulin resistance is found both in obese and lean patients with hypertension. The underlying molecular and pathological mechanisms for this clustering in metabolic syndrome have not been defined, but it is believed to involve the interplay between behavioral, cultural, socioeconomic, and genetic determinants.

HERITABILITY AND THE METABOLIC SYNDROME

Heritability is a measure for assessing genetic components in diseases. It is defined as the fraction of variation in liability across the population due to genetic factors. Heritability can be estimated using either twin studies, which look for greater concordance between monozygotic (MZ) twin pairs than between dizygotic (DZ) twin pairs, or family studies, which examine the degree of similarity within families versus between families. Accumulated evidence suggests that metabolic syndrome most likely results from the interplay between several genes and an affluent environment. Although the estimate on heritability of metabolic syndrome has not been reported, it is clear that all components of the syndrome are strongly inherited.[14] Numerous twin and family studies have shown significant genetic contributions to hypertension. Estimates of heritability range from 22% to 62% for systolic BP and from 38% to 63% for diastolic BP. The contribution of genetics to the development of diabetes is demonstrated by the high incidence of diabetes among first-degree relatives of type 2 diabetic patients and the high concordance in identical twins.[15] It is estimated that the probability that one twin of a MZ pair is diabetic given that the other has diabetes is 50%; the estimated probability in DZ pairs is 37%. Family aggregation studies have shown that 45% of first-degree relatives of patients with type 2 diabetes are insulin resistant compared with 20% of individuals without a family history of diabetes.[16] For obesity, a strong relationship has been

observed between the biologic parents-child pairs[17] and twins[18] in regards to BMI. It is estimated that genetic factors explain approximately 40% of the variance in body fat[19] and up to 70% of variance in abdominal obesity.[20] In addition, concordance rates for glucose intolerance, overall obesity, and low HDL-cholesterol are significantly higher among MZ than DZ twins.[18]

GENETIC APPROACHES

Common genetic variants in a number of genes may increase susceptibility to metabolic syndrome. These genetic variants may act in concert with other gene variants and a number of environmental factors in disease development. Identification of genes associated with disease pathogenesis utilize 3 complementary approaches in searching for genetic variations: animal studies, human candidate gene studies, and human genome scans followed by positional cloning.

Animal Models

The search for genetic components of common diseases has motivated a series of important studies in animal models. The study of the etiopathogenesis of metabolic syndrome is difficult because it is a multifactorial and polygenic disease. The use of animal models is substantially advantageous in genetic dissections because inbred animal strains are genetically homogeneous and their environment can be controlled and standardized. In addition, a particular gene of interest can be studied by specific gene manipulation using knockout, knock-in, and transgenic technologies.

Currently, the rodent models for metabolic syndrome include but are not limited to the Dahl salt-sensitive/resistant rat, spontaneously hypertensive rat, Zucker diabetic fatty rat, KKAy mouse, and ob, db, tubby, agouti, and fatty acid translocase (FAT) mice. A new animal model that has developed almost all components of metabolic syndrome, the Wistar Ottawa Karlsburg W (WOKW) rat, is emerging as a new rodent model of the metabolic syndrome.[21] Genomes of these animals, which closely resemble the complex human disease, can be thoroughly scanned to estimate the number, location, and effect of quantitative trait loci using comparative genomics. In parallel with genome scans, congenic and consomic strategies can be used in animals to yield a powerful platform for functional studies, especially when combined with microarray technologies. Molecular and biochemical analyses on these animal models may elucidate the role of candidate genes in the pathogenesis of metabolic syndrome. Moreover, the role of biologically relevant candidate genes in metabolic syndrome can be examined by studying the phenotypic traits in animals with specific overexpression or gene disruption of selected genes.

It is well known that results from animal experiments cannot always be translated into human physiology and pathology. Although the predisposing genes in rodents may not be the same as the predisposing genes in humans, animal studies provide crucial clues in the search for susceptibility genes in humans by delineating pathophysiologic pathways. Consequently, animal studies have identified a large number of candidate genes based on biologic and pathologic relevance.

Genome Scan Approaches in Human Populations

The development of genome-wide genetic maps has facilitated the widespread application of genome-wide linkage analysis to disease states. Genome scans are systematic and hypothesis-free scans of the entire genome in search for genetic loci predisposing to complex human diseases. The aim is to localize the genetic regions harboring the disease-predisposing genes by using genetic markers and linkage analyses. If a chromosomal region has been linked to the disease, linkage disequilibrium mapping will be done to narrow the region, and then positional cloning will be used to eventually identify the gene and its disease-causing variants without determining the function and biologic role of the gene. Genome scans are one of the leading approaches currently used to identify novel genes associated with complex human diseases. The advantage of the genome-wide scan approach is that it does not assume any knowledge about the pathophysiologic mechanisms leading to the diseases; the disadvantages include the requirement of significant resources and the high risk for false-positive results.

Candidate Gene Approaches in Human Populations

The candidate gene approach is built upon a hypothesis drawn from information on a gene's biologic function. Candidate genes can be identified using prior knowledge about biological function, linkage studies, or animal studies. The relationship between candidate genes and human disease traits can be tested by linkage or association analysis. Linkage analyses test for the segregation of a marker and disease phenotype in a pedigree, whereas association studies test for significant differences in the allele frequencies of genetic variants between patient and control groups.

The last decade has seen revolutionary advances in human genetics.[22] Among these, the most relevant to association studies include the completion of the human genome project, the identification of large numbers of genetic markers, mostly single nucleotide

polymorphisms (SNP), the development of rapid high-throughput methods to genotype SNPs, and the understanding of linkage disequilibrium. These recent advances allow comprehensive and large-scale association studies with SNPs to survey genes or regions for variants that contribute to genetic susceptibilities to complex human diseases.

Because of the multifactorial and polygenic nature of complex traits, each individual genetic variant generally has only a modest effect. The interactions between genetic variants and interactions between genetic variants and environmental factors may play a crucial role in the expression of disease traits. Therefore, sample size, carefully matched groups, well-chosen genetic markers, and adequate standards in genotyping, statistical analysis, and interpretation are all integral parts of a high-quality association study.

Interpretation of Association Studies and Genome Scans

Association studies have become an increasingly popular approach to mapping variants that affect complex traits, but caution must be used when interpreting the results of this approach because very few associations have been consistently replicated in different samples.[23] Recent meta-analyses suggest that most reported findings of associations are incorrect.[24] Reasons for limited success include insufficient sample size, genetic heterogeneity of human populations, the late onset of diseases, the complex nature of the disease, and concomitant presence of confounding risk factors. Moreover, this hypothesis-driven approach is limited by its reliance on the existing knowledge of disease pathophysiology.

Eleven million SNPs of greater than 1% frequency are estimated to exist in the genome.[25] Some SNPs are more likely to be functional (increase or decrease risk of disease) than others. Functional SNPs, including missense coding SNPs and nonexonic regulatory SNPs, are more likely to be evolutionarily deleterious or beneficial, and therefore, may more likely be functional variants that contribute to common diseases. Testing potentially functional noncoding variants will be much more difficult because these regulatory noncoding variants are harder to recognize than missense variants due to our limited knowledge of regulatory sequences. The discovery of disease-relevant genetic variants and their underlying biologic pathways is a major challenge in human genetic studies.

Genome Scans of Metabolic Syndrome

Genome scans have been carried out to identify genes responsible for the inherited component of polygenic disorders such as diabetes, hypertension, and obesity in rodents and humans. Chromosome locations for these disease traits can be found in the National Center for Biotechnology Information's Online Mendelian Inheritance in Men database under the entries of each disease, such as essential hypertension and type 2 diabetes.

Several genome scans have been carried out recently on metabolic syndrome. A genome scan performed in 507 white nuclear families using a 10-cM map demonstrated a strong link between chromosome band 3q27 and 6 traits (weight, waist circumference, leptin, insulin, insulin/glucose ratio, and hip circumference), with logarithmic odds (LOD) scores ranging from 2.4 to 3.5. (The LOD score is a statistical estimate of whether 2 loci are likely to lie near each other on a chromosome and are therefore likely to be inherited together. An LOD score of 3 means the odds are 1000 to 1 in favor of genetic linkage.) This chromosome location (3q27) has been replicated in another genome scan conducted in 99 Indian families. The chromosome locus of 16p13-pter (LOD = 3.06; $P = 0.00017$) was also implicated in the metabolic syndrome. A recent genome scan using families and sibpairs of the National Heart, Lung, and Blood Institute Family Heart Study found significant linkage on chromosome 2 at 240-cM (LOD = 3.34; $P = 0.00004$).[26] This same broad region of chromosome 2 has been implicated by at least 14 other studies for phenotypes related to metabolic syndrome. Suggestive linkage has been observed for regions on chromosomes 7, 12, 14, and 15.[26]

The differences in chromosome positions of disease loci among different ethnic populations may reflect variation in allelic diversity and the pattern of linkage disequilibrium. Alleles at different loci are sometimes found together more than expected. In population genetics, this nonrandom pattern is called linkage disequilibrium. Linkage disequilibrium appears to be organized in block-like structures.[27] The linkage disequilibrium block structure usually varies among populations with different ethnohistories. The differential linkage disequilibrium block structure between different ethnic groups can help to refine the target region in mapping the disease susceptibility alleles (linkage disequilibrium mapping).

Genome scans have facilitated the identification of a number of loci for metabolic syndrome and its individual components; however, the chromosomal regions implicated by genome scans are relatively large. After those studies are replicated to confirm the susceptibility loci in different populations, the challenge is how to identify disease genes and their etiologic

genetic variants to explain disease phenotypes from a biologic standpoint. Linkage disequilibrium mapping and positional cloning can be used to narrow these target chromosome regions and eventually identify the disease-predisposing genetic variants.

CANDIDATE GENES OF METABOLIC SYNDROME

It is believed that the clustering of metabolic syndrome components is a consequence of metabolic abnormalities. Two hypotheses have been proposed to explain the interindividual variations of susceptibility to metabolic syndrome and variations in its associated phenotypes. According to the *thrifty genotype hypothesis* proposed by Neel in 1962,[28] individuals living in a harsh environment with unstable food supply would maximize their probability of survival if they could maximize storage of surplus energy. Genetic selection would thus favor energy-conserving genotypes in such environments. However, the selected genetic variations that were favored during malnutrition would become unfavorable when nutrition improved. Support for this hypothesis comes from a study in the ob and db mouse,[29] in which heterozygous animals (only homozygous animals will develop obesity or diabetes) with the same body weight as the wild type survived longer during total fasting than the insulin-sensitive wild type mice. This hypothesis assumes that common genetic variants of thrifty genes predispose to metabolic syndrome. The *thrifty phenotype hypothesis* was introduced by Hales and Barker in 1992.[30] According to this hypothesis, babies who experienced intrauterine malnutrition may have adapted to poor nutrition by reducing energy expenditure and becoming "thrifty." These metabolic adaptations are beneficial when individuals are poorly nourished during childhood and adult life; however, with increased food intake, these adaptations are no longer beneficial and would lead to increased risk of metabolic syndrome in later life. Support for this hypothesis comes from the observed associations of low birth weight with later development of insulin resistance and type 2 diabetes in several populations.[31–34]

Based on the thrifty genotype hypothesis, genes involved in efficiently storing and saving energy could predispose to metabolic syndrome. Several potential candidate genes have been suggested by their biologic relevance, such as genes in systems of energy balance, nutrient partitioning, lipid and insulin metabolism, lipolysis, thermogenesis, fuel oxidation, and glucose uptake in skeletal muscle. Many of these genes have been associated with metabolic syndrome in various ethnic populations. These candidate genes include but are not limited to peroxisome proliferator-activated receptor (PPAR γ), adiponectin, CD36, β-adrenergic receptors, insulin receptor substrates (IRS), 11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), CRP, tumor necrosis factor-α (TNF-α), calpain-10 (CAPN10), upstream transcription factor 1, and skeletal muscle glycogen synthase 1 (**Table**).

Table. Candidate Genes Associated with Metabolic Syndrome

Genes causing monogenic obesity	Leptin
	Leptin receptor
	Melanocortin receptor
	Pro-opiomelanocortin
Genes regulating free fatty acid metabolism	Adiponectin
	β-Adrenergic receptors
	Fatty acid binding protein-2
	Lipases
	Uncoupling proteins
Genes affecting insulin sensitivity	Peroxisome proliferator-activated receptor γ
	Glycoprotein PC-1
	Insulin receptor substrates
	Skeletal muscle glycogen synthase 1
	Calpain-10
Genes affecting lipid metabolism	CD36
	Apolipoprotein E
	11 β-Hydroxysteroid dehydrogenase type 1
	Upstream transcription factor 1
Genes related to inflammation	Tumor necrosis factor-α
	C-reactive protein

PPARγ

PPARs are lipid-activated nuclear receptors that play multiple physiological roles, including control of fatty acid metabolism in various tissues. Three PPAR isotypes, α, δ (also called β), and γ, have been identified. PPARα plays a central role in fatty acid catabolism in liver and other tissues by upregulating ω- and β-oxidation and mediates the lipid-lowering action of fibrates.[35] PPARδ agonists normalize blood lipids and reduce insulin resistance and adiposity in rodents and primates.[36] PPARγ controls many different target genes involved in both lipid metabolism and glucose homeostasis.[37] All 3 PPARs have been implicated in metabolic syndrome.

PPARγ can be activated by endogenous arachidonic acid metabolites such as 15-deoxy-delta 12, 14-prostaglandin J2.[38] It is also the molecular target of

the insulin-sensitizing thiazolidinedione compounds used in the treatment of type 2 diabetes.[39] Homozygous PPARγ-deficient mice are embryonic lethal, and heterozygous PPARγ-null mice exhibit greater insulin sensitivity, decreased food intake, and increased energy expenditure than wild-type littermates. They are also protected from high fat diet (HFD)-induced obesity and diabetes.[40,41] Adipose-specific PPARγ knockout mice exhibit reduced fat formation and are protected from the development of HFD-induced obesity and insulin resistance.[42] Muscle-specific PPARγ knockout mice show progressive insulin resistance combined with increased adipose tissue mass.[43,44] Fat-specific PPARγ knockout mice have lipodystrophy (hypocellularity and hypertrophy), elevated plasma free fatty acids and triglycerides, and decreased plasma leptin and adiponectin.[45] In the vascular endothelial cell-specific PPARγ null mice, systolic BP and heart rate were significantly elevated by HFD.[46] In the new WOKW rat model for metabolic syndrome, PPARγ expression is lower in visceral adipocytes compared to control rats.[21] In these animal models, PPARγ is a major regulator of adipogenesis and has a significant role in the pathogenesis of metabolic syndrome.

The human PPARγ gene maps to 3p25 (chromosome 3, short arm, band 25).[47] The genomic locus of the PPAR gene has been implicated in several genome scans for type 2 diabetes and obesity in humans and mice.[48] The candidate gene approach has been carried out in different populations using the genetic variants identified in the PPARγ gene. A C/G SNP resulting in a proline12-to-alanine (Pro12Ala) substitution in the PPARγ2-unique exon B[49] has been associated with BMI, insulin sensitivity, HDL cholesterol levels, type 2 diabetes, systolic and diastolic BP, carotid intima media thickness (IMT), triglyceride levels, and glucose concentration.[50] The association of this mutation with diabetes has been successfully replicated in various ethnic populations, and was also confirmed in 2 large meta-analyses.[51] With this SNP, the alanine provides resistance to diabetes, and proline leads to susceptibility to diabetes. Functional studies have shown that the alanine isoform of PPARγ2 was less effective in activating transcription than the proline form.[52] This Pro12Ala variant of the PPARγ2 gene may also interact with the intrauterine environment to influence lipid metabolism in adult life. Alanine at position 12 was also associated with increased total serum low-density lipoprotein (LDL) and non-HDL cholesterol concentrations among elderly patients with low birth weights. In addition to the Pro12Ala mutation, 2 mutations (Val290Met and Pro467leu) were identified in the ligand-binding domain of the PPARγ gene, and patients with these mutations developed insulin resistance, type 2 diabetes, and hypertension at an early age.[53] Functional experiments have shown that these are loss-of-function and dominant-negative mutations. They have markedly impaired transcriptional activity, and moreover, they could inhibit the action of coexpressed wild-type PPARγ in a dominant-negative manner.[53] A missense pro115Gln mutation was found immediately adjacent to a serine-114 phosphorylation site of the PPARγ gene and has been associated with severe obesity.[54] These studies support the contributing role of PPARγ in the clinical manifestations of metabolic syndrome.

Adiponectin

Adiponectin is a hormone secreted by adipocytes that regulates energy homeostasis, glucose, and lipid metabolism. Biochemical, genetic, and animal studies have established a critical role for adiponectin in controlling whole-body metabolism, particularly by enhancing insulin sensitivity in muscle and liver and by increasing fatty acid oxidation in muscle. Cell culture experiments have suggested that adiponectin may attenuate the inflammatory response associated with atherogenesis by its suppressive effects on TNF-α-induced monocyte adhesion to aortic endothelial cells and on gene expression of adhesion molecules.[55] Recombinant adiponectin blocks fat cell formation in long-term bone marrow cultures and inhibits the differentiation of cloned stromal preadipocytes.[56]

Adiponectin-deficient mice exhibit severe diet-induced insulin resistance,[57] severe neointimal thickening, and increased proliferation of vascular smooth muscle cells following balloon angioplasty.[57] Virus-mediated supplementation of adiponectin attenuates these phenotypes.[57] These mice have a delayed clearance of free fatty acids in plasma, low levels of fatty acid transport protein-1 expression in muscle, and high levels of TNF-α mRNA in adipose tissue.[57] Transgenic overexpression of adiponectin in the leptin-deficient ob/ob mice reduced insulin resistance, beta-cell degranulation, and diabetes.[58] Transgenic overexpression of adiponectin in the apolipoprotein E–deficient mice reduced atherosclerosis even though plasma glucose and lipid levels remained the same.[58]

In humans, plasma adiponectin level is reversely correlated with BMI and body fat mass.[59] Weight reduction increases plasma adiponectin levels.[60] Among Pima Indians, individuals with high adiponectin concentrations were less likely to develop type 2 diabetes than those with low concentrations.[61] In Pima Indian children, plasma adiponectin level was reversely correlated with percentage body fat and fasting plasma

insulin concentrations cross-sectionally, and it was reversely correlated to adiposity longitudinally.[62] In gestational diabetes mellitus, a condition that is biochemically and epidemiologically similar to type 2 diabetes, adiponectin concentrations were significantly lower in women with gestational diabetes than in controls.[63] The plasma adiponectin levels were also significantly lower in patients with coronary artery disease compared with age and BMI-matched controls.[55] It was found that the adiponectin levels in fetal cord blood were extremely high and were positively correlated with fetal birth weights.[64] Several genetic polymorphisms identified on this gene have been associated with adiponectin levels, BMI, plasma insulin, homeostasis model assessment estimated insulin resistance, and type 2 diabetes.[65] These biochemical, cellular, animal, and human epidemiologic data support the role of adiponectin in metabolic syndrome.

CD36

CD36, also known as thrombospondin receptor, platelet collagen receptor, FAT, platelet glycoprotein IV, and glycoprotein IIIb, is a multifunctional membrane receptor widely expressed in different tissues binding and internalizing oxidized LDL. CD36 facilitates the membrane transport of long-chain fatty acids into muscle and adipose tissues.[66] CD36 is regulated by PPARγ and is a gene target of thiazolidinediones.[67] Upregulation of adipocyte or muscle CD36 by thiazolidinediones appears to mediate some of the insulin-sensitizing effects of these drugs.[67,68]

The role of CD36 in metabolic syndrome was found by linkage analysis in spontaneously hypertensive rats (SHR). The SHR is both insulin-resistant and hypertensive and is a good model for metabolic syndrome in humans. A single chromosomal segment on rat chromosome 4 was discovered to be linked to defects of insulin resistance, dyslipidemia, and hypertension. The CD36 gene, which is located within this chromosomal region, emerged when microarray technology was applied and found that CD36 was differentially expressed in white adipose tissue between SHR congenic strains.[69] The role for CD36 in the pathogenesis of insulin resistance, dyslipidemia, and hypertension was confirmed by rescuing the abnormal metabolic phenotypes through either transgenic expression or congenic breeding on the SHR background.[69,70] In addition, the role of CD36 in lipid processing was further demonstrated in CD36 knockout mice.[71]

In humans, a glucose-mediated increase in CD36 mRNA translational efficiency has been observed.[72] CD36 expression is increased in endarterectomy lesions from patients with a history of hyperglycemia.[72] Macrophages that are differentiated from human peripheral blood monocytes in the presence of high glucose concentrations show increased expression of cell surface CD36 secondary to an increase in translational efficiency of CD36 mRNA.[72] A rare mutation of Pro90Ser that leads to CD36 deficiency has been associated with metabolic syndrome in Japanese patients. CD36-deficient individuals have impaired glucose disposal in response to insulin and increased levels of free fatty acids, triglycerides, fasting blood glucose, and BP.[73] Other studies have reported that variability at the CD36 locus is associated with higher plasma free fatty acid levels.[74] These studies suggest that CD36 may be a link between insulin resistance, obesity, and hypertension and may play an important role in the pathogenesis of metabolic syndrome.

11β-HSD1

Largely based on observations in patients with Cushing's syndrome who exemplify the pathological effects of circulating cortisol excess, there is currently great interest in 11β-HSD1 and its putative role in insulin sensitivity and metabolic syndrome. Glucocorticoids are important regulators of glucose, lipid, and protein metabolism, acting mainly in the liver, adipose tissue, and muscle. Chronic glucocorticoid excess is associated with the clinical features of insulin resistance and visceral obesity. 11β-HSD1 is a key intracellular enzyme that catalyses the conversion of inactive cortisone to active cortisol. Transgenic mice overexpressing 11β-HSD1 selectively in adipose tissue develop visceral obesity, pronounced insulin-resistant diabetes, hyperlipidemia, hyperphagia, and hypertension.[75] Transgenic mice overexpressing 11β-HSD1 selectively in liver exhibit mild insulin resistance, fatty liver, dyslipidemia, impaired hepatic lipid clearance, and hypertension.[76] 11β-HSD1 knockout mice resist HFD-induced obesity despite increasing food intake and display enhanced insulin sensitivity.[77] Experimental animal models have provided strong evidence for the role of 11β-HSD1 in the development of metabolic syndrome; however, results of human studies are less convincing. Studies that examined the association of 11β-HSD1 activity with obesity have reported contrasting results.[78]

β-Adrenergic Receptors

The β-adrenergic receptors regulate lipolysis and free fatty acid metabolism. The β_3-adrenergic receptor (β3AR) is a candidate gene for abdominal obesity. The β3AR gene is expressed in visceral fat.[79] Increased β3AR function leads to increased catecholamine-induced lipolysis in visceral fat from subjects with abdominal obesity.[80]

It has been reported that carriers of a missense mutation (Trp64Arg) in the first intracellular loop of this receptor showed more abdominal obesity, higher insulin concentrations, more insulin resistance, and higher BP than individuals homozygous for the wild type (Trp64Trp). All are features of metabolic syndrome[81]; together with a lower metabolic rate[82] and lower resting sympathetic nervous system activity,[83] these observations are consistent with a "thrifty gene" theory. Functional analysis of the Trp64Arg mutation has been associated with an impairment in catecholamine-stimulated lipolysis.[84] Although a number of negative population studies have been reported,[85] β3AR appears to be a strong candidate gene for susceptibility to metabolic syndrome.

Calpain-10

CAPN10 is the first type 2 diabetes susceptibility gene identified through genome scans and positional cloning. Genome scans have identified a region of 2q37.3 that encompasses 3 potential candidate genes for diabetes.[86] Additional intergenic and intragenic SNPs within this region have been used to identify the CAPN10 gene as the most likely candidate gene for the disease susceptibility locus.[87] CAPN10 is a cysteine protease that regulates a variety of cellular functions. CAPN10 is implicated in the control of glucose homeostasis. In the beta-cell, it may be a determinant of fuel sensing and insulin exocytosis; in fat and muscle cells, it modifies insulin-mediated glucose transport.[88] CAPN10 gene polymorphisms have also been associated with type 2 diabetes, insulin action, insulin secretion, hip measurement, BMI, adipocyte biology, and microvascular function.[89] Meta-analyses of association studies assessing CAPN10 and type 2 diabetes risk have confirmed a role for CAPN10 polymorphisms in susceptibility to type 2 diabetes.[90,91] However, the association has not always been with the same SNP or haplotype, suggesting that there may be more than 1 disease-associated CAPN10 variant or that these variants are not causative but rather in linkage disequilibrium with causative variants.

C-Reactive Protein

CRP is a marker for systemic inflammation. Baseline plasma CRP levels are significantly associated with metabolic syndrome and its components[92,93] and are highly predictive of subsequent risk of cardiovascular events and diabetes in apparently healthy men and women.[94] Various factors seem to influence the CRP level, such as obesity, smoking, alcohol, physical activity, and genetic factors.[92] CRP may provide a link between obesity, insulin resistance, and CVD through chronic low-grade systemic inflammation. The question still remains whether CRP plays a direct biological role in disease pathogenesis or is only a marker resulting from various stimuli.

Insulin Receptor Substrates

The docking protein IRS1 links the tyrosine-phosphorylated insulin receptor to the downstream part of the insulin signaling pathway.[95] IRS1 knockout mice suffer from embryonal and postnatal growth retardation and muscle insulin resistance while maintaining normoglycemia by compensatory beta-cell hyperplasia. IRS2 knockout mice are normal in size but develop diabetes because of liver insulin resistance and lack of beta-cell compensation.[96,97] In humans, 2 genetic polymorphisms in the IRS1 gene,[98] Gly972Arg and Ala513Pro, occurred slightly more frequently in type 2 diabetic patients than in controls. Both IRS genes could be candidate genes for insulin resistance and metabolic syndrome.

CONCLUSION

Metabolic syndrome is a consequence of multiple gene–environment interactions. The gradual increase in prevalence of overweight and obesity as well as obesity-related metabolic syndrome in the industrialized world is clearly not caused by changes in the genetic make up of the human species. This increase indicates the importance of environmental influences, such as low levels of physical activity and availability of calorie-rich diets. However, identification of susceptibility genes of metabolic syndrome and their functional variants as well as the associated pathophysiological mechanisms are of utmost importance, because it may enable investigators to design preventive strategies and targeted treatments. Although the significant heritability of the individual components of the metabolic syndrome has been well recognized and substantial progress in understanding the physiology of this syndrome has been made, the underlying genetic basis and the molecular mechanisms remain obscure. Given the substantial clinical and public health burden imposed by this condition, the genetic underpinnings of metabolic syndrome is a topic of growing interest. **HP**

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