Genetics of Metabolic Syndrome

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Metabolic syndrome (MetS) is a common phenotype, affecting about 24% of the US population. It is associated with an increased risk for type 2 diabetes and cardiovascular disease. Although there is no universally accepted definition for MetS, affected individuals commonly have a cluster of features, including abdominal obesity, hypertension, dyslipidemia, and dysglycemia. Recently, there has been extensive interest in potential genetic contributions to MetS. At present, no single gene or cluster of genes has been consistently replicated for MetS among different populations, likely due to the complex interplay between gene and environment necessary for expression of this phenotype. We review recent studies regarding the genetic contributions to MetS.

Introduction

Metabolic syndrome (MetS), previously called insulin resistance syndrome or syndrome X, is characterized by the clustering of several risk factors for coronary artery disease, including abdominal obesity, hypertension, dysglycemia, and dyslipidemia (increased triglyceride and depressed high-density lipoprotein [HDL] cholesterol levels). There have been at least six different published definitions for MetS, as proposed by the World Health Organization, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), European Group for the Study of Insulin Resistance, American Association of Clinical Endocrinologists, American Heart Association/National Heart, Lung, and Blood Institute, and most recently the International Diabetes Federation; all use varying combinations of the above listed risk factors [1–6].

Despite the varied definitions and the controversy regarding its existence, MetS is the focus of intense research, particularly given its high prevalence. Data from the NHANES III (Third National Health and Nutrition Examination Survey) revealed that the overall age-adjusted prevalence of MetS (using the NCEP ATP III definition) in the United States was about 24%, with the prevalence of individual components being 38.6% for increased waist circumference, 30.0% for hypertriglyceridemia, 37.1% for low HDL cholesterol levels, 34.0% for hypertension, and 12.6% for dysglycemia [7]. Genetic influences are thought to play a crucial role in MetS development, and as a result, genetic studies have become an active research area. A thorough discussion of all genetic influences on each component metabolic trait is beyond the scope of this article. We instead discuss the genetic influences to date related to the MetS phenotype, focusing primarily on recent genetic strides in the context of the proposed MetS pathophysiology.

Evidence for a Genetic Component

The importance of a genetic contribution to MetS has been implied by the high clustering of components in family and twin studies. In a seminal study of 2508 male twin pairs, concordance for the clustering of three MetS components (hypertension, diabetes, and obesity) was found in 31.6% for monozygotic pairs versus 6.3% for dizygotic pairs [8]. Similarly, among 236 female twin pairs, heritability estimates for obesity, insulin/glucose, and dyslipidemia were found to be 0.61, 0.87, and 0.25, respectively, using a classical non-molecular approach, indicating an important genetic contribution for each of these components [9]. Among 803 individuals from 89 Caribbean-Hispanic families in the Northern Manhattan Family Study, the heritability of MetS itself was found to be 24%, with significant heritability for the lipid/glucose/obesity (44%) and hypertension (20%) components [10]. The marked variability in heritability between studies might be attributable in part to ethnicity. Based on these demonstrations of heritability for MetS and its components, several investigators have directly examined the genetic determinants for MetS using linkage or association studies.

Linkage analysis

Linkage scanning through positional cloning uses genotypic and phenotypic data from families to find a chromosomal region that is preferentially inherited among family members with MetS. This approach often relies

on detecting quantitative trait loci, which are sections of DNA closely linked to the genes underlying quantitative components of MetS. Because the causative genes for MetS are passed down through generations, nearby markers in close linkage to these genes are also passed down. Cosegregation of markers with MetS or its components helps to specify chromosomal regions harboring genes possibly causative for MetS; these are called "positional candidate" genes. However, there are two main drawbacks to using linkage analysis in MetS. First, the lack of a standard definition for MetS and the multiple possible combinations of phenotypes can lead to the discovery of multiple linked loci that might be specific to one subphenotype. Second, MetS probably results from the interplay among multiple genes on different chromosomes, obscuring detection of discrete and unique linkage signals.

A wide range of loci linked to MetS is evident from the studies reported thus far. Linkages have been demonstrated between MetS and loci such as 3q27, 17p12, chromosome 6 (D6S403, D6S264), chromosome 7 (D7S479-D7S471), and 1q23-31 [11–13]. 3q27 was strongly associated with six traits, including body mass index, weight, waist circumference, insulin, insulin-to-glucose ratio, and hip circumference [11]. Even within a single study examining North American families, several chromosomal regions (1p34.1, 1q41, 2p22.3, 7q31.3, 9p13.1, 9q21.1, 10p11.2, 19q13.4) were linked with MetS [14]. Evaluation of 234 Chinese families revealed major regions of suggestive linkage for MetS and overlapping signals from related metabolic traits on chromosomes 1, 2, and 16. Significant linkage of MetS was seen with chromosome 1q21-q25, an area previously linked to type 2 diabetes across different ethnicities [15–19]. Other regions associated with single component traits included 5q for diastolic blood pressure; 2q, 3q, 6q, 9q, 10q, and 17q for triglyceride; and 12p, 12q, and 22q for HDL [20]. More recently, 1p36.13 has been suggested as a possible locus for MetS in 250 German families [21]. Among 977 white subjects from the Diabetes Heart Study, evidence for coincident linkage among the traits of type 2 diabetes, MetS, and cardiovascular disease was shown for four chromosomal loci: 3p, 3q, 4q, and 14p [22]. These studies demonstrate that no single locus is reproducibly linked with MetS across populations, perhaps explained by the effects of ethnicity, the unclear definition of MetS itself, or by false-positive results from numerous studies of this type. Linkage studies to explore the genetics of complex traits such as MetS must be interpreted with caution.

Association studies

Genetic association studies relate genetic factors to a phenotype using cohort, case-control, or family-based studies. These studies often involve many individuals using various single nucleotide polymorphism (SNP) markers across the genome. An SNP is a locus where two or more base pair alternatives occur in the population at an allele frequency of ≥ 1%. Because SNPs occur frequently (~ 1 per 300–400 base pairs), this type of analysis can indirectly mark the location of the actual causative gene mutation. Other types of markers can also be studied, such as insertion-deletion polymorphisms. Typically, SNP variants are selected from candidate genes and chosen because the gene product plays a functional role in pathogenesis.

Because adipokines, inflammation, adipose distribution, and insulin signaling are thought to play crucial roles in MetS pathogenesis, examining candidate genes from these areas for MetS may be fruitful. Tables 1 and 2 list the reported candidate genes associated with an increased or decreased risk for MetS.

Adipokine candidate genes

Recently, among 1438 Taiwanese individuals (mean age ~ 72 years), the G allele of *ADIPOQ* SNP276 in intron 2 was associated with decreased risk of obesity, MetS, and type 2 diabetes [23]. Examination of the -420C>G SNP in the resistin gene (*RSTN*) revealed that G/G homozygotes had an increased prevalence of MetS, elevated triglycerides, body mass index, and systolic and diastolic blood pressure values compared with other genotypes. In a follow-up case-control study, the *RSTN* -420C>G SNP was associated with an increased MetS prevalence but did not influence MetS prevalence among individuals at high cardiovascular risk [24]. However, the exact role of genetic variants of resistin in insulin resistance or obesity is unsettled.

Adipokine release occurs directly from the adipocyte, and differentiation of fat cells is partly under the control of the peroxisome proliferator-activated receptor (PPAR) family. Several studies evaluated genetic contributions of the PPAR family to MetS, including PPAR-γ, PPAR-α, and PPAR-δ. Conflicting results for the *PPARG* P12A polymorphism have been shown [25,26]. In Korean women, no relation between the common *PPARG* exon 6 C>T polymorphism and MetS was demonstrated [26]. Recent meta-analysis of 57 studies in nondiabetic individuals revealed no significant association of the *PPARG* P12A polymorphism with diabetes-related traits. There was an association of the A12 allele with greater body mass index and greater insulin sensitivity among whites and obese individuals only [27•]. In a French sample, the *PPARG* GTGC haplotype conferred a higher risk for MetS (OR = 2.37) [28]. A study of French-Canadian men revealed no association of the *PPARA* L162V polymorphism with MetS, despite a higher frequency among men exhibiting increased abdominal circumference, high triglycerides, and low HDL levels [29]. The *PPARD* -87T>C polymorphism in French-Canadian men and women conferred protection from the MetS phenotype (OR = 0.62), which was further enhanced if carriers consumed less than 34.4% calories from fat, suggesting a gene-environment interaction [30].

Lipoprotein candidate genes

Determinants of plasma triglyceride metabolism might also be determinants of MetS. Apolipoprotein C-III is

Table 1. Selection of association studies showing susceptibility alleles for metabolic syndrome

Gene	Polymorphism	*P* value	Sample size (ethnicity)	Definition	Comments
ADIPOQ [23]	SNP276	0.011	1438 (Taiwanese, > 65 years old)	NCEP ATP III*	
		0.001		IDF	GT vs GG genotype
APOA5 [33]	-1131T→C	< 0.0009	1788 (Japanese)	NCEP ATP III*	
APOA5 [34]	c.56C→G	0.026	3124 (Caucasian)	NCEP ATP III	
APOA5 [66••]	-3A→G	< 0.0001	2417 (Japanese)	AHA/NHLBI†	
	553G→T	0.0001‡			
APOC3 [31,77]	-455T→C	0.029	515 (Oji-Cree)	NCEP ATP III	Women only
		< 0.0001	122 (Indians, Americans [white, black])	NCEP ATP III	
C1QTNF5 [66••]	1014T→A	0.007	2417 (Japanese)	AHA/NHLBI†	
CYP11B2 [70]	-344C→T	0.02	1540 (European)	IDF	Men only, C allele confers risk
ESR1 [52]	rs6902771	0.012	548 (African American)	NCEP ATP III	
	rs9340799	0.029			
	rs2431260	0.005			
	rs1033182	0.02			
	rs2175898	0.006			
HTR2C [73]	rs1414334C	0.01	112 patients with schizophrenia (Netherlands)	NCEP ATP III§	
	rs518147C	0.049			
	HTR2C:c.1-142948$(GT)_n$13R	OR 3.12			
IL6 [36,37]	-174G→C	0.007	571 (Caucasian)	WHO	
	-597G→A, -572G→C, -174G→C	< 0.01	2828 (Danes)	WHO	
LPL [35]	S447X	0.04	1586 (Turkish)	NCEP ATP III§	SS confers risk in women only
NOS3 [57]	Haplotype 212	0.01	738 (Spanish)	NCEP ATP III	
PC-1 [54]	K121Q	< 0.01	130 (Serbian)	NCEP ATP III	Association found in CHD patients only
RSTN [24]	-420C→G	0.042	1542 (Italian)	NCEP ATP III	GG vs CG genotype
UCP2 [64]	-866G→A	0.015	4018 (Asians [Chinese, Malay, Indian])	NCEP ATP III	Indian men only

*NCEP ATP III: Variation in waist circumference criteria ± use of BMI criteria ± lower fasting blood glucose cutoff value.
†AHA/NHLBI: Modified with BMI replacing waist circumference criteria.
‡Best *P* value chosen from different analyses.
§NCEP ATP III: Variation in waist circumference and/or fasting blood glucose level.
AHA—American Heart Association; BMI—body mass index; CHD—coronary heart disease; IDF—International Diabetes Federation; MetS—metabolic syndrome; NCEP ATP III—National Cholesterol Education Program Adult Treatment Panel III; NHLBI—National Heart, Lung, and Blood Institute; WHO—World Health Organization.

present on triglyceride-rich lipoproteins and inhibits lipoprotein lipase, thereby delaying catabolism of triglycerides. More recently, a case-control study consisting of whites, South Asians, and blacks demonstrated that the *APOC3* promoter polymorphisms -482C>T and -455T>C were associated with an increased OR of 4.3 and 3.6, respectively, for MetS [31]. Meanwhile, apolipoprotein A-V is strongly associated with triglyceride levels [32]. Among 1788 Japanese individuals, of whom 1017 had MetS and 771 were controls, the *APOA5* -1131T>C polymorphism was strongly associated with the MetS prevalence, with the C allele being significantly related to increased triglyceride and decreased HDL levels [33]. In contrast, a study of 3124 white individuals from Germany

Table 2. Association studies showing protective alleles for metabolic syndrome

Gene	Polymorphism	*P* value	Sample size (ethnicity)	Definition	Comments
CYP3A4 [66••]	13989A→G	0.015	2417 (Japanese)	AHA/NHLBI*	
GHRL [78]	R51Q (Q_{51} allele carriers)	0.031	856 (Amish)	NCEP ATP III	
LDLR [66••]	2052T→C	0.0005†	2417 (Japanese)	AHA/NHLBI*	
	1866C→T	0.003†			
PPARD [30]	-87T→C, 5′UTR (CT and CC)	*P* = 0.04 (-87C vs -87T/T)	340 (Quebec-Caucasian)	NCEP ATP III	< 34.4% fat intake among -87C carriers, decreased MetS (*P* = 0.008)
Mitochondrial haplogroups [71••]	N9a	0.004	1337 (Japanese)	NCEP ATP III‡	Women only
	G1	0.013			
	D5	0.047			

*AHA/NHBLI modified with BMI replacing waist circumference criteria.
†Best *P* value chosen from different analyses.
‡NCEP ATP III modified with BMI replacing waist circumference criteria.
AHA—American Heart Association; BMI—body mass index; MetS—metabolic syndrome; NCEP ATP III—National Cholesterol Education Program Adult Treatment Panel III; NHLBI—National Heart, Lung, and Blood Institute.

and Austria examined 10 *APOA5* polymorphisms, including -1131T>C and c.56C>G, in relation to MetS. Unlike the Japanese study, this study did not find an association between the *APOA5* -1131T>C polymorphism and MetS, but instead found that the *APOA5* c.56C>G variant conferred an increased risk of MetS (OR = 1.28) [34]. These varied results for genetic associations are likely due to ethnic differences. Recently, the lipoprotein lipase S447X variant has been associated with MetS among Turkish women only. In particular, this study showed that females with the more common SS genotype had a significantly increased likelihood for MetS (OR = 1.46) and low HDL levels (OR = 1.58) [35]. Thus, genetic variations affecting triglyceride metabolism might be associated with the composite MetS phenotype.

Candidate genes in inflammation

Proinflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein (MCP)-1, are postulated to have a role in the MetS pathogenesis and thus also represent candidate genes. Among 6916 Danes, the AGC/GGG composite genotype of three common *IL6* promoter polymorphisms, including -597G>A, 572G>C, and -174G>C, were more common among those with MetS, whereas the AGC/AGC composite genotypes were more common among controls without the MetS [36]. Examination of the *IL6* -174G>C promoter polymorphism in 571 whites revealed a higher MetS prevalence among those with the CC genotype [37]. Conversely, a population-based sample of 1630 Germans revealed that none of the seven SNPs of the proinflammatory cytokine *MCP1* gene were associated with MetS [38]. Meanwhile, although a meta-analysis of 31 studies revealed that the *TNFA* -308G>A polymorphism conferred a risk of 1.23 for obesity and an increase in systolic blood pressure by 3.5 mm Hg, it was not examined in relation to MetS [39]. Zinc finger protein 36 (*ZFP36*), which is involved in TNF-α regulation, has been proposed as a novel candidate gene for MetS based on its position on the long arm of chromosome 19, a region linked with MetS, and a significant differential expression (4.6-fold higher) among obese individuals without MetS compared to those with MetS [40–42]. The *ZFP36* rs251864 polymorphism has been associated with a lower body weight among women and the c.1564_1565delTT allele with glucose levels in men. Furthermore, *ZFP36* haplotype was associated with plasma low-density lipoprotein (LDL) in men and women [41]. Thus, future studies might replicate *ZFP36* associations with MetS.

Candidate genes in adipose distribution

The adipose distribution of MetS shares many clinical features with rarer disorders, such as Dunnigan-type familial partial lipodystrophy (FPLD) and Cushing's syndrome. FPLD is an autosomal-dominant disorder characterized by subcutaneous peripheral fat loss, visceral and central fat gain, insulin resistance/type 2 diabetes, and dyslipidemia (elevated triglycerides and low HDL). Mutations in the *LMNA* gene, encoding the nuclear envelope protein lamin A/C, can cause FPLD [43–45]. Moreover, the lamin A/C gene is located in the 1q21 region, an area previously associated with MetS and type 2 diabetes [15–20]. A recent study examining 1572 Europeans revealed no association between 13 common SNPs in *LMNA* and MetS [46•]. Similarly, Cushing's syndrome is associated with central obesity and insulin resistance, features coincident with MetS. Because Cushing's syndrome is associated with glucocorticoid excess, candidate genes include 11-β-

hydroxysteroid dehydrogenase type 1 (*HSD11B1*), and the glucocorticoid receptor (*GR*). Unfortunately, *HSD11B1* SNPs are not consistently associated with MetS, despite overexpression producing a classic MetS phenotype in mice [47,48]. The effects of glucocorticoids through the *GR* are primarily mediated through the functional isomer GRα, whose activity is inhibited by GRβ [49]. The *GRB* 3669A>G SNP results in increased GRβ protein expression [50]. Evaluation of this SNP among 322 European and 262 South-Asian individuals revealed no significant association with the MetS composite phenotype but instead revealed an association with reduced central obesity among European women and a more favorable lipid profile (increased HDL and decreased total cholesterol) among European men [51].

Genes involved in estrogen metabolism have also been investigated. Seventeen SNPs from introns 1 and 2 of the estrogen receptor-α (*ESR1*) gene were examined in 548 blacks. Five SNPs (rs6902771, rs9340799, rs2431260, rs1033182, and rs2175898) were associated with increased MetS risk (OR 1.53–2.51). Of these five, three were also associated with MetS components: rs2175898 and rs2431260 were associated with waist circumference, and rs6902771 was associated with insulin sensitivity [52].

Candidate genes in glucose and energy metabolism

Novel associations have been made with ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP or PC-1) or endothelial nitric oxide (NO) synthase with MetS. PC-1 is a class II transmembrane glycoprotein that is postulated to contribute to insulin resistance through inhibition of insulin receptor signaling [53]. However, among 130 Serbs, carriers of the *PC1* Q121 allele with coronary heart disease were at increased risk of MetS (OR = 5.5), central obesity, low HDL, and high triglycerides [54]. Endothelial NO synthase is responsible for producing NO, which is important for normal endothelial function. NO also plays a critical role in glucose metabolism [55,56]. Among 738 Spanish individuals, haplotype analysis demonstrated that compared to the most common haplotype 121, the haplotype 212 was associated with an increased risk for MetS (OR = 1.81), decreased HDL levels (OR = 1.52), insulin resistance, and hypertriglyceridemia [57].

The β3-adrenergic receptor (*ADRB3*) plays a role in energy metabolism and lipolysis; it is expressed in visceral adipose tissue [58,59]. A recent analysis of 1416 Japanese individuals revealed no relationship between *ADRB3* Y64R polymorphism and MetS [60]. Uncoupling protein 2 (*UCP2*), a member of the mitochondrial transporter superfamily, is important for thermogenesis in white adipose tissue [61]. It is also possibly involved in lipid and glucose metabolism [62,63]. Analysis of the *UCP2* -866G>A polymorphism in 4018 Asians of three ethnic subgroups revealed that Indian men with the -866A/A genotype had an increased risk of MetS (OR = 2.66) compared to those homozygous for the wild-type. This *UCP2* -866A/A genotype was also associated with a higher waist-to-hip ratio among Chinese and Indian men [64]. The *UCP2* -866A/A genotype was associated with decreased *UCP2* mRNA levels in adipose tissue, possibly leading to decreased energy expenditure and thereby increased adiposity [65].

Other novel candidate gene associations

A recently published large genetic association study examined 44 polymorphisms of 31 candidate genes of lipid metabolism among 2417 unrelated Japanese individuals. The *APOA5* polymorphisms -3A>G and 553G>T and the *C1QTNF5* (complement 1q- and TNF-related protein 5) 1014T>A polymorphism were risk factors for MetS, whereas the *LDLR* (LDL receptor) 2052T>C and 1866C>T polymorphisms and *CYP3A4* (cytochrome P450 enzyme) 13989A>G polymorphism were protective against MetS [66••]. The C1QTNF5 protein is thought to be important in cell adhesion, with previous associations with obesity [67,68]. LDLR plays a crucial role in LDL cholesterol regulation, and polymorphisms in the *LDLR* gene previously have been linked to MetS among women with coronary heart disease [69]. The *CYP3A4* G allele was postulated to have a favorable effect on fasting plasma glucose levels [66••]. This was the largest association study among Japanese individuals for genetic determinants of MetS; however, results may be different in other ethnicities.

The aldosterone synthase (*CYP11B2*) gene has been an attractive candidate for hypertension and, by extension, MetS. Among 802 European male/female couples, the -344C allele was associated with MetS among men only. The OR for MetS was positively associated with C allele copy number, such that CC homozygotes had an OR of 2.25 compared with TT homozygotes [70]. Such gender-related susceptibility requires further investigation in other populations.

Because mitochondrial dysfunction has been implicated in the pathogenesis of type 2 diabetes, the importance of mitochondrial haplotypes in MetS has been investigated. Among 1337 Japanese individuals, genotypes of 25 polymorphisms were determined and classified into 10 mitochondrial DNA haplotypes. Haplogroup N9a was significantly associated with protection from MetS (OR = 0.21) among women only. Haplogroups G1 and D5 also conferred protection from MetS, with ORs of 0.22 and 0.32, respectively [71••].

With the weight gain associated with use of atypical antipsychotic drugs, MetS is becoming a more common problem among individuals with schizophrenia. One genetic factor that has recently been evaluated among patients with schizophrenia is the serotonin 2C (*5-HT2C*) receptor because *5HT2C* knockout mice demonstrate obesity [72]. Among 112 patients with schizophrenia, the *5HT2C* variant alleles—rs518147, rs1414334, and *HTR2C*:c.1-142948(GT)n—were associated with an increased MetS

risk, with ORs of 2.62, 4.09, and 3.12, respectively [73]. Thus, serotonin receptor regulation may play a role in MetS development in this vulnerable population.

Genome-Wide Association Studies

Genome-wide association studies (GWAS) examine large populations with and without the disease or trait in question using numerous SNP markers spread across the genome. As a result, statistically significant associations between certain SNP genotypes and disease status can be determined. GWAS can be a powerful tool for identifying disease-causing gene variants but require large numbers of study subjects to demonstrate the associations between gene variants and disease status. Recently, a polymorphism within the *FTO* (fat mass and obesity) gene was associated with type 2 diabetes ($P = 5 \times 10^{-8}$) [74] and early-onset and severe obesity ($P = 1.67 \times 10^{-26}$) [75] among European whites. Because MetS, obesity, and type 2 diabetes often occur together, studies of the association between *FTO* and MetS may be fruitful.

However, GWAS have limitations. The impressive *P* values are a consequence of the large sample sizes. The actual effect sizes are relatively modest (OR ~ 1.5). The clinical relevance of these associations for a single individual may not be that valuable. Also, GWAS results must be validated by replications in other populations to avoid false-positive associations due to systemic bias, technical artifacts, or population stratification [76].

Conclusions

MetS represents a complex phenotypic trait consisting of several clinical factors and associated with an increased risk of type 2 diabetes and cardiovascular disease. Genetic studies thus far have provided conflicting associations rather than consistently reproducible associations and linkages. Nonetheless, the hope remains that understanding the genetic determinants of MetS will lead to early detection of new cases and possibly preventive strategies, keeping in mind the important caveats for genetic studies of complex traits. Thus, although genetics likely plays a crucial role in MetS development, elucidating the exact genes involved has been hindered by the lack of a consistent MetS definition, the varying combination of phenotypes even within a single definition, ethnic disparities, and gender influences. Furthermore, lifestyle determinants for MetS development should not be ignored, and these determinants are also likely under genetic control. In short, MetS development represents an intricate interaction between genetic susceptibilities and environmental influences, and genetic studies increase our appreciation of this complexity. Meaningful reproducible genetic studies can only appear once we have learned to adjust for these key confounders, accurately specify a phenotype, study large sample sizes, and apply even more advanced analytical methods and bioinformatics.

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