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An Overview of the Genomics of Metabolic Syndrome

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Abstract

Purpose—This article provides a brief overview of the diagnostic criteria and genomic risk factors for the components of metabolic syndrome (MetS).

Organizing Constructs—Contributions of cardiovascular, obesity, and diabetes genomic risk factors to the development of MetS as reported in the literature have been reviewed.

Findings—The genomic risk factors for the development of MetS are strongly linked to the genomic risk factors that make up the components of the disease. Many of the cardiovascular and renal genomic risk factors for MetS development are similar to those found in the development of hypertension and dyslipidemia. Obesity may act as a master trigger to turn on the gene expression changes necessary for the other components of the disease. Studies in the genomics of type 2 diabetes show a number of overlapping genes and polymorphisms that influence both the development of diabetes and MetS.

Conclusions—Although health practitioners now have some insights into the genomics of risk factors associated with MetS, the overall understanding of MetS remains inadequate. Clinical applications based on some of the discussed genomic risk factors are being developed but are not yet available for the diagnosis and treatment of MetS.

Clinical Relevance—A broad knowledge of the genomic contributions to disease processes will enable the clinician to better utilize genomics to assess and tailor management of patients.

Keywords

Genomics; metabolic syndrome; cardiovascular; diabetes; obesity

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Metabolic syndrome (MetS) is a widely recognized concept generally defined as a clustering of risk factors including hypertension, insulin resistance, and obesity. This clustering of risk factors then leads to an increased risk for diabetes and cardiovascular disease (CVD; Ford, Li, & Zhao, 2010). It is estimated that in the United States, MetS affects more than 34% of the population and contributes to a threefold increase in cardiovascular-related deaths (Ford et al., 2010). Still, diagnostic criteria of MetS differ among experts and organizations (American Association of Clinical Endocrinologists [AACE]; National Cholesterol Education Program Adult Treatment Panel III [ATPIII]; World Health Organization [WHO]), and this difference leads to a lack of consensus in the clinical utility of the diagnosis (Simmons et al., 2010). In 2009, an effort was made by many expert organizations to standardize the diagnosis of this complex disorder by using a harmonizing definition (Table 1; Alberti et al., 2009). Diagnosis of MetS using the harmonizing definition is contingent on meeting a threshold value in at least three of the following five factors: waist circumference, triglycerides, high-density lipoprotein-cholesterol, blood pressure, and glucose (Alberti et al., 2009).

Even with a harmonizing definition, the global prevalence of MetS can be difficult to estimate because it can affect patients by gender groupings differently. For example, in India, the prevalence of MetS for men is approximately 8%, whereas for women it is estimated at 46% (Cameron, Shaw, & Zimmet, 2004). In Iran, 30% of men and 55% of women met the diagnostic criteria for MetS (Azimi-Nezhad et al., 2012). Some of these differences are clearly due to gender, but racial and ethnic differences may also play a role.

When the U.S. population is divided by both gender and ethnicity, adult African American women have a 38.8% prevalence of MetS, and African American men have 25.3% prevalence, whereas their Caucasian counterparts have a prevalence of 31.5% and 37.2%, respectively (Roger et al., 2011).

Risk factors associated with the development of MetS are similar to those associated with hypertension, diabetes, renal disease, and obesity, with variables such as lifestyle, gender, ethnicity, and genomic precursors playing important roles in the development of MetS. Because MetS is the combination of the effects of more than one risk factor, pinpointing a causative genotype has been difficult. Genomic and molecular methodologies including linkage analysis, genome-wide association (GWA) studies, epigenetics, and proteomics have all been used to attempt to unravel this genetic puzzle (Table 2). The results of these studies have shown that MetS is a polygenetic (under the control of more than one gene) condition with varying influence from multiple environmental factors. Therefore the inheritance of a single specific risk allele may be less important than the additive effects of many alleles, some of which may be “high risk,” some which may be “moderate risk,” and others of which may be “low risk.” However, the current understanding of the disease shows that certain risk alleles that have relevance for the individual components of the disease may also have an overlapping value in the overall risk for the development of MetS. This review will examine the possible contributions of cardiovascular, obesity, and diabetes genomic risk factors to the development of MetS as reported in the literature.

Cardiovascular Factors in MetS

The two most important cardiovascular risk factors for MetS are dyslipidemia and hypertension, both of which are polygenetic diseases. A summary of relevant genetic influences for MetS are provided below.

Dyslipidemia

Having alterations in circulating blood lipid levels can predispose a person to the development of MetS (Alberti et al., 2009). While dietary intake plays a role, one of the most common genetic reasons for dyslipidemias is familial hypercholesterolemia, a relatively common disorder that affects about 1 in every 500 individuals (Goldstein, Hobbs, & Brown, 2001). This disorder results in high levels of low-density lipoprotein (LDL), with more than 700 distinct mutations in LDL receptor genes known (Jensen, 2002). Other disorders of lipoprotein metabolism are characterized by high triglyceride, and low high-density lipoprotein (HDL) cholesterol levels have been found mainly to have mutations in the lipoprotein lipase (*LPL*) and apolipoprotein E (*APOE*) genes, which are important for lipoprotein metabolism. In particular, one isoform of APOE, apo E4, is most strongly associated with vascular inflammation and cardiovascular disease (Gungor et al., 2012). Mutations in these genes have also been associated with increased risk for myocardial infarction (an increased cardiovascular risk factor for MetS; Hoffmann et al., 2001).

Hypertension

An increase in blood pressure is universally recognized as a hallmark of MetS from all three major organizations (AACE, ATPIII, WHO) and in the harmonizing definition. More than 50 genes have been identified as being significantly associated with blood pressure and/or hypertension (Basson, Simino, & Rao, 2012). In African-American women, several single-nucleotide polymorphisms (SNPs; variants found in the genetic code) in these genes have been found to also have significant associations with body mass index (BMI) and systolic and diastolic blood pressure (Taylor, Sun, Hunt, & Kardia, 2010).

Individuals who have familial hypertension are at higher risk for developing MetS than individuals with secondary types of hypertension. These relatively uncommon syndromic disorders of blood pressure regulation generally follow traditional Mendelian inheritance patterns with high penetrance (a person with the allele in question also has the disease). The genes responsible for these disorders create proteins that can affect renal electrolyte and water handling (Lifton, Gharavi, & Geller, 2001). This can happen indirectly by altering the expression of adrenal/mineralocorticoid hormones, or directly by impacting the function of renal sodium transporters (Lifton et al., 2001). Several other rare mutations (such as in Liddle's syndrome) can result in real or apparent mineralocorticoid excess with hypernatremia, hypokalemia, and metabolic alkalosis, and variable aldosterone levels (Martinez-Aguayo & Fardella, 2009).

Obesity in Metabolic Syndrome

Excess body weight has also been shown to influence the development of MetS (Cameron et al., 2004) and to increase the risk for cardiovascular, renal, and diabetes complications (Ogden, Yanovski, Carroll, & Flegal, 2007). Although an imperfect method, clinicians usually evaluate patients for obesity by calculating their BMI and classifying them using the National Institutes of Health BMI guidelines (Clark, Taylor, Morrison, Wu, & Smith, in review). A patient with a BMI of > 25 is classified as overweight, and a patient with a BMI > 30 is classified as obese. In these terms, being overweight increased the risk for developing MetS five- to six-fold, but adults classified as obese were up to 32 times more likely to develop MetS than their normal weight counterparts (Ervin, 2009). It has been hypothesized that obesity's role in MetS is as a "genetic trigger" that flips the on switch for the interactions between the genes for MetS's component parts (Ordovas & Corella, 2008).

However, not all obese patients are at equal risk. The genetic underpinnings that cause MetS have been shown to depend in part on where the fat is distributed on the patients' body. Central fat distribution obesity (around the abdominal area) indicates a greater risk for the

development of MetS (Cheung et al., 2011; Glickman, Marn, Supiano, & Dengel, 2004). Central obesity can be attributed to an overaccumulation of fat between the organs (visceral adipose tissue) or an overaccumulation of fat just below the skin's surface (subcutaneous adipose tissue). In general, women tend to have a higher ratio of subcutaneous fat than men, and this fat tends to cluster around the hips and buttocks in a noncentral (gynoid) distribution (Ogden et al., 2007). It has been suggested that a gynoid fat distribution is somewhat protective for the development of MetS (Wiklund et al., 2008). Conversely, the accumulation of visceral fat tissue in a central obesity pattern is thought to predict the development of MetS.

Obesity Risk Alleles

Elucidating the risk alleles for obesity is complex, and research methodologies to collect and manage specimens as well as to extract genetic material continue to be refined (Cashion, Umberger, Goodwin, & Sutter, 2011). Two of the main genes implicated in obesity are melanocortin receptor 4 (*MC4R*) and fat mass and obesity associated gene (*FTO*). The first has been shown to be associated with fat accumulation, and the other is more directly associated with the development of MetS.

MC4R encodes for a membrane receptor that mediates hormonal signals from adipose tissue. MC4R has been associated most commonly with monogenic forms of obesity (such as in human *MC4R* deficiency mutations (Farooqi & O'Rahilly, 2004), but may also play a role in polygenic forms of common central obesity. Most importantly, the SNP rs17782313 showed an association between BMI and subcutaneous fat accumulation that may be protective against the development of MetS (Haupt et al., 2009; Wiklund et al., 2008).

Although its physiologic function is not fully understood, the *FTO* gene was one of the first genes to be associated with BMI (Frayling et al., 2007). In particular, the SNP rs9939609 is associated with increased intake of nutrients and decreased satiety (Speakman, Rance, & Johnstone, 2008). This particular SNP has also been found to be more prevalent in subjects with MetS (Povel, Boer, Reiling, & Feskens, 2011). Association studies also have shown a relationship between other FTO SNPs and MetS in a Japanese population, suggesting that the relationship between this gene and the development of MetS may be more direct, rather than through the mediation of body weight (Hotta et al., 2011).

Diabetes in Metabolic Syndrome

Like obesity and hypertension, these increases in blood glucose levels are mentioned in every definition of MetS (see Table 1). Usually these increases in blood glucose are due to insulin resistance in type 2 diabetes (T2D). T2D is clinically defined as having an overnight fasting glucose of > 126 mg/dL or a hemoglobin A1c (HbA1c) > 6.5% (Chakkera et al., 2010)[O2]. Diabetes is more prevalent among specific ethnic/racial groups, providing evidence for genetic predisposition (differences in allele frequencies of predisposing genetic polymorphisms) to this complex disease. In a U.S. national sample, 15.7 million non-Hispanic Whites (10.2%) and 4.9 million non-Hispanic Blacks (18.7%) 20 years or age or older have diabetes (National Center for Chronic Disease Prevention and Health Promotion, 2011). Among Hispanics, T2D rates vary substantially depending on population group. T2D rates for Cubans and Central and South American Hispanics are slightly lower than for Caucasians (7.6%), while T2D rates were higher for Mexican Americans and Puerto Ricans (13.3% to 13.8%, respectively; National Center for Chronic Disease Prevention and Health Promotion, 2011).

Type 2 Diabetes Risk Alleles

There is some evidence to show that the genetics of T2D and MetS may have influences from overlapping genes, although individual effect sizes (the strength of a relationship between two variables) of each genetic variant are small (Kraja et al., 2011). Variants of the *TCF7L2* gene are especially associated with both an increased risk for T2D and MetS (Kho et al., 2012). *TCF7L2* may contribute to MetS by causing excess fat and glucogen deposition in the liver and hyperlipidemia, glucose intolerance, and eventually T2D (Delgado-Lista et al., 2011). Because the effects of individual SNPs are relatively small, it is hypothesized that possessing a variant known to put an individual at increased risk for MetS does not act independently of itself. Instead they interact and create a synergistic effect in MetS and T2D development (Delgado-Lista et al., 2011). A summary of recent findings for genes associated with MetS and T2D as recorded in genetic databases such as NCBI dbGaP are presented in Supplemental Tables 1 and 2 online (see end of article for URL).

Implications for Practice and Research

Multiple genes may play a role in the development of MetS (Table 3). Clearly, a deeper understanding of these biochemical pathways involved in MetS is necessary. It is hopeful that these intricate functions will continue to be further elucidated to unveil an understanding of the biochemical interactions that lead cells, tissues, and organs to become diseased in MetS.

Clinical Practice

Genomic-based applications to diagnose, treat, and manage individuals with MetS are being developed but are not yet available clinically. The combinations of environmental and genetic factors that make MetS a multifactorial disorder add to the complexity of clinical management. Currently, the best approach to clinical management is to address each component (e.g., cardiovascular, obesity, diabetes) separately using established guidelines. Nurses should promote lifestyle intervention strategies (i.e., healthy eating, increased activity) that address prevention and management of the individual and the family. A landmark study showed that lifestyle intervention strategies were effective in reducing the incidence of T2D by 58% as compared with a placebo group (Vattikuti, Guo, & Chow, 2012). In addition, obtaining a minimum of a three-generation family history provides a pictorial representation of conditions associated with MetS running through families and is a useful way to identify individuals “at risk” for MetS. For more information on obtaining a family history, visit the Surgeon General’s Family Health History Initiative at http://www.hhs.gov/familyhistory/.

In the future, personalized health care may revolutionize the treatment of MetS. Personalized health care uses genomic knowledge to tailor health care to the person’s needs (U.S. Department of Health and Human Services, 2012). An example of personalized health care for an individual with MetS would be using an individual’s genetic test results to identify specific biologic mechanisms and then tailoring management to that individual’s specific needs. As evidence-based practice moves in this direction, it is the responsibility of the healthcare provider to be aware of best practices for interpreting and delivering results to the patient and using them to manage patient care.

Currently, some individuals may want to determine if they are at risk for MetS and other diseases. There are online vendors that sell direct-to-consumer (DTC) genetic testing for this purpose. These Web sites should be approached with caution, since the clinical validity, reliability, and utility of these test results have not been determined (Skirton, Goldsmith, Jackson, & O’Connor, 2012). In addition, with DTC testing there is concern that genetic results may be given without the benefit of genetic counseling or nursing management.

Research Practice

Determining the biologic underpinnings and identifying genes associated with complex disorders such as MetS is an evolving area of science. Initially, researchers studied individuals with rare monogenetic or chromosomal disorders to identify specific alleles associated with the disorder using linkage analysis and SNPs. Today, GWA studies are replacing these older technologies, and more rapidly identifying putative genes. Although research has increased the understanding of genomic risk factors associated with MetS, the apparent success of GWA studies is tempered by the knowledge that our understanding of disease remains inadequate. Even when significant and replicated associations are combined across studies, only a small percentage (< 2%) of the variance in heritable disorders for many MetS-related traits are explained by genetic markers (Zhang, Ma, Brismar, Efendic, & Gu, 2009). Equally important, the incremental predictive performance of genetic markers over traditional cardiovascular and other risk factors remains uncertain (Ioannidis, 2009). While there may be a number of reasons to explain this “missing heritability” (Maher, 2008; Zhang et al., 2009), an inherent limitation of GWA studies is that the effect size (attributable risk for disease phenotype) for each genetic variant that is positively associated with the disease is often very small (Mechanic et al., 2011).

Another problem with most GWA studies available today is that available genotyping platforms typically represent only relatively common SNPs derived from a Caucasian reference sequence. But it has been shown that some genetic markers may only have relevance in certain racial or ethnic populations (Yancy, 2008). To address the issue of ethnic ancestry in diverse populations, admixture mapping should be utilized to determine percent ancestry. This method enables researchers to associate the degree of ancestry with disease phenotype, such as hypertension in African Americans. If admixture mapping is not used, genetic associations can be confounded by variances in markers that are only appropriate for certain ethnic and racial groups.

The future for genomics of MetS may lie in systems-based approaches (i.e., expression arrays, mass spectrometry, bioinformatics) to address input from hundreds of genes and environmental factors. The interactions of the components are possibly more important than the individual components themselves (Lusis, Attie, & Reue, 2008). As direct sequencing becomes more affordable, analysis of rare variants may play an increasing role in the understanding the genomics of MetS (Fung, Zhang, Zhang, Rao, & O’Connor, 2011). Other sequence changes (e.g., gene copy number variations) and nonsequence changes (e.g., epigenetics, or heritable changes to the genome that alter gene expression without alterations in sequence) will be increasingly studied for their association with MetS disease traits.

For clinical practice the goal of genomic health care is to integrate clinical and biological data for improving patient outcomes. Clinicians should be aware of the genetic tools that are available to improve their understanding and development of patient treatment plans based on screening for complex disorders such as MetS. However, clinicians need to have realistic expectations in this area of emerging research. There are still many potential benefits and limitations of genetic-based assessment, treatment, and management for many common disorders (Calzone et al., 2010). However, as MetS is better understood, we are hopeful for continued improvement in diagnostic testing and genetic-based treatment options for those affected by this disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Resources

- Evaluation of Genomic Applications in Practice and Prevention: www.egappreviews.org
- Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indications: www.genome.gov/pages/careers/healthprofessional education/geneticscompetency.pdf
- Gene Tests: www.ncbi.nlm.nih.gov/sites/GeneTests
- Genetic Testing Registry: www.ncbi.nlm.nih.gov/gtr
- Genetic/Genomic Competency Center for Education (G2C2): http://www.g-2-c-2.org
- Online Mendelian Inheritance in Man: www.ncbi.nlm.nih.gov/omim
- Surgeon General's Family Health History Initiative: www.hhs.gov/familyhistory

Table 1

Harmonizing Definition of Metabolic Syndrome (MetS)

Diagnostic criteria for MetS	Primary outcome CVD	Primary outcome insulin resistance	Obesity	Elevated triglycerides	Reduced HDL-C	Elevated BP	Elevated FBS or type 2 DM	UACR	Elevated CRP	Elevated PAI-1 and fibrinogen
ATPIII[a]	✓		Waist circumference: > 102 cm males > 88 cm females	≥ 150 mg/dL	< 40 mg/dL males < 50 mg/dL females	≥ 130/≥ 85 mm Hg	≥ 110 mg/dL		✓	✓
WHO[b]		✓	BMI ≥ 30 kg/m^2 and/or waist:hip ratio > 0.9 males > 0.85 females	≥ 150 mg/dL (≥ 1.695 mmol/L)	< 35 mg/dL males < 39 mg/dL females	≥ 140 /≥ 90 mm Hg and/or anti-hypertension medication	✓	≥30 mg/g or urinary albumin excretion rate ≥ 20 μg/min		
AACE[c]		✓	✓	✓	✓	✓	✓			
Harmonizing definition	Increased waist circumference by population + country specific definitions	≥ 150 mg/dL (1.7 mmol/L)	< 40 mg/dL males < 50 mg/dL females	≥ 130/ ≥ 85 mm Hg	≥ 100 mg/dL					

Note. ATPIII = National Cholesterol Education Program Adult Treatment Panel III; WHO = World Health Organization; AACE = American Association of Clinical Endocrinologists; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure; FBS = fasting blood sugar; DM = diabetes mellitus; UACR = urine albumin/creatinine ratio; CRP = c-reactive protein; PAI-1 = plasminogen activator inhibitor; BMI = body mass index.

[a]Diagnosis made on the presence of three of the following five risk factors.

[b]Diagnosis made on the basis of several markers of insulin resistance (type 2 diabetes, impaired fasting glucose, impaired glucose tolerance, or, for those with normal fasting glucose levels (> 100mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions) plus two additional risk factors.

[c]No diagnosis cutpoints, AACE left up to clinical judgment.

Data from Alberti et al. (2009) and Simmons et al. (2010).

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Table 2

Definitions of Common Methodologies Used in the Study of Metabolic Syndrome

Type of study	Description
Linkage analysis	Traces patterns of inheritance in large, high-risk families to locate a disease-causing gene mutation by identifying traits that are co-inherited with it
Genome-wide association studies	Search the genome for small variations, called single nucleotide polymorphisms (SNPs), that occur more frequently in people with a particular disease than in people without the disease
Epigenetic studies	Search for changes in the regulation of the expression of gene activity without alteration of the DNA sequence
Proteomics	Study the complete complement of proteins (proteome) of organisms

Note. Definitions adapted from www.http://ghr.nlm.nih.gov/

Table 3

Genes That May Play a Role in the Development of MetS

Gene symbol	Gene name	Proposed function	Component condition	Portion of the harmonizing definition affected
LPL	Lipoprotein lipase	Hydrolyzes triglycerides and participates in the uptake of lipoproteins from circulation	Cardiovascular	High-density lipoprotein-cholesterol
APOE	Apolipoprotein E	A protein that binds to a receptor to remove lipoproteins from circulation	Cardiovascular	High-density lipoprotein-cholesterol
MC4R	Melanocortin receptor 4	A membrane-bound receptor that interacts with adrenocorticotropic hormones	Obesity	Waist circumference
FTO	Fat mass and obesity associated	Exact physiological function unknown	Obesity	Waist circumference
TCF7L2	Transcription factor 7-like 2	Transcription factor that is involved in blood glucose homeostasis	Type 2 diabetes	Glucose