The Metabolic Syndrome

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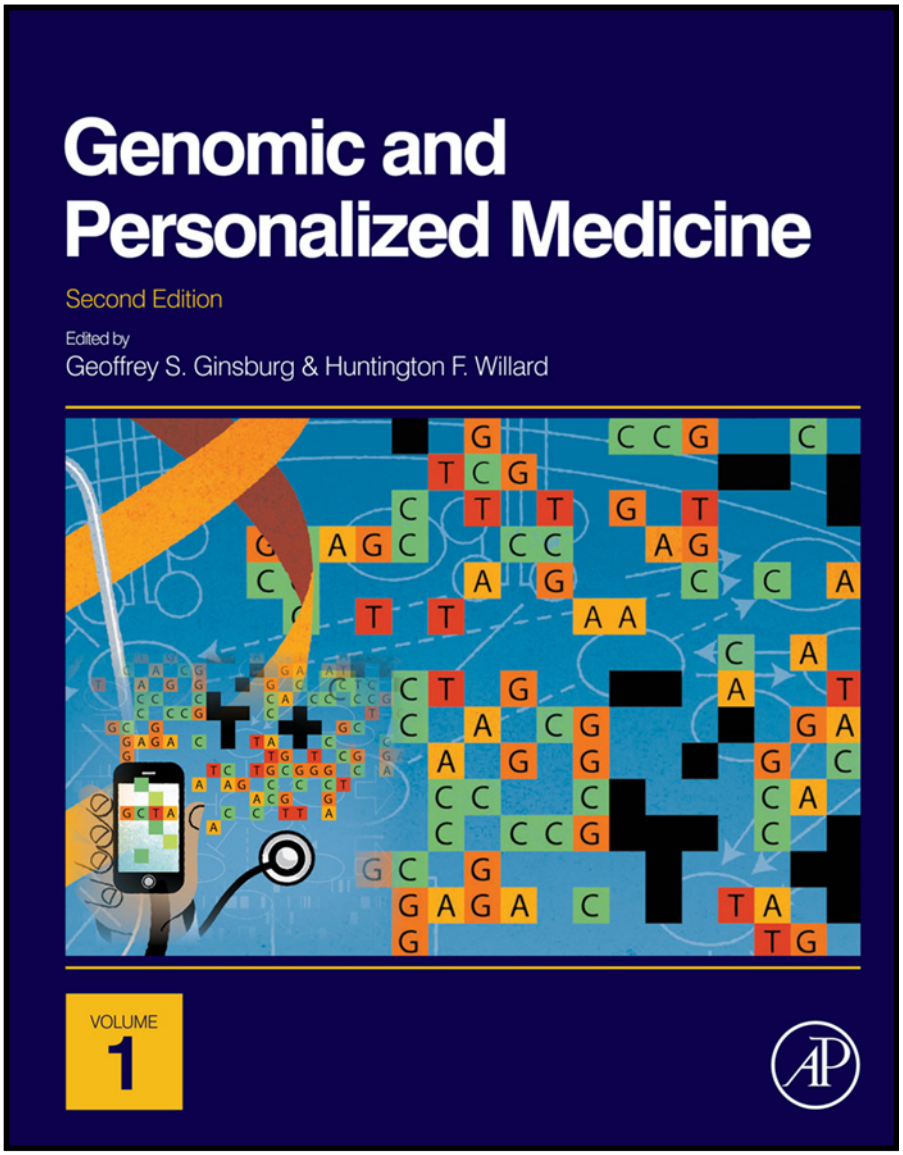

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CHAPTER

The Metabolic Syndrome

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INTRODUCTION

The clustering of several metabolic abnormalities, including dyslipidemia [elevated serum triglycerides and depressed high-density lipoprotein (HDL) cholesterol], dysglycemia, hypertension, and central obesity, has been termed the metabolic syndrome (MetS) (Reaven, 1988). The term syndrome, originating from Greek and literally meaning "running together," refers to a set of signs or symptoms occurring together where the underlying pathophysiology leading to the concurrence is unknown (Jablonski, 1991). Several lines of evidence suggest that a MetS definition is important both clinically and as a research tool, though some controversy exists regarding the importance of a MetS diagnosis for prediction of the development of diabetes and atherosclerotic cardiovascular disease, compared to the sum of the risk factors independently (Eckel et al., 2010; Ford et al., 2008; Gami et al., 2007). Nonetheless, it is clinically apparent that these risk factors occur together more often than one would expect if they were independent processes, and a five-fold increased risk of diabetes and two-fold increased risk for cardiovascular disease is observed with a diagnosis of MetS (Alberti et al., 2009). Additionally, in patients with an extreme perturbation of one of the components of MetS, as observed, for example, in lipodystrophy, disruption of the other components almost inevitably follows (Hegele, 2003). The common form of MetS is a classic complex genetic trait involving the interaction of a multitude of genetic and environmental factors, and genetic and genomic investigations into MetS may yield insights into the responsible mechanisms.

Defining Metabolic Syndrome

At least six different organizations have published criteria for MetS diagnosis (Alberti et al., 2005; Balkau and Charles, 1999; Einhorn et al., 2003; Grundy et al., 2005; NCEP, 2001; WHO, 2007). A recent consensus statement of stakeholders has unified the definition for clinical use, as well as for epidemiological and basic research studies (Alberti et al., 2009). The debate over the criteria for metabolic syndrome has largely revolved around whether elevated abdominal obesity should be a mandatory component, and what the threshold for continuous variables should be. The revised definition includes five criteria, three of which must be met for a diagnosis (Table 83.1). The criteria include elevated waist circumference, triglycerides, blood pressure, and fasting glucose, and depressed HDL cholesterol. Differences in baseline waist circumference observed between the sexes and ethnicities have also been a concern, and sex- and ethnicity-specific guidelines have been specified (Table 83.2).

Regardless of the definition used, MetS is a common diagnosis (Grundy, 2008). Data from the Third National Health and Nutrition Examination Survey (NHANES III), which used the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) MetS criteria, found the prevalence of MetS to be 24% in the United States (Ford et al., 2002). Using the International Diabetes Foundation MetS definition, in a large study including >26,000 participants from 52 countries, the average MetS prevalence was 16.8% (Mente et al., 2010). Due to its high prevalence, an improvement to our understanding of MetS could yield large benefits to public health.

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Table 83.1 Criteria for metabolic syndrome diagnosis

Metabolic syndrome component	Threshold for criteria
Waist circumference	Population- and sex-specific definitions*
HDL cholesterol	<1.0 mmol/L
Triglycerides	≥1.7 mmol/L or drug therapy for high triglycerides†
Blood pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or drug therapy for hypertension
Fasting glucose	≥5.5 mmol/L or drug therapy for elevated glucose

HDL, high density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.
*See Table 83.2 for waist circumference definitions.
†Fibrates and nicotinic acid are the most commonly used triglyceride lowering therapies.
Data taken from stakeholder consensus on metabolic syndrome definition (Alberti et al., 2009).

Table 83.2 Sex- and ethnicity-specific waist circumference thresholds for metabolic syndrome definition as given by the International Diabetes Federation

Ethnicity	Waist circumference threshold for metabolic syndrome criteria	
	Male	Female
Europid	≥94 cm	≥80 cm
Asian	≥90 cm	≥80 cm
Middle Eastern	≥94 cm	≥80 cm
Mediterranean	≥94 cm	≥80 cm
Sub-Saharan African	≥94 cm	≥80 cm
Ethnic Central and South American	≥90 cm	≥80 cm

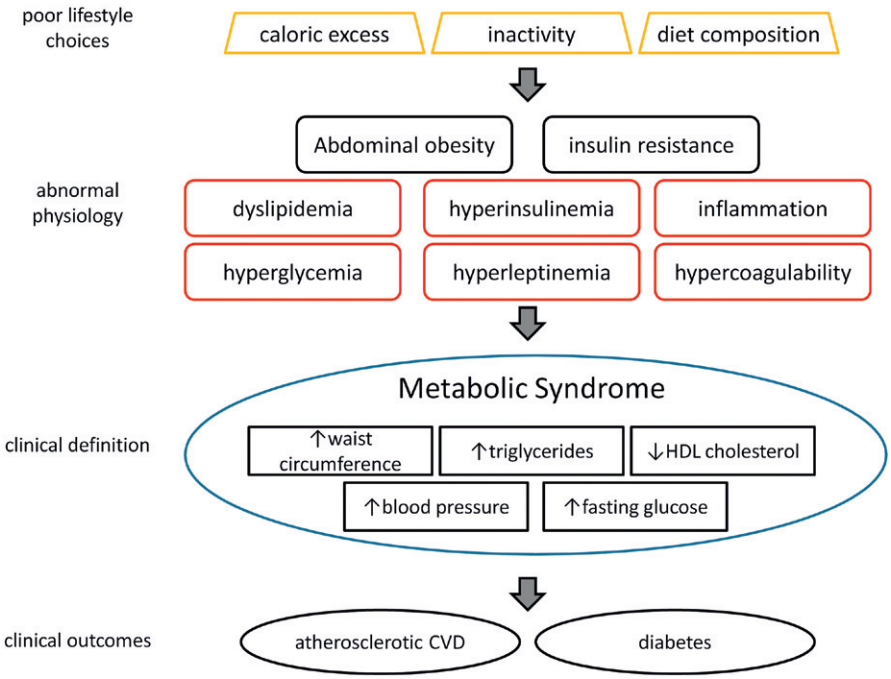

Figure 83.1 Poor lifestyle choices lead to the development of inciting factors for metabolic syndrome (black boxes) and abnormal physiology. Disrupted metabolism is clinically measured by the components of the metabolic syndrome. Metabolic syndrome subsequently increases risk for development of atherosclerotic cardiovascular disease (CVD) and diabetes.

Pathophysiology

The inciting factors in the development of MetS are abdominal obesity and insulin resistance (Reaven, 1988) (Figure 83.1). The accumulation of visceral fat, typically caused by over-nutrition and physical inactivity, results in the release of free fatty acids, leading to lipotoxicity and insulin resistance (Samuel et al., 2010), and eventually hyperinsulinemia and hyperglycemia (Pollex and Hegele, 2006). Insulin has numerous molecular effects beyond glucose homeostasis: upregulation of amino acid uptake and protein synthesis, activation of lipoprotein lipase, and inhibition of very low-density lipoprotein (VLDL) secretion (Cornier et al., 2008). Abundance of fatty acids and diacylglycerol within skeletal muscle inhibits insulin signaling and reduces its ability to transport and utilize glucose (Samuel

et al., 2010). Visceral fat accumulation creates a dysregulation of adipokine secretion, specifically hyposecretion of adiponectin and hypersecretion of both leptin and pro-inflammatory cytokines (such as tumor necrosis factor alpha and interleukin 6), each of which may contribute to the MetS pathophysiology (Kadowaki et al., 2006; Shoelson et al., 2006). In response to hyperinsulinemia and hyperglycemia, the liver secretes C-reactive protein and pro-thrombotic molecules such as fibrinogen and plasminogen activator inhibitor-1 (PAI-1) (Cornier et al., 2008). Clearly, MetS is a complicated phenotype involving a complex network of causative and associated biochemical players; disentangling their relationships to further our understanding and develop novel therapeutics is thus a difficult task.

HERITABILITY OF METABOLIC SYNDROME

Strong evidence exists for the heritability of both MetS and its components, arising from studies of both twins and families. In a study of 2508 pairs of American male twins, the MetS concordance between monozygotic pairs was 31.6% compared to 6.3% for dizygotic twins (Carmelli et al., 1994). In a study of 109 American female twin pairs, MetS and its components were also significantly better correlated in monozygotic than dizygotic twins (Edwards et al., 1997). Among 803 individuals from 89 Caribbean-Hispanic families, the heritability of a MetS diagnosis was 24%, with significant heritability for lipid/glucose/obesity (44%) and hypertension (20%) components (Lin et al., 2005). In a study of 1277 Omani Arab individuals in five large consanguineous families, a large degree of heritability was observed for MetS (38%), while the heritability of the individual MetS components ranged from 38% to 63% (Bayoumi et al., 2007). In an examination of 1942 Korean twin pairs and their families, significant heritability of both MetS (51–60%) and all of its components (46–77%) was observed (Sung et al., 2009). Variation in the reported heritability of MetS and its components is likely partially due to differences in ethnicity, variation in environmental exposures between family members, and the statistical techniques employed. Based upon the demonstrated heritability of MetS and its components, investigations to identify responsible genetic variants have been undertaken using both linkage analysis and association mapping strategies, the results of which are discussed later in this chapter.

LESSONS FROM MONOGENIC MODELS OF METABOLIC SYNDROME

Monogenic diseases, also termed Mendelian diseases, are the result of a single genetic mutation and thus have high penetrance, follow Mendelian inheritance patterns, and include small or non-existent environmental components (Moore et al., 2005). In contrast, in complex diseases such as MetS, there is no apparent inheritance pattern, many genetic loci are involved, and there are large environmental components (Moore et al., 2005). In the last 30 years, the genetic basis of several monogenic diseases that include multiple components of MetS have been discovered, garnering insight into potential mechanisms of MetS, despite being responsible for a very small proportion of MetS in the population.

Since monogenic disorders segregate through families, linkage analysis of severely affected families followed by sequencing of genes within the identified region has discovered the responsible genetic variant for many monogenic models of MetS. Whole-exome studies, in which the transcribed portion of the genome is sequenced, have already been successful identifying variants responsible for Mendelian disorders (e.g., Ng et al., 2010). With the increasing availability of next-generation sequencing technologies, our ability to identify rare genetic variants responsible for monogenic models of MetS will only improve.

Lipodystrophy

Lipodystrophy is a heterogeneous group of disorders characterized by selective or generalized atrophy of anatomical adipose tissue stores (Table 83.3) (Garg, 2004). Loss of the ability to retain excess lipids in "classical" adipose tissue stores leads to the over-development of ectopic fat stores, such as within and around skeletal muscle, heart, liver, pancreas, and kidneys and within the arterial wall, presenting as atherosclerosis (Dulloo et al., 2004). In patients with congenital generalized lipodystrophy (CGL), an absence of adipose tissue is noted in early infancy (Garg, 2004). In familial partial lipodystrophy (FPLD), patients have normal fat distribution during childhood, but during or shortly after puberty there is a progressive and gradual loss of subcutaneous adipose tissue of the extremities, a triggering event for the development of the other components of MetS including extreme insulin resistance, dyslipidemia and hypertension (Garg, 2004).

A total of 11 genes have been identified that contain mutations causative of at least one form of lipodystrophy (Lanktree et al., 2010) (Table 83.3). The two most commonly mutated genes causing lipodystrophy are those encoding nuclear lamin A/C (*LMNA*) and peroxisome proliferator-activated receptor γ (*PPARG*). Currently, over 200 mutations have been identified in *LMNA*, causing 13 different diseases, together termed laminopathies: FPLD, Emery–Dreifuss muscular dystrophy, limb-girdle muscular dystrophy type 1B, dilated cardiomyopathy type 1A, Charcot–Marie–Tooth, Hutchinson–Gilford progeria syndrome, atypical Werner syndrome, and a range of overlapping syndromes (Stenson et al., 2009). *LMNA* mutations have also been identified in patients with a less severe form of lipodystrophy, closely resembling common MetS, which was named "metabolic laminopathy" (Decaudain et al., 2007). *LMNA* encodes an intermediate filament protein vital for the structural integrity of the nuclear envelope, transcriptional regulation, nuclear pore functioning, and heterochromatin organization. However, it remains unknown how the mutations observed in *LMNA* specifically cause the observed phenotypes.

TABLE 83.3 Monogenic lipodystrophy observed in humans

Disease	OMIM #
Generalized	
Congenital generalized lipodystrophy (CGL) (Berardinelli–Seip)	
CGL1 – caused by mutations in *AGPAT2*	608594
CGL2 – caused by mutations in *BSCL2*	269700
CGL3 – caused by mutations in *CAV1*, *PTRF*	612526
Partial	
Familial partial lipodystrophy (FPLD)	
FPLD2 (Dunnigan) – caused by mutations in *LMNA*	151660
FPLD3 – caused by mutations in *PPARG* FPLD caused by newly-discovered mutations – *CAV1*, *AKT2*	604367
Acquired partial lipodystrophy (APL) (Barraquer–Simmons)	
APL – some cases associated with *LMNB2* mutations	608709
Syndromes that include lipodystrophy as a component	
Mandibuloacral dysplasia (MAD)	
MADA – caused by mutations in *LMNA*	248370
MADB – caused by mutations in *ZMPSTE24*	608612
SHORT syndrome – potentially caused by mutations in *PITX2*	269880
Hutchinson–Gilford progeria syndrome (HGPS) – caused by mutations in *LMNA*	176670
Werner syndrome (WRN) – caused by mutations in *RECQL2*, *LMNA*	277700

PPARG was selected as a candidate for sequencing in FPLD patients due to its important role as a ligand-inducible transcription factor regulating adipogenesis, and the re-partitioning of fat stores observed in patients taking the thiazolidinedione (TZD) class of drugs, which are agonists for PPARG. Sequencing of *PPARG* resulted in the discovery of causative mutations (Agarwal and Garg, 2002; Hegele et al., 2002). Through functional studies, different *PPARG* mutations were observed to work through both a dominant negative mechanism, in which the mutant receptor is able to inhibit the action of the wild-type receptor (Southam et al., 2009), and a haploinsufficiency mechanism, in which the 50% reduction in wild-type expression was sufficient to create the phenotype (Hegele et al., 2002).

TABLE 83.4 Monogenic diseases of obesity and insulin resistance observed in humans

Disease	OMIM #
Obesity	
Alstrom syndrome – *ALMS1*	203800
Bardet–Biedl syndrome – *BBS1-14*	209900
Cohen syndrome – *COH1*	216550
Leptin deficiency – *LEP*	164160
Leptin receptor deficiency – *LEPR*	601007
Melanocortin-4 receptor deficiency – *MC4R*	155541
NTRK2 mutation	600456
Prader–Willi syndrome – *SNRPN*	176720
Prohormone convertase-1 deficiency – *PCSK1*	600955
Proopiomelanocortin deficiency – *POM1*	609734
Pseudohypoparathyroidism – *GNAS*	103580
SIM1 deletion	603128
WAGR syndrome – *BDNF*	612469
Insulin resistance	
Donohue syndrome – *INSR*	246200
Disrupted insulin signaling – *AKT2*	164731

Monogenic Diseases of Obesity and Insulin Resistance

Over 20 genes have been implicated in rare monogenic diseases that include extreme obesity and/or insulin resistance, that could provide insight into more common forms of MetS (O'Rahilly, 2009) (Table 83.4). The most common monogenic cause of extreme obesity is mutation in melanocortin receptor 4 (*MC4R*) [Online Mendelian Inheritance in Man (OMIM) number: 155541], accounting for approximately 4% of extremely obese individuals (Tan et al., 2009). *MC4R* is primarily expressed in the brain and is thought to impact obesity through central effects on appetite and satiety (Farooqi et al., 2003). Proopiomelanocortin (POMC) (OMIM: 176830) is a precursor protein for multiple biologically active peptide hormones, including but not limited to adrenocorticotropic hormone (ACTH), β-liptropin, β-endorphin, and α-, β- and γ-melanocyte-stimulating hormone, which bind with varying affinity to five homologous melanocortin receptors, including MC4R (Krude et al., 2003). *Pomc -/-* mice develop obesity and abnormal pigmentation (Yaswen et al., 1999), and complete loss-of-function mutations in *POMC* were first described in patients with hypocortisolism, red hair, and early-onset extreme obesity (Krude et al., 1998). Melanocortin signaling has also been implicated in modulating both blood pressure

and lipid metabolism, independent of weight and insulin signaling, indicating a potentially greater role for *MC4R* and *POMC* in MetS (Greenfield et al., 2009; Nogueiras et al., 2007).

Bardet–Biedl syndrome (BBS) is a group of at least six molecularly distinct but clinically similar diseases that include obesity as a central component (OMIM: 209900). As well as abdominal obesity, patients with BBS have diabetes, hypertension, mental retardation, dysmorphic extremities, retinal dystrophy or pigmentary retinopathy, hypogonadism and abnormal kidney structure and/or function (Moore et al., 2005). Knockout mice for three of the responsible genes have been developed: *Bbs2 -/-*, *Bbs4 -/-*, and *Bbs6 -/-* (Rahmouni et al., 2008). All three mice strains were hyperphagic, had low locomotor activity, and elevated circulating leptin concentrations (Rahmouni et al., 2008). Further examination of the knockout mice, as well as cellular work, suggests that the proteins mutated in BBS are required for leptin receptor signaling, and the impaired leptin signaling was associated with decreased *Pomc* expression (Seo et al., 2009). Rare mutations in the genes encoding both leptin (*LEP*) (OMIM: 164160) and the leptin receptor (*LEPR*) (OMIM: 601007) also cause obesity, hyperinsulinemia, and insulin resistance, and are knocked out in the commonly studied ob^-/ob^- and db^-/db^- mice, respectively.

Alstrom syndrome is an autosomal recessive disorder characterized by childhood obesity, insulin resistance, hyperglycemia, hyperlipidemia, and neurosensory defects, caused by mutations in a gene at chromosomal locus 2p13 subsequently named *ALMS1* (Collin et al., 2002) (OMIM: 203800). Dilated cardiomyopathy, hepatic dysfunction, and hyperthyroidism are also variably present. Mice with *ALMS1* knocked out recapitulate the findings observed in humans, providing evidence that loss of *ALMS1* alone is sufficient to cause the phenotype (Collin et al., 2005).

Mutations in the insulin receptor (*INSR*) can directly cause insulin resistance, creating several syndromes with variable insulin receptor dysfunction: leprechaunism (Donahue syndrome), Rabson–Mendenhall syndrome, and type A insulin resistance (OMIM: 147670). Patients with the most severe syndrome, Donahue syndrome, have marked hyperinsulinemia, fasting hypoglycemia, post-prandial hyperglycemia, growth restriction, and premature mortality (Longo et al., 2002).

GENETICS OF COMMON METABOLIC SYNDROME

Linkage Analysis

Studies to identify genes contributing to common MetS began by searching for chromosomal regions that were transmitted between affected individuals in large families using linkage analysis. While at least 38 regions have been reported to be linked with one or more MetS components (Teran-Garcia and Bouchard, 2007), few conclusions can be drawn, for three reasons: (1) linkage analysis is poorly powered in the context of a genetic locus that explains only a small percentage of variation in the trait, (2) resolution is very poor and identified regions often include 100 genes, and (3) there has been little concordance between regions identified.

Association Studies

Genetic association studies test if alleles at a single nucleotide polymorphism (SNP) are found more often in cases than in controls, or in individuals with elevated levels of a quantitative trait. To find genetic variations of small effect, association studies have greater resolution and are better powered than linkage analysis. The first genetic association studies were candidate gene studies, with >20 studies focused upon investigations of genes with known roles in MetS (Pollex and Hegele, 2006). Genes that have been replicated in multiple studies include those in: lipid metabolism pathways, such as apolipoprotein A5 (*APOA5*) (Grallert et al., 2007; Yamada et al., 2007, 2008), and apolipoprotein C3 (*APOC3*) (Guettier et al., 2005; Pollex et al., 2007); inflammation, such as interleukin-6 (*IL6*) (Hamid et al., 2005; Stephens et al., 2007); and adipose tissue partitioning, such as *LMNA* (Hegele et al., 2000; Steinle et al., 2004) and *PPARG* (Frederiksen et al., 2002; Meirhaeghe et al., 2005).

Since the publication of the reference human genome sequence, advancements in high-throughput genotyping technologies and databases of common genetic variation have enabled genome-wide association studies (GWAS) to test over a million SNPs in a single experiment. To date, no GWAS of MetS has been reported in the literature. Genome-wide investigations into the individual components of MetS using GWAS, however, have been enormously successful. As reviewed in other chapters in this book, GWAS of the components of MetS including blood lipid and lipoprotein concentrations, blood pressure, body mass index, and fasting blood glucose have identified >100 genes involved in metabolic pathways relevant to MetS (Table 83.5). Many of the identified genes have previously known functional roles or are mutated in monogenic disease and represent positive controls for the GWAS approach. Additionally, many novel genes with no previously known roles in metabolic pathways have been robustly associated and their biological functions are under study.

Pleiotropy describes the situation where a gene impacts multiple phenotypic traits. In the interacting metabolic pathways involved in MetS pathophysiology, pleiotropy is to be expected. While no genes have been identified to be associated with all five components of the metabolic syndrome, many of the identified genes are associated with more than one component. Due to the high correlation between plasma HDL cholesterol and triglyceride concentration, it is unsurprising that 14 genes are associated with both traits (Table 83.5). With respect to genes associated with more than one of the other MetS components, glucokinase (hexokinase 4) regulatory protein (*GCKR*) is associated with both fasting triglyceride and glucose concentrations (Teslovich et al., 2010; Zeggini et al., 2008). The fat mass- and obesity-associated gene (*FTO*)

TABLE 83.5 Genes associated with components of metabolic syndrome in genome-wide association studies

HDL	Triglycerides	Blood pressure	Obesity*	Fasting glucose and insulin-related†
PABPC4	*ANGPTL3*	*CASZ1*	*NEGR1*	*PROX1*
ZNF648	***GALNT2***	*MTHFR*	*SEC16B*	*NOTCH2*
GALNT2	***APOB***	*ULK4*	*SDCCAG8*	*THADA*
APOB	***GCKR***	*ITGA9*	*TMEM18*	***IRS1***
COBLL1	***COBLL1***	*FGF5*	*ETV5*	*BCL11A*
IRS1	***IRS1***	*CACNB2*	*GNPDA2*	***GCKR***
SLC39A8	*MSL2L1*	*c10orf170*	*PCSK1*	*CALPN10*
ARL15	*KLHL8*	*CYP17A1*	*NCR3-BAT2*	*G6PC2*
C6orf106	*MAP3K1*	*PLEKHA7*	*PTER*	*ADAMTS9*
CITED2	*TIMD4*	*ATP2B1*	*TNKS-MSRA*	*ADCY5*
LPA	*HLA*	*SH2B3*	*MTCH2*	*SLC2A2*
MLXIPL	*TYW1B*	*TBX3-5*	*BDNF*	*PPARG*
KLF14	***MLXIPL***	*CSK-ULK3*	*FAIM2*	*IGF2BP2*
PPP1R3B	*PINX1*	*CYP1A2*	*MAF*	*WFS1*
LPL	*NAT2*	*ZNF652*	*NRXN3*	*CDKAL1*
TRPS1	***LPL***	*PLCD3*	*SH2B1*	*VEGFA*
TRIB1	***TRIB1***		***FTO***	*GCK*
TTC39B	*JMJD1C*		*NPC1*	*TMEM195*
ABCA1	*CYP26A1*		*MC4R*	*GLIS3*
AMPD3	***FADS1-2-3***		*KCTD15*	*JAZF1*
LRP4	***APOA1***			*SLC30A8*
FADS1-2-3	***LRP1***			*CDKN2B*
APOA1	***ZNF664***			*CDC123*
UBASH3B	*CAPN3*			*TCF7L2*
PDE3A	*FRMD5*			*ADRA2A*
LRP1	***LIPC***			*HHEX*
MVK	***CETP***			*KCNJ11*
SBNO1	*CTF1*			*MTNR1B*
ZNF664	*CILP2*			*MADD*
SCARB1	***APOE***			*CRY2*
LIPC	***PLTP***			*FADS1*
LACTB	*PLA2G6*			***FTO***
CETP				*HNF1A-TCF2*
LCAT				*TSPAN8*
CMIP				*C2CD4B*

(*continued*)

TABLE 83.5 (Continued)

HDL	Triglycerides	Blood pressure	Obesity*	Fasting glucose and insulin-related†
STARD3				
ABCA8				
PGS1				
LIPG				
MC4R				
ANGPTL4				
LOC55908				
APOE				
LILRA3				
HNF4A				
PLTP				
UBE2L3				

Genes in bold type are associated with multiple components of metabolic syndrome.
*Genes for obesity taken from studies of waist circumference, body mass index and extreme obesity.
†Genes for fasting glucose, fasting insulin and type 2 diabetes.
Data from Dupuis et al., 2010; Levy et al., 2009; Newton-Cheh et al., 2009; Scherag et al., 2010; Takeuchi et al., 2010; Teslovich et al., 2010; Zeggini et al., 2008.

is associated with both adiposity and measures of insulin sensitivity (Do et al., 2008). Variants in insulin receptor substrate 1 (*IRS1*) are associated with type 2 diabetes risk, insulin resistance, HDL cholesterol, and triglycerides (Rung et al., 2009; Teslovich et al., 2010). Contrarily, it is interesting that some genes that are associated with one of the MetS components with large effect are not associated with other components. For example, common variants in endothelial lipase (*LIPG*) are robustly associated with HDL concentration, but have not been identified to be associated with plasma triglycerides (Teslovich et al., 2010). As meta-analyses of GWAS are performed, creating sufficient power to identify genetic variants of smaller effect, the pleiotropic effect of more genes is likely to be uncovered.

THE THRIFTY GENE HYPOTHESIS

The "thrifty gene" hypothesis has been proposed to explain the high prevalence of obesity, diabetes, and subsequent MetS in modern times. In this hypothesis, genetic variants that lead to the accumulation of adipose stores for preservation of nutrition until times when it would be required are under positive selection, and thus become more common in the population (Neel, 1962). Thus, in current times of caloric excess, previously beneficial alleles have become deleterious. Contradicting this hypothesis are the facts that in times of starvation, death is primarily caused by infection, not loss of adipose tissue, and that obese individuals may be at higher risk of succumbing to predation (Speakman, 2007). Furthermore, as many common genetic variants have now been identified that contribute to variation in obesity and diabetes, it has become possible to test the hypothesis by examining the obesity-, diabetes- and metabolic-risk alleles. Work by Southam and colleagues examined the characteristics of risk alleles as either minor or major alleles, ancestral or derived alleles, as well as the population differentiation statistics [fixation statistic (F_{st})]. Ultimately, they were able to uncover little evidence in support of the thrifty gene hypothesis (Southam et al., 2009).

FINDING THE MISSING HERITABILITY

Despite the success of GWAS for identifying genes involved in individual MetS components, the genetic variants identified as associated with such components typically explain <10% of variation in the traits across the population, despite heritability measurements of >50% in family studies. This contrast reflects what has been termed the "missing heritability," and efforts to identify genetic variants that explain additional trait variation is the focus of a tremendous research effort (Manolio et al., 2009). Examples of potential sources of missing heritability are rare variants, copy number variation (CNV), and

micro RNA genes (*miR*), as well as gene–gene and gene–environment interactions.

Sequencing of genes identified by GWAS reveals rare reduced- or loss-of-function mutations, especially in individuals in the extremes of the distribution of the trait (Johansen et al., 2010). CNV involves the duplication and deletion of genomic DNA, typically defined as >1000 base pairs in size. CNVs are common in the population (Conrad et al., 2010) and have been associated with extreme obesity (Bochukova et al., 2010; Walters et al., 2010). Micro RNAs are short transcribed RNA segments that bind complementary messenger RNA (mRNA), causing translational repression and transcript degradation (Ghildiyal and Zamore, 2009). Two such *miR* genes, *miR-33b* and *miR-33a*, lie within the introns of sterol regulatory element-binding protein-1 (*SREBP1*) and -2 (*SREBP2*), genes encoding two transcription factors that control important glucose and fatty acid regulatory programs, respectively (Najafi-Shoushtari et al., 2010; Rayner et al., 2010). These micro RNAs target genes with opposing actions to *SREBP1* and *SREBP2*, most notably ATP binding cassette transporter A1 (*ABCA1*) (Najafi-Shoushtari et al., 2010; Rayner et al., 2010). Increased *SREBP1* and *miR-33b* expression leads to increased fatty acid synthesis and decreased cholesterol efflux to HDL, two of the hallmarks of MetS (Brown et al., 2010).

Since a relatively small percentage of variation in MetS components and MetS risk has been explained through variants identified in genetic studies, and since environment undoubtedly plays a role in MetS etiology, additional research into potential gene–environment interactions is required. In order to ensure valid assessment of gene–environment interactions in studies of MetS, suitable sample sizes and appropriate statistical methodologies must be employed (Thomas, 2010). Measurement of plasma fatty acid concentration may be less biased than reported dietary fat measurement (Phillips et al., 2010), and two recent studies have attempted to examine gene–environment interactions in the context of plasma fatty acid concentration and MetS. In a study of 1754 European participants, a significant association between leptin receptor (*LEPR*) polymorphisms and MetS was modulated by plasma fatty acid concentrations, which was replicated in a separate cohort (Phillips et al., 2010). Similarly, a gene–environment interaction has been reported between plasma fatty acid concentration and polymorphisms in the adiponectin gene (*ADIPOQ*) and its receptors (*ADIPOR1* and *ADIPOR2*) (Ferguson et al., 2010). These reports require additional validation but provide an interesting basis for further research into gene–environment interaction in MetS.

In systems biology, computational techniques attempt to find patterns in large networks of data derived from high-throughput technologies such as genomic variation, gene expression, proteomics, and metabolomics (Lusis et al., 2008). In this manner, MetS can be evaluated using a broad perspective, incorporating information from multiple sources and multiple physiological pathways, including gene–gene and gene–environment interactions. Using this approach in rodents, evidence for the involvement of lipoprotein lipase (*Lpl*), lactamase β (*Lactb*), and protein phosphate 1-like (*Ppm1L*) in metabolic syndrome and obesity was obtained (Chen et al., 2008). Similar approaches in human systems would also likely yield novel insights into MetS biology.

CLINICAL IMPLICATIONS TO GENETIC FINDINGS IN METABOLIC SYNDROME

Genetic testing of common variants associated with small changes in MetS components, such as lipid concentration or fasting glucose, or associated with risk of MetS complications, such as coronary artery disease or type 2 diabetes, is of little clinical utility at this point (Humphries et al., 2010; Johansen and Hegele, 2009; Talmud et al., 2010). Identification of large-effect mutations may assist with diagnosis in individuals with monogenic forms of MetS, such as lipodystrophy. However, it is premature to currently recommend genetic testing in the context of general MetS diagnosis or treatment.

CONCLUSION

MetS is a complex, heterogeneous diagnosis with numerous causative and associated biochemical players. Much can be learned about MetS pathophysiology by the identification and characterization of individuals with extreme disturbance of one of the MetS components. GWAS of the MetS components have been very successful, verifying known genes and uncovering novel genes, but a GWAS of MetS diagnosis is yet to be reported. As our understanding of the components of MetS improves, we need to begin to understand how these pathways interact and combine to form MetS, and the subsequent risk for atherosclerosis and diabetes.

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