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Metabolic Syndrome: Genetic Insights into Disease Pathogenesis

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Abstract

Purpose of review—Metabolic syndrome (MetS) is a cluster of inter-related and heritable metabolic traits, which collectively impart unsurpassed risk for atherosclerotic cardiovascular disease and type 2 diabetes. Considerable work has been done to understand the underlying disease mechanisms by elucidating its genetic etiology.

Recent findings—Genome-wide association studies (GWAS) have been widely utilized albeit with modest success in identifying variants that are associated with more than two metabolic traits. Another limitation of this approach is the inherent small effect of the common variants, a major barrier for dissecting their cognate pathways. Modest advances in this venue have been also made by genetic studies of kindreds at the extreme ends of quantitative distributions. These efforts have led to the discovery of a number of disease genes with large effects that underlie the association of diverse traits of this syndrome.

Summary—Substantial progress has been made over the last decade in identification of genetic risk factors associated with the various traits of MetS. The heterogeneity and multifactorial heritability of MetS, however, has been a challenge towards understanding the factors underlying the association of these traits. Genetic investigations of outlier kindreds or homogenous populations with high prevalence for the disease can potentially improve our knowledge of the disease pathophysiology.

Keywords

Genetics; Metabolic syndrome; obesity; hypertriglyceridemia; diabetes

1. Introduction

Metabolic syndrome is a cluster of metabolic traits that confer high risk for cardiovascular disease (CVD) and diabetes. While this entity has been known for more than 6 decades [1], its significance has only been recently realized as a public health threat with a prevalence that is soaring across all age groups [2].

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Conflicts of Interest

None

Patients with MetS have an estimated relative risk (RR) of 2.35 (2.02-2.73) for CVD [3]. Their RR for CVD mortality after adjusting for diabetes and conventional risk factors is estimated between 1.39 (1.03-1.86) [4] to 1.54 (1.32-1.79) [5]. The RR for death appears to be independent of body weight and can be as high as 4.05 (2.38-6.89) in normal weight patients with MetS compared to those without MetS [4]. Even among subjects with angiographically significant coronary artery disease (CAD), the hazard ratio for cardiovascular events is much greater in those with MetS compared to those without [6].

MetS remains a heterogeneous disorder with multiple components encompassing truncal obesity, atherogenic dyslipidemia, hypertension, glucose intolerance, a proinflammatory state, and a prothrombotic state that commonly cluster together. The spectrum of traits in a patient at the time of diagnosis may vary considerably even in affected members of the same family. This heterogeneity creates a challenge for genetic studies that hinge on a well-defined clinical phenotype for success. Attempts have been made by national and international organizations to establish a universal definition for this syndrome. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria are widely used and require the presence of any 3 out of 5 metabolic traits for the diagnosis. These include: hypertension ($>130/85$ mmHg), abdominal obesity (a waist circumference of 102 cm in men, 88 cm in women, 90 cm in Asian-American men, and 80 cm in Asian-American women), elevated triglycerides (TG ≥ 150 mg/dl), reduced plasma high-density lipoprotein cholesterol (HDL <40 mg/dl in men and <50 mg/dl in women), and impaired glucose tolerance (>100 mg/dl) [7; 8].

Recently, the CardioMetabolic Health Alliance think tank further categorized the syndrome into subtypes and stages. The subtypes include lipid dominant, adiposity dominant, vascular dominant, insulin resistance dominant, and “other subtype” that contains patients with hyperuricemia, chronic kidney disease or hormonal dysfunction. This effort was made to improve the characterization of the phenotype and prognostication of end-organ consequences [9*].

2. Genetic causes of Metabolic syndrome

Family and twin studies have provided the initial evidence for the heritability and co-occurrence of the metabolic traits. Heritability estimates for each of the MetS traits exceed 50%.

Genetic studies have successfully identified a number of mutations for individual traits. In this regards progress in understanding the genetics of obesity, which plays a central role in MetS, has been substantial.

2.1. Monogenic disorders of obesity

Total body fat is determined by calories from food intake and energy expenditure, which are both influenced by genetic factors. Rare recessive mutations in the genes encoding leptin and its receptor have been associated with obesity and insulin resistance. Leptin is secreted from adipose tissue and provides an important feedback signal between the peripheral fat deposit and the hypothalamic proopiomelanocortin (POMC) neurons in the arcuate and

paraventricular nuclei. Post-translational processing of POMC generates melanocortin peptides α , β , and γ MSH, which stimulate the melanocortin receptors 3 and 4 (MC4R and MC3R) to generate an anorectic response and reduce the fat deposit [10]. In addition, leptin inhibits the orexigenic pathway via inhibiting the agouti-related peptide (AGRP) and neuropeptide Y (NPY) neurons in the arcuate nucleus [11]. Mutations in MCR3, MC4R, and POMC genes have been associated with monogenic forms of obesity. Moreover, MC4R mutations account for about 6% of monogenic obesity cases in children [12].

3. Genetic approaches for discovery of MetS genes

In the following section we will briefly explain the different approaches and their results.

3.1. Candidate gene approach

Mutation burden analysis of candidate genes is among the first methods used for discovering MetS genes. Given its biased nature, most genetic associations failed to be replicated or be identified through GWAS. Such examples include polymorphisms in or near genes encoding SLC6A14, GAD2, and ENPP1.

Furthermore, the majority of the identified disease genes underlie only one metabolic trait. Few exceptions include variations in ADIPOQ associated with diabetes, hypertension, and dyslipidemia. Other examples include variations in NR3C1, FOXC2, SREBP1, and GNB3 genes.

3.2. Genome-wide Linkage Analysis

Genome wide linkage analysis has been widely used to map disease genes for MetS. Several loci have been reported in Caucasian Americans (1p34.1, 1q41, 2p22.3, 3q27, 7q31.3, 9p13.1, 9q21.1, 10p11.2, 17p12, and 19q13.4) [13] and in Hispanics (6q and 1q23–q31) [14]. No specific gene has been identified for these loci.

3.3. Genome Wide Association Studies (GWAS)

GWAS examine the genome for common polymorphisms associated with the disease and are particularly suitable for complex traits. This unbiased approach takes advantage of linkage disequilibrium between a disease allele and nearby polymorphisms. These studies have been powered by the discovery of a massive number of polymorphisms in the human genome. Nonetheless, they also suffer from several limitations. First, uncovered genetic variants are not necessarily causative. Another setback is the requirement of a minimum allele frequency, often set at 5% in the study population. This means that the associated mutation should be ancient enough to be widespread in the study population. However, genetic variants that withstand the pressure of time often impart small effects on the trait. Moreover, these studies fall victim of multiple testing corrections that are necessary given the large number of variants used in each assay. The threshold for a “genome-wide significance” is set at $p < 5 \times 10^{-8}$. Nonetheless, a number of variants have been identified by GWAS that have provided insight into disease pathogenesis (table 1-5).

The BMI (body mass index) associated loci are over 100 (table 1). The largest GWAS meta-analysis study to date included about 340,000 individuals mainly of European descent. The analysis attributed 2.7% of BMI variation to the 97 identified loci [15**]. Each SNP contributed roughly a 0.1 unit increase in BMI or 0.3 Kg of weight to a 1.7 meters tall individual. In other words, a 29 kg weight increase is expected in an individual that harbors all the 97 at-risk variants. Interestingly, secondary analysis showed that $6.6 \pm 1\%$ of additional BMI variation could be explained by 2,346 SNPs that were associated with obesity but with a $p < 5 \times 10^{-3}$, well below the threshold for GWAS significance. Further directionality analysis estimated that about 1,000 of these SNPs represent true BMI associations. This is in comparison to the $21.6 \pm 2.2\%$ of BMI variance explained by the 1.4 million SNPs in HapMap3.

Of note, some of the obesity-associated loci showed evidence for association with other traits of MetS based on directionality analysis. For instance, FTO and TMEM18 were associated with higher triglycerides (TG), lower HDL, increased fasting insulin, increased blood pressure (BP), and coronary artery disease (CAD). HIP1, MC4R and PRKD1 were associated with higher TG, lower HDL, increased fasting insulin, and CAD. FOXO3 was associated with higher TG, lower HDL, increased blood pressure (BP), and CAD. Finally, data-driven expression-prioritized integration of complex traits (DEPICT) analysis showed that of the 31 tissue types enriched with the obesity associated genes, 27 were in the central nervous system and in dynamic pathways related to synaptic plasticity and glutamate signaling, which confirms the role of neurohormonal regulation and behavior in the pathogenesis of obesity [15**].

One of the strong and reproducible GWAS BMI-associated signals is in the FTO gene (fat mass and obesity associated gene), which encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Latest follow up mechanistic studies showed that the pathogenic alleles repress mitochondrial thermogenesis in adipocyte precursor cells and shift their differentiation from beige (energy dissipating cells) to white (energy storing) adipocytes [16**]. The ARID5B-IRX3-IRX5 pathway mediates this process.

Another recent GWAS included about 224,500 individuals mainly of European descent in a study of the adipose tissue distribution as measured by the BMI-adjusted waist-to-hip ratio (WHR) [17**]. Out of the 49 loci identified, 20 had significant sexual dimorphism and the majority had stronger effects in women. It is worth mentioning the loci that were significantly associated with multiple MetS traits. The GRB14-COBLL1 locus was associated with increased TG, decreased HDL, increased fasting insulin, T2DM, and increased LDL. The MAP3K1, VEGFA and CCDC92 loci were associated with increased TG and decreased HDL. The CCDC92 locus was associated with decreased BMI-adjusted-adiponectin levels (BAA). The PPARG locus was associated with increased TG and LDL. CMIP was associated with decreased HDL and BAA [17**].

In a meta-analysis of GWAS for dyslipidemias in over 188,000 people, 69 microRNAs were identified in genomic regions in proximity to identified SNPs. Further analysis for predicted miRNAs targets identified 4 miRNAs with links to cardiometabolic traits; miR-128-1, miR-148a, miR-130b and miR-301b. In vitro and in vivo studies showed that the latter two

miRNA influence lipid trafficking via modulating the expression of low-density lipoprotein (LDL) receptor (LDLR) and ATP-binding cassette A1 cholesterol transporter (ABCA1) [18]. The study, however, did not examine the allele specific effects of the associated SNPs on miRNAs' expression and function. Nonetheless, the findings are quite intriguing and prompt further studies to examine the association of miRNAs with metabolic traits.

In an interesting application of genetic risk scores using 19 variants associated with insulin resistance from prior GWAS studies, patients with more than 17 at-risk alleles were at significantly increased risk for T2DM, CAD, and HTN compared to those with less than 9 at-risk alleles. Analysis of genetic risk scores revealed that 11 variants out of the 19 were associated with a metabolic profile consistent with MetS; higher TG, lower HDL, greater hepatic steatosis, and lower adiponectin. Moreover, these variants were associated with lower BMI and increased visceral-to-subcutaneous adipose tissue ratio, which is consistent with a subtle form of lipodystrophy [19*].

Lastly, some of the BMI-associated loci negatively correlate with other elements of the MetS. For instance, HHIP is associated with lower risk of T2DM and with increased levels of HDL. Similarly, IRS1 is associated with lower levels of TG, higher levels of HDL, lower fasting insulin levels, and decreased CAD risk; all opposite to what would be expected with MetS [15**]. These findings echo prior observations that obesity doesn't necessarily cause metabolic abnormalities, as one third of obese subjects have normal metabolic profile and harbor no CVD risk [20]. On the other hand, up to 45% of normal weight subjects harbor other metabolic abnormalities placing them at higher risk for CVD and T2DM [21].

4. Monogenic causes of Metabolic Syndrome

Studying monogenic forms of MetS and its form fruste partial lipodystrophies has resulted in identification of factors that underly the association of diverse metabolic traits.

4.1. Hereditary lipodystrophies

Hereditary lipodystrophies are characterized by metabolic traits similar to MetS, except for major differences in the amount and distribution of adipose tissue and decreased leptin levels. These rare disorders include early onset congenital generalized lipodystrophy (CGL) and progeroid syndrome as well as adult onset familial partial lipodystrophies (FPLD) and mandibuloacral dysplasia.

CGL has been associated with mutations in AGPAT2, BSCL2, CAV1, PTRF, and PPARG, which are mainly involved in lipid droplet formation and the biosynthesis of triglycerides and phospholipids [22].

FPLD is the closest disorder to MetS. To date mutations in nine different genes have been associated with FPLD. The autosomal dominant form of FPLD results from mutations in LMNA, PPARG, AKT2, and PLIN1. The autosomal recessive form involves mutations in CIDEC, LIPE, WRN, PCYT1A, and ZMPSTE24 genes [23; 24; 25].

4.2. Wnt and low-density lipoprotein receptor-related protein 6 (LRP6)

MetS has been associated with mutations in the highly conserved Wnt-LRP6 pathway that plays a pivotal role in embryonic development and nutrient sensing. The canonical Wnt pathway is activated via Frizzled family receptors and LRP5/6 co-receptors. Both canonical and non-canonical pathways inhibit mesenchymal stem cell differentiation into adipocytes via repressing PPARG [26; 27]. Several other lines of evidence indicate the importance of Wnt signaling in regulating body weight and food intake as it is expressed in the hypothalamus. Moreover, Wnt ligands and their LRP6 co-receptor are downregulated in NPY neurons in the arcuate nucleus of leptin deficient mice [28]. LRP6 mutations such as R611C, R473Q, R360H, and N433S are associated with autosomal dominant MetS and early onset CAD [29]. Some of these mutations reduce the canonical Wnt function by up to 40% [29]. The role of LRP6 in regulation of plasma lipids was investigated, as it is a member of the LDLR family. Studies of skin fibroblasts in LRP6^{R611C} mutation carriers showed reduced LDL uptake attributed to interference with LDLR internalization and clathrin mediated LDL uptake [30]. Mouse studies implicated LRP6 in regulating LDL synthesis, de novo lipogenesis, and VLDL secretion [31]. Finally, mice with LRP6^{R611C} mutation develop coronary artery disease caused by excessive proliferation of undifferentiated vascular smooth muscle cells. This is triggered by excess activity of growth factors due to the lack of TCF7L2 inhibition of Sp-1 [32]. This variant of CAD phenocopies an entity known as plaque erosion and is linked to increased activity of noncanonical Wnt signalling. Mutations in LRP6 have also been associated with non-alcoholic steatohepatitis (NASH). Studies of mouse models have linked activation of noncanonical Wnt and downstream TGF pathway to liver fibrosis and inflammation.

Subjects with LRP6 mutations have reduced insulin receptor (IR) expression and are insulin resistant [33]. LRP6 transcriptional regulation of IR is important for adipogenic transformation of 3T3L1 cells [34] and for preferential glucose uptake in a drosophila model of insulin resistance [35]. Reduced IR expression can be rescued by either TCF7L2 overexpression or high doses of Wnt3a [Figure 1]. Insulin resistance in LRP6^{R611C} mutation carriers is also accounted for by activation of mTORC1 pathway and serine phosphorylation of IRS1 at multiple residues.

4.3. Dyrk1B a novel gene for metabolic syndrome

We recently discovered a gain of function mutation in Dyrk1B that results in autosomal dominant MetS with early onset CAD. Early mechanistic studies of the R102C mutation suggested increased adipocyte differentiation of precursor cells and increased transcription of glucose-6-phosphatase, the rate-limiting enzyme of gluconeogenesis [36**]. Dual specificity tyrosine-regulated kinase (Dyrk) family has been implicated in nutrient sensing. Dyrk kinases regulate GSK3B's phosphorylation of NFAT and FOXO1 transcription factors, thereby influencing pancreatic function, skeletal muscle development, glucose, and insulin homeostasis [37].

Dyrk1B is positively regulated at the transcriptional level by Rho GTPase-Rac 1, and negatively regulated by RAS-MEK-ERK. Interestingly, loss of function mutations in the latter inhibitory pathway is linked to obesity and insulin resistance in humans [38]. Targets

of Dyrk1B include FOXO1, SIRT1/2, HIF1a, and glycogen synthase all of which are involved in glucose homeostasis [39]. Dyrk1A promotes food intake via direct phosphorylation and activation of SIRT1, which in return deacetylates and activates FOXO. FOXO increases the expression of NPY thus promoting food intake [40]. Moreover, Dyrk1A and 1B are highly expressed in the arcuate nucleus, olfactory bulb and hippocampus. This suggests that Dyrk1B may play an important role in appetite regulation. NPY is also postulated to increase Dyrk1B expression via the PKA-CREB pathway, as Dyrk1B has a CREB motif in its promoter region [41].

Additionally, Dyrk1B has been shown to influence cell cycle activity by increasing the turnover of p27^{kip} (CDKN1B) [42]. Interestingly, mice deficient in p27 develop atherosclerosis, obesity and insulin resistance whereas those overexpressing p27 are protected against atherosclerosis [43].

Conclusion

With the advent of modern molecular genetics different approaches have been used to identify the genetic causes of MetS. Most progress has been made in identification of common variants that increase the risk for one or two metabolic risk factors. Study of larger and more homogenous populations is necessary to identify variants that underlie the association of the diverse metabolic traits of this syndrome. Genetic studies of outlier kindreds with extreme forms of MetS have led to identification of variants with large effects. The advantage of this approach is in the effect size of the variants and the potential in characterizing their functional effects in vitro and in vivo. Many of these variants such as Dyrk1B are potential targets for development of novel drugs against this syndrome.

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Key points

1. Metabolic syndrome is a combination of heritable cardio-metabolic abnormalities that tend to cluster together and significantly increase the risk of cardiovascular events.
2. Only a few genes with large effects have been discovered that can explain the association of diverse traits in this syndrome
3. Study of homogenous populations at the extreme ends of quantitative distribution is necessary to identify variants that underlie the association of the diverse metabolic traits of this syndrome.
4. Elucidating the genetics of MetS can lead to pharmacotherapies that improve all the metabolic profiles in patients with this syndrome.

Figure 1.

Schematic of Wnt mediated regulation of lipid metabolism, glucose metabolism and vascular smooth muscle differentiation via the canonical and noncanonical pathways. LDL: low density lipoprotein, TG: triglycerides, IR: insulin receptor, VSMC: vascular smooth muscle cell, and FZD: frizzled receptor.

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Table 1

Obesity associated genes based on genome wide association studies.

Chr ¹	Genes ²
1	DNM3/PIGC GORAB PTBP2 ELAVL4 FUBP1 USP33 FPGT TNNI3K GNAT2 AMPD2 NEGR1 LYPLAL1 TBX15-WARS2 NAV1 SLC30A10 SEC16B AGBL4 DCST2 TAL1
2	LINC01122 NCOA1 SH2B1 GRB14-COBL1 KCNK3 EHBPI TMEM18 MEIS1 FIGN

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Chr ¹	Genes ²
3	UBE2E3
	CALCRL
	CREB1
	KLF7
	LRP1B
	IRS1; PLCD4
	CYP27A1
	USP37
	TTL14
	STK36; ZNF142
	RQCD1
	POMC/ADCY3
	ERBB4
	FANCL
	PLXND1
	CADM2
	ETV5
	RASA2
	LEKR1
	PPARG
	PBRM1c
4	FHIT
	ADAMTS9
	GBE1
	NISCH/STAB1
	RARB
	MRPS22
	GNPDA2
	GABRG1
	HHIP
	NT5C2

Chr ¹	Genes ²
10	CYP17A1 SFXN2 HIF1AN GRID1 TCF7L2 BDNF MTCH2 MACROD1 VEGFB CADM1 HSD17B12 TRIM66 TUB
11	RPL27A
12	ITPR2-SSPN CLIP1 HOXC13 HECTD4 CCDC92 BCDIN3D FAIM2 MTIF3 GTF3A OLFM4 MIR548A2 SPRY2 MIR548X2 PCDH9 SLC39A8 NUP54 SCARB2
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Chr ¹	Genes ²
5	SPATA5-FGF2
	NMU
	FAM13A
	TNFAIP8
	HSD17B4
	POC5
	HMGCR
	COL4A3BP
	PCSK1
	ZNF608
	FGFR4
	CPEB4
	GALNT10
	MAP3K1
6	LY86
	PARK2
	IFNGR1
	OLIG3
	VEGFA
	HMGAI
	RSPO3
	TDRG1
	LRFN2
	SNRPC
7	NUDT3
	CDKAL1
	TFAP2B
	BTNL2
	MIR3144
	FOXO3
	NFE2L3

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Chr ¹	Genes ²
8	HIP1
	PMS2L3
	PMS2P5
	WBSCR16
	SNX10
	PMS2L11
	ASB4
	HOXA11
	CALCR
	HSA-miR-653
9	MSC
	ZBTB10
	HNF4G
	RALYL
	MSRA
	NKX2-6
	LMX1B
	LINGO2
	ABCA1
	KLF9
14	PAX5
	TLR4
	CCDC171
	EPB41L4B
	STXBP6
15	NRXN3
	PRKD1
	SMAD6
	LBXCOR1
	SCG3
	DMXL2

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Chr ¹	Genes ²
16	BBS4
	ADPGK-AS1
	RFX7
	KLF13
	FTO
	GPRC5B
	IQCK
	GP2; CBLN1
	CMIP
	SBK1; APOBR
	ATXN2L
	SULT1A2; TUFM
	MAPK3
	KCTD13
	INO80E
	TAOK2
17	YPEL3
	SH2B1
	NLRC3
	KAT8; ZNF646
	VKORC1
	ZNF668
	STX1B
	FBXL19
	RABEP1
	RPTOR
18	PEMT
	KCNJ2
	SMG6
	BCL2
	MC4R

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Chr ¹	Genes ²
19	NPC1
	RIT2
	GRP
	KCTD15
	GIPR
	QPCTL
	JUND
	GDF15
	PGPEP1
	TOMM40
	APOE
	APOC1
	ZC3H4
20	CEBPA
	GDF5
	EYA2
	ZFP64
	BMP2
21	ETS2
22	ZNRF3
KREMEN1	

¹Chromosome number

²Nearest genes to loci identified in association with BMI, or waist-to-hip ratio as markers of obesity

Table 2

Blood pressure associated genes based on genome wide association studies

Chr ¹	Genes ²
1p	CASZ1
	MTHFR
	CAPZA1
	MOV10
2q	FIGN
3p	SLC4A7
	ULK4
	MAP4
3q	MECOM
4q	CHIC2
	FGF5
	SLC39A8
	ENPEP
	GUCY1A3
5p	NPR3
5q	EBF1
6p	HFE
	HIST1H1T
	BAG6
7q	PIK3CG
	NOS3
8q	NOV
10p	CACNB2
10q	PLCE1
	CYP17A1
	NT5C2
	ADRB1
11p	ADM

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Chr ¹	Genes ²
11q	PLEKHA7
	ARHGAP42
	ADAMTS8
12q	POC1B
	ATP2B1
	SH2B3
	ATXN2
	ALDH2
	NAA25
	HECTD4
15q	TBX3
	CSK
	ULK3
	FES
	ACBD4
17q	WNT3
	GOSR2
18p	ZNF652
	c18orf1
	JAG1
	ZNF831
Chromosome number	

²Nearest genes to loci identified in association with blood pressure

Table 3

Insulin resistance associated loci based on genome wide association studies

Chr ¹	Genes ²
1p	NOTCH2 ADAM30 SLC44A3
1q	PCNXL2 CR2 F3
2p	BCL11A THADA
2q	IRS1 GRB14 G6PC2-ABCB11 RBM43 RND3 RBMS1 ITGB6 SYN2 PPARG ADAMTS9 PSMD6
3q	ST6GAL1 ZPLD1 PLS1 IGF2BP2 PEX5L WFS1 PPP2R2C MAEA CETN3

Chr	Genes
6p	ZBED3
	KCNK16
	CDKAL1
	ZFAND3
	VEGFA
7p	DGKB
	AGMO
	GCC1
	JAZF1
7q	PAX4
	ACHE
	KLF14
	SLC30A8
8q	TP53INP1
	PTPRD
	CDKN2A
	CDKN2B
9p	GLIS3
	CHCHD2P9
	CDC123
	CAMK1D
10p	TCERG1L
	PANK1
	HHEX
	VPS26A
10q	KIF11
	TCF7L2
	KCNQ1
	GALNTI8
11p	KCNJ11
	MTNR1B

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Chr ¹	Genes ²
	ARAP1
	TMEM45B
	BARX2
12q	DCD
	HMG A2
	HNF1A
	TSPAN8
	LGR5
13q	SPRY2
14q	C14orf70
15q	ZFAND6
	C2CD4B
	AP3S2
	C2CD4A
	C2CD4B
	HMG20A
	PRC1
16q	CMIP
	WWOX
	FTO
17p	SRR
17q	HNF1B
18p	LPIN2
19q	PEPD
	ACP7
20q	HNF4A
21q	HUNK
Xq	DUSP9

¹Chromosome number

²Nearest genes to loci identified in association with insulin resistance

Table 4

Hypertriglyceridemia associated loci based on GWAS studies

Chr ¹	Nearest genes ²	Gene name
1p	ANGPTL3	Angiotensin- like 3
	DOCK7	Dedicator of cytokinesis 7
	ATG4C	Autophagy related 4C, cysteine peptidase
1q	GALNT2	Polypeptide N-acetylgalactosaminyltransferase 2
2p	GCKR	Glucokinase (hexokinase 4) regulator
7q	APOB	Apolipoprotein B
	BAZ1B	Bromodomain adjacent to zinc finger domain 1B
	BCL7B	B-cell CLL/lymphoma 7B
	TBL2	Transducin (beta)-like 2; MLX interacting protein-like
8p	MLXIPL	
	LPL/SLC18A1	Lipoprotein lipase; Solute carrier family 18A1
	XKR6	XK Kell blood group complex subunit-related 6
	SLC35G5	Solute carrier family 35, member G5
11q	TRIB1	Tribbles pseudokinase 1
	FADS1-FADS2-FADS3	Fatty acid desaturase 1, 2 and 3
	APOA1-C3-A4-A5	Apolipoprotein A1-C3-A4-A5
	ZNF259, BUD13	Zinc finger protein 259; BUD13 homolog
15q	RASGRP1	RAS guanyl releasing protein 1
19p	NCAN, SUGP1	Neurocan; SURP and G patch domain containing 1
19q	CILP2	Cartilage intermediate layer protein 2
	PBX4	Pre-B-cell leukemia homeobox 4
	TOMM40	Translocase of outer mitochondrial membrane 40 homolog;
	APOE-C1-C2	Apolipoprotein E; Apolipoprotein C-I
20q	PLTP	Phospholipid transfer protein

¹Chromosome number

²Nearest genes to hypertriglyceridemia associated loci

Table 5

Genes associated with blood high density lipoprotein levels based on genome wide association studies

Chr ¹	Nearest genes ²	Gene name
1q	GALNT2	Polypeptide N-acetylgalactosaminyl transferase 2
2p	APOB	Apolipoprotein B
8p	LPL, SLC18A1	Lipoprotein lipase, solute carrier family 18A1
9p	TTC39B	Tetratricopeptide repeat domain 39B
9q	GRIN3A	Glutamate receptor ionotropic N-methyl-D-aspartate 3A
	PPP3R2	Protein phosphatase 3 regulatory subunit B beta
	ABCA1	ATP-binding cassette, sub-family A (ABCI)
11p	MADD	MAP-Kinase activating death domain
	NR1H3	Nuclear receptor subfamily 1 group H member 3
11q	FADS1-FADS2-FADS3	Fatty acid desaturase 1, 2 and 3
	APOA1-C3-A4-A5, ZNF259	Apolipoprotein A1-C3-A4-A5; Zinc finger protein 259;
	BUD13	BUD13 homolog
15q	LIPC	Lipase hepatic
16q	CETP	Cholesteryl ester transfer protein, plasma
	LCAT	Lecithin-cholesterol acyltransferase
	CTCF	CCCTC-binding factor (zinc finger protein)
17p	METTL16	Methyltransferase like 16;
	PAFAH1B1	Platelet-activating factor acetylhydrolase 1b, regulatory subunit 1
18q	LIPG, ACAA2	Lipase endothelial; Acetyl-CoA acyltransferase 2
19p	ANGPTL4	Angiotensin-like 4
20q	HNF4A	Hepatocyte nuclear factor 4, alpha
	PLTP	Phospholipid transfer protein

¹Chromosome number

²Genes nearest to identified loci that are associated with high density lipoprotein (HDL) levels in the blood