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REVIEW

Recent Updates on the Role of Genetic and Epigenetic Factors in the Pathogenesis of the Metabolic Syndrome

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Background: Metabolic syndrome (MetS) is a multifactorial disorder characterized by obesity, hypertension, dyslipidemia, and diabetes, all of which contribute to the global burden of cardiovascular diseases. Growing evidence highlights the interplay between genetic predisposition and epigenetic modifications in shaping susceptibility to MetS and its complications.

Scope of Review: This systematic review analyzed 55 relevant studies published in the last decade, exploring genetic polymorphisms, DNA methylation, and non-coding RNAs (ncRNAs) associated with MetS.

Result and Conclusion: Our findings reveal that MetS arises from the convergence of inherited genomic risk and environmentally driven epigenetic reprogramming in the forms of DNA methylation changes and ncRNAs involvement, which affect important genes related to crucial biological functions such as neuroendocrine, adipogenesis and insulin signaling, glucose and lipid metabolism, and immune response and inflammatory signaling. Understanding these interactions may facilitate the development of predictive biomarkers and targeted interventions to mitigate cardiometabolic risks.

Keywords: DNA methylation, epigenetics, genetics, metabolic syndrome, non-coding RNAs

Introduction

Metabolic syndrome (MetS) refers to a collection of metabolic disorders that represent a global health challenge and contribute substantially to high socioeconomic burdens. It is characterized by a combination of factors that elevate the risk of metabolic-related conditions, including cardiovascular diseases (CVD) such as coronary artery disease (CAD), obesity, high blood pressure, and diabetes mellitus (DM).[1,2] According to World Health Organization (WHO), an estimated 17.9 million people died from CVDs in 2019, accounting for 32% of all global deaths, most of which were due to CAD.[3] In Indonesia, the Basic Health Research (In Indonesian: *Riset Kesehatan Dasar, Riskesdas*) survey revealed the rising prevalence of cardiovascular conditions, with hypertension increasing from 25.8% in 2013 to 34.1% in 2018, and the prevalence of coronary heart disease reached 1.5%, with a case fatality rate of 14.4%.[4]

The genetic basis of MetS involves several chromosomal loci, numerous polymorphisms, and various genetic variants either as independent traits or as entities primarily related to metabolic processes. Consequently, inherited deoxyribose nucleic acid (DNA) variants play a significant role in conferring disease risk.[5] Although several MetS-genetic association studies have

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been conducted,[6] the results remain unclear, with only about 13 studies showing positive associations. Positive associations of MetS with common Apolipoprotein C3 (*APOC3*) single-nucleotide polymorphisms (SNPs) (T–455C and C–482T) have been demonstrated in an urban Chennai population in South India, where CVD prevalence linked to MetS is high.[7] Similarly, it has been revealed that *APOC3* gene polymorphisms were associated with lipoprotein levels and blood pressure in 515 adults and 115 adolescents.[8] It has also been reported that a specific haplotype of Peroxisome Proliferator-activated Receptor Gamma (*PPARG*) polymorphisms was associated with an increased risk of MetS in 279 adults with MetS in France.[9] Moreover, minor alleles of genes such as Fat Mass and Obesity-associated (*FTO*), Transcription Factor 7 Like 2 (*TCF7L2*), Apolipoprotein A5 (*APOA5*), and Apolipoprotein C-III (*APOC3*) were more commonly observed in certain MetS populations.[10]

Numerous studies have demonstrated that epigenetic factors play a significant role in MetS development. Epigenetics, often a reflection of lifestyle imbalances, profoundly impacts health outcomes. Historical evidence, such as the Dutch Winter Famine, provides compelling insight into the role of early-life nutritional deprivation. Analysis of children born during the famine in November 1944 showed an increased susceptibility to metabolic disorders in later generations.[11] A comparative study in rats with hypertension found no difference in Angiotensin type 1A receptors (AT1aR) messenger RNA (mRNA) and protein expression between hypertensive and non-hypertensive rats at 4 weeks of age. However, AT1aR expression was significantly higher in hypertensive rats by 20 weeks. Bisulfite sequencing analysis revealed progressive hypomethylation of the AT1aR promoter in the aorta and mesenteric arteries of hypertensive rats with age. This hypomethylation correlated with increased gene expression, indicating the role of epigenetic changes in hypertension as part of MetS.[12] Another study found that epigenetic alterations, particularly hypermethylation, significantly influenced MetS progression. Hypermethylation of genes such as Monocarboxylate Transporter 3 (*MCT3*), Polypeptide N-acetylgalactosaminyltransferase 2 (*GALNT2*), 3-Hydroxy-3-Methylglutaryl-CoA Reductase (*HMGCR*), cGMP-dependent Protein Kinase (*CGK*), Endothelial Nitric Oxide Synthase (*eNOS3*), Low-Density Lipoprotein Receptor (*LDLR*), and Interleukin-6 (*IL6*) is associated with an elevated risk of CAD. Hypomethylation of the *PPARG* gene has been demonstrated in individuals with MetS, particularly obesity, leading to increased gene expression, whereas hypermethylation of this gene was linked to enhanced insulin sensitivity, reduced plasma triglycerides, decreased atherogenic inflammation, and weight loss.[13,14] Histone modifications, another key epigenetic mechanism, have also been linked to MetS. Significant differences in histone modifications between healthy blood vessels and vessels at various stages of atherosclerosis have been revealed, highlighting their role in MetS-related conditions.[15]

Additionally, non-coding RNAs (ncRNAs), which are not translated into proteins but regulate various cellular mechanisms, have been implicated in MetS. Among these, microRNAs (miRNAs) have been shown to influence adipogenesis-related genes like *PPARG*. It has been confirmed that miRNAs target signaling factors such as Mitogen-activated protein kinase kinase 5 (MAP2K5) and Extracellular Signal-Regulated Kinase 5 (ERK5), which is encoded by the Mitogen-Activated Protein Kinase 7 (*MAPK7*) gene. These signaling pathways regulate *PPARG* expression and adipogenesis, affecting obesity.[16] Similarly, miRNA families, such as miR-19, miR-19a, and miR-19b, have been identified as key players in adipogenesis, lipid accumulation, and adipose tissue expansion in obesity. Also, miR-19a and miR-19b levels increased alongside reduced *PPARG* mRNA expression in subcutaneous abdominal adipose tissue of patients with morbid obesity.[17]

Despite significant progress, the precise roles of genetics and epigenetics in the changes of cellular biological functions, especially those related to metabolic dysregulation, in metabolic syndrome remain unclear. Therefore, further research is needed to explore how epigenetic modifications and genetic factors influence the development of MetS. This is crucial due to the significant impact they have on the progression of non-communicable diseases, which are major causes of mortality.[6,18] This review aims to systematically analyze studies related to the roles of genetics and epigenetics in the MetS, including its associations with CAD, obesity, hypertension, and DM.

Materials and Methods

Article Sources and Search Strategy

A comprehensive literature search was conducted in five databases, including PubMed, ProQuest, EBSCOHost, Scopus, and Sage Journals, utilizing the keywords: "genetic" AND "epigenetic" OR "epigenomic" AND "metabolic syndrome" up to April 2024. The search was restricted to articles published within the last 10 years, studies written in English, and original

research papers by applying appropriate filters, yielding a total of 1,805 articles. The article selection process is illustrated in the PRISMA chart below (Figure 1).

Eligibility Criteria

The inclusion criteria encompassed original research articles investigating the genetic outcomes, including SNPs, polymorphisms, Genome-Wide Association Study (GWAS) loci, and genotyping, and/or epigenetic outcome, including DNA methylation, miRNA expression, and other epigenetic modifications associated with MetS. Eligible articles were those involving human studies and published in English within the past decade. No restrictions were placed on age, sex, ethnicity, country, or study design.

A total of 1,805 records were initially identified through database searching. Following the exclusion of 30 duplicate articles, 1,775 articles were subjected to screening. Of these, 1,514 were excluded based on title and abstract screening due to a lack of relevance to genetic or epigenetic outcomes associated with MetS and 58 were excluded due to inaccessibility for full-text articles. Reports were considered inaccessible when full texts could not be obtained despite institutional access and manual search efforts. Consequently, 203 studies were evaluated, of which 36 were excluded for

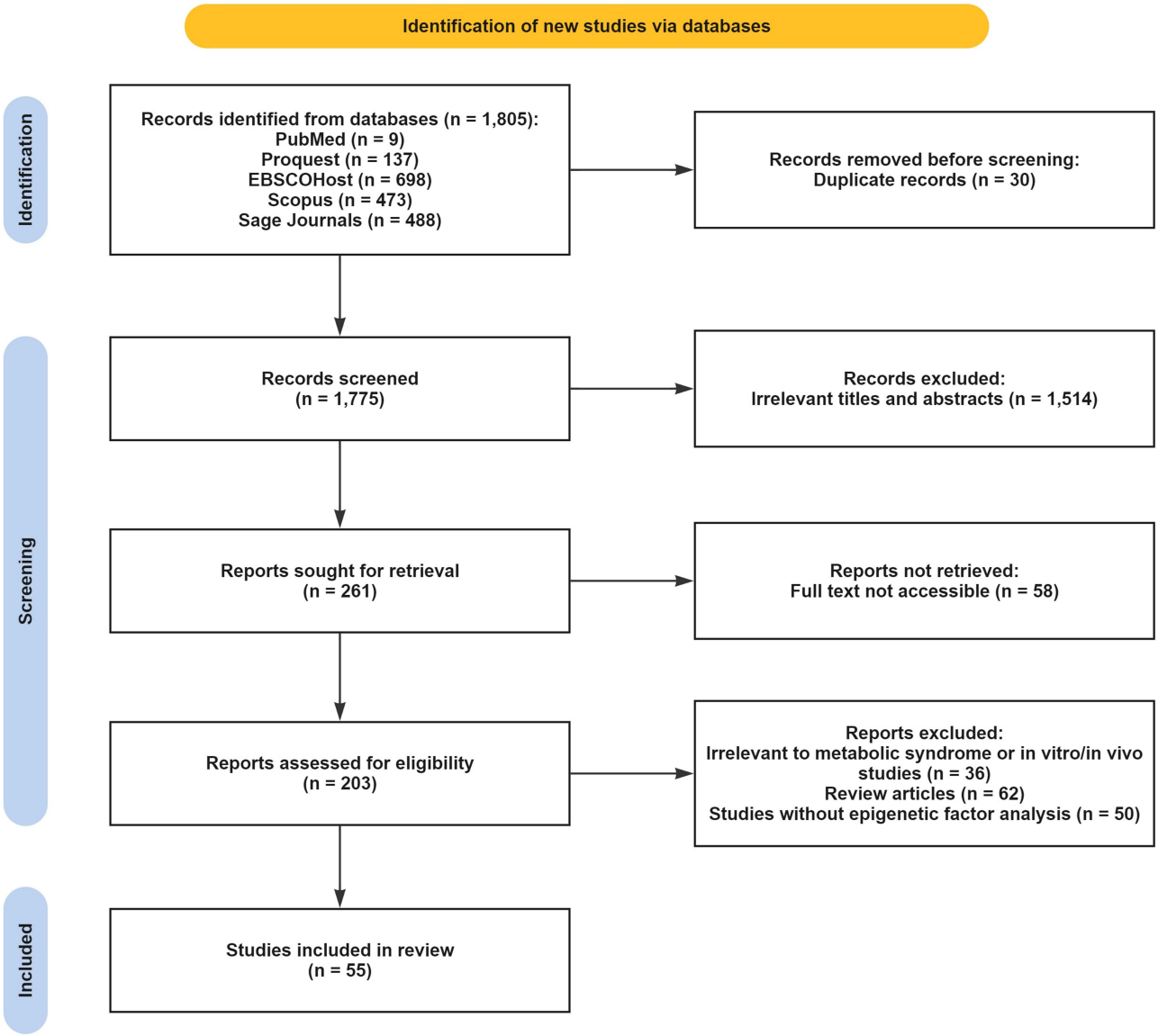

Figure 1 Study flowchart.

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not being related to metabolic syndrome or for being in vitro and in vivo studies, 62 were review articles, and 50 articles did not provide epigenetic outcomes. Finally, 55 articles were included in this review (Figure 1).

Data Extraction

The following data were extracted from the articles reviewed: author names, year of publication, study design, country, sample size, mean or median age, type of population and inclusion criteria, type and duration of intervention, characteristics of control, sample, method, and outcome (Table 1).

Results

The literature search retrieved 1,805 articles (n=9 PubMed, n=137 ProQuest, n=698 EBSCOHost, n=473 Scopus, and n=488 Sage Journals) of which 55 articles discussed the genetic and epigenetic associations with MetS (Figure 1 and Table 1). All eligible articles indicating a correlation between genetic and epigenetic factors with MetS were those involving human studies and published in English within the past decade.

Genetic Variants/SNPs

Regarding the relationship between genetics and metabolic syndrome, a study on 692 MetS patients and 878 healthy controls in Northern China investigated the association of methylenetetrahydrofolate (*MTHFR*) C677T and methionine synthase reductase (*MTRR*) A66G polymorphisms with MetS, showing that the *MTHFR* 677T allele was linked to increased MetS risk, including high fasting blood glucose and large waist circumference. The *MTRR* A66G polymorphism alone was not linked to MetS, but significantly increased MetS risk when combined with *MTHFR* 677T. The *MTRR* 66GG genotype also heightened susceptibility to MetS when paired with *MTHFR* 677T.[19] Genetic effects on weight and metabolic changes in 7,998 participants from Nord-Trøndelag County, Norway, who were part of both HUNT2 (1995–1997) and HUNT3 (2006–2008) surveys, were investigated by genotyping, revealing that the dopamine receptor D2 (*DRD2*) gene influenced weight gain, particularly the transition from normal weight to overweight/obesity in adults.[20] The fat mass and obesity-associated gene (*FTO*) gene was linked to weight gain from adolescence to early adulthood, while zinc finger protein 259/apolipoprotein A (ZNF259/APOA) significantly impacted long-term triglyceride development. These findings highlight the genetic factors underlying obesity and metabolic disorders over time.

Koochakpoor et al explored the interaction between melanocortin-4 receptor (*MC4R*) polymorphisms and dietary factors in the risk of MetS in 1,630 participants from the Tehran Lipid and Glucose Study.[21] The authors reported that individuals with the A allele of *MC4R* had a higher MetS risk when they consumed a western diet with a high saturated fat intake (P trend = 0.007). Interactions between *MC4R* variants and fat and iron intake were also observed for abdominal obesity (P interaction < 0.05), highlighting the combined influence of genetics and diet on MetS risk.

A 2017 study on 140 women aged 16–35 years investigated interleukin-1 beta (IL-1β), interleukin-1 receptor antagonist (IL-1Ra), and fatty acid-binding protein 1 (*FABP1*) gene polymorphisms in polycystic ovarian syndrome (PCOS), showing that while there was no direct association with PCOS, these polymorphisms influenced key biochemical and metabolic parameters in affected women.[22] A cross-sectional study examining the association between candidate gene polymorphisms and excess weight in 1,005 Colombian adolescents (aged 10–18) found that AGT-rs699 and FTO-rs17817449 variants increased the risk of excess weight and a higher body mass index (BMI), while IRS2-rs1805097 had a protective effect.[23] Additionally, UCP3-rs1800849 was linked to reduced waist circumference, suggesting that genetic polymorphisms influence adiposity and metabolic health in adolescents. A case-control study of the association between the *FTO* gene polymorphism (rs9939609) and MetS in Egyptian women demonstrated that the rs9939609 polymorphism in the *FTO* gene is a genetic risk factor for MetS, potentially affecting high-density lipoprotein cholesterol (HDL-C). The findings highlight the genetic influence on MetS and suggest further exploration of its relationship with alanine aminotransferase (ALT) levels in other populations.[24]

Multiple studies have explored the role of SNPs in influencing MetS risk factors such as obesity, insulin resistance, lipid metabolism, and hypertension. A study on 1,381 northern urban Han Chinese women investigated the role of genetic variation in the potassium voltage-gated channel, subfamily Q, member 1 (*KCNQ1*) gene in MetS susceptibility, identifying that the rs163182 variant significantly increased the MetS risk, as well as BMI and systolic blood pressure

Table 1 Study Results

Author, Year	Study Design	Country/ Population	Subjects	Sample	Method used for Genetic/Epigenetic Analysis	Gene(s) Analyzed	Biological Function(s) Related with Corresponding Genes	Outcome/Result	Ref.
Yang et al, 2014	Case control	China	692 MetS patients (48.8±10.1 years) vs 878 healthy control (46.5±9.9 years); excluded if prior to MI, stroke, diabetes, cancer, renal, or liver disease.	Blood sample	Genotyping of MTHFR C677T and MTRR A66G variants.	MTHFRC677; MTRR A66G	Protein metabolism	MTHFR 677T allele was associated with higher risk of MetS, elevated FBG, and increased WC. MTRR A66G polymorphism increased the risk of MetS only when present with the MTHFR 677T genotype.	[19]
Kvaloy et al, 2015	Longitudinal study	Norway	3999 adults who were enrolled in both the HUNT2 and HUNT3 surveys. The mean age in HUNT2 was 37.38±6.0 years for male and 33.98±5.3 years for females, increasing to 48.5±5.9 years for male and 45.16±5.3 years for female	Blood	Genotyping was conducted using the MassARRAY iPlex system on the Sequenom platform	DRD2; FTO	Eating behavior	DRD2 is associated with weight gain in adults, while FTO affects weight gain from adolescence to early adulthood. ZNF259/APOA strongly influences long term TG levels.	[20]
Koochakpoor et al, 2016	Case control	Iran	1630 participants with and without MetS.	Blood sample	Genotyping was performed by Tetra-Primer ARMS-PCR	MC4R	Energy metabolism; Eating behavior; Adipogenesis	Carriers of the MC4R A allele with high western diet and saturated fat intake had a greater risk for Mets. Saturated fat also influenced the link between the MC4R A allele and MetS. An interaction was found between rs12970134 and fat as well as iron intake affecting abdominal obesity risk.	[21]
Rashid et al, 2017	Case control	India	140 women aged 16–35, diagnosed with PCOS.	Blood sample	Polymorphisms were analyzed by PCR, PCR-RFLP and sequencing methods.	FABP1	Lipid metabolism	IL-1β, IL-1Rα, and FABP1 polymorphisms were not linked to PCOS risk but affect biochemical and metabolic traits in PCOS.	[22]
Muñoz et al, 2017	Cross sectional	Colombia	1005 young participants (267 excess weight, 738 normal weight) aged 10–18 randomly selected on MetS diagnostic criteria	Blood sample	Genotyping was conducted by PCR-RFLP	AGT; FTO; IRS2; UCP	Lipid metabolism; Glucose metabolism; Eating behavior	AGT rs699 and FTO rs17817449 linked to a higher BMI/overweight risk; IRS2 rs1805097 exhibit a protective role; UCP3 rs1800849 linked to a lower WC.	[23]
Khella et al, 2017	Case control	Egypt	197 participants with and without MetS	Blood sample	Genotyping done by TaqMan SNP assay.	FTO gene rs9939609	Insulin metabolism	FTO rs9939609 was associated with MetS risk, likely via HDL-C	[24]
Liu et al, 2018	Cohort	China	1381 participants with and without MetS	Blood sample	SNPs selected and genotyped	KCNQ1 gene rs163182	Glucose metabolism; Insulin metabolism	KCNQ1 rs163182 increased MetS risk, BMI, and systolic BP.	[25]

(*Continued*)

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Table 1 (Continued).

Author, Year	Study Design	Country/ Population	Subjects	Sample	Method used for Genetic/Epigenetic Analysis	Gene(s) Analyzed	Biological Function(s) Related with Corresponding Genes	Outcome/Result	Ref.
Tao et al, 2022	Case control	China	690 unrelated adult participants aged 40–65; no hyperlipidemia, hypertension, or family history of diabetes	Blood sample	Genotyping performed using PCR-CTPP	Sirt1; Nrf2	Glucose metabolism; Lipid metabolism; Immune response; Mitochondrial biogenesis; Adipogenesis	Sirt1 rs7895833 linked to higher MetS risk in Chinese Han; associated with increased LDL-C, HOMA-IR, and TG	[26]
Mirzababaei et al, 2018	Cross sectional	Iran	263 adults aged 18–55, non-smokers, non-drinkers	Blood sample	Genotyping by PCR-RFLP	9p21 alleles/CDKN2B genotypes: CC, AC, AA	Adipogenesis	rs1333048 on 9p21 linked to higher MetS risk; high H-ORAC and L-ORAC intake reduced this risk	[27]
Moon et al, 2018	Cohort	Korea	7211 and 2838 genotyped study subjects for discovery and replication, respectively, aged between 40–69.	Blood sample	Multi-SNP-multi-trait analysis	SNP: rs7107152, express SIDT2 and TAGLN	Lipid metabolism; Insulin metabolism	There is a significant association between MetS and rs7107152 and rs1242229 in SIDT2 gene. Both SNPs affect SIDT2 and TAGLN genes expression, which induces insulin secretion and lipid metabolism.	[28]
Udler et al, 2018	Cohort	USA	Initiated with 94 independent T2D genetic variants and 47 diabetes-related traits, then continued in four studies involving individuals with T2DM from: Metabolic Syndrome in Men Study (METSIM), n=487; Ashkenazi, n=509; Partners Biobank, n=2,065; and UK Biobank (UKBB), n=14,813	Cell	Clustering method: Bayesian nonnegative matrix factorization (bNMF). Data analysis: GWAS, epigenomic data analysis, genetic risk scores by cluster, evaluation of clinical impact	Cluster 1: MTNR1B, HHEX, TCF7L2, SLC30A8, HNF1A, and HNF1B. Cluster 2: ARAP1 and SPRY2. Cluster 3: FTO and MC4R. Cluster 4: PPARG, ANKRD55, ARL15, GRB14, IRS1, and LYPLAL1. Cluster 5: GCKR, CILP2/TM6SF2, and PNPLA3.	Insulin metabolism	Cluster 1: Lower insulin secretion and beta cell function measures; higher proinsulin adjusted for fasting insulin. Cluster 2: Reduced insulin secretion and beta cell function; lower proinsulin suggesting a distinct beta cell mechanism. Cluster 3: Higher waist/hip circumference, BMI, and body fat percentage. Cluster 4: Lower insulin sensitivity and adiponectin; higher TG. Cluster 5: Altered serum lipids, linked to non-alcoholic fatty liver disease and liver lipid metabolism.	[29]
Fernández-Rhodes et al, 2018	–	USA	1105 participants with MetS and 995 adults	Methylation and genotypic data	Quantifying the environmental and genetic contributors to the observed heritability and familial correlations using real data made available through the GAW20	CPT1A, SOCS3, ABCG1	Lipid metabolism; Immune response	Heritability of MetS and its four key CpG sites is influenced by both shared environmental factors and genetic variation.	[30]

Nalkiran et al, 2019	Cohort	Turkey	203 women aged 16–40 with ovarian volume >10cm^3	Blood sample	Genotyping by PCR-RFLP	PON1	Lipid metabolism	Q192R polymorphism was significantly associated with PCOS, with the R allele linked to a higher risk. Together with BMI, Q192R may serve as a stronger predictive marker for PCOS and related atherosclerosis	[31]
Kong et al, 2019	Case control	Korea	Female subjects: 2276 MetS cases and 1692 controls	Blood sample	GWAS and GRS. Genotyping using Affymetrix Genome-Wide Human SNP array 5.0, Illumina HumanOmni I-Quad vI array, and Affymetrix Genome-Wide Human SNP array	DSCAM, SIK3	Immune response; Glucose metabolism; Insulin metabolism; Energy metabolism	GWAS identified 14 female-specific genetic signals for MetS, including two genome-wide significant loci: rs455489 (DSCAM, linked to fasting glucose) and rs7115583 (SIK3, linked to HDL-C)	[32]
Chuluun-Erdene et al, 2020	Case control	Mongolia	160 MetS patients aged 18-60	Blood sample after overnight fasting	Genotyping by PCR-RFLP	ADIPOQ, LPL, PGC1α	Glucose metabolism; Lipid metabolism; Immune response; Carbohydrate metabolism; Mitochondrial biogenesis	ADIPOQ +45T>G, LPL PvII, and PGC-1α Gly482Ser variants may increase MetS risk.	[33]
Bojang et al, 2021	Cross sectional	Gambia	136 subjects aged at least 18 years	Blood sample	Genotyping using BigDye Terminator v3.1 Cycle Sequencing Kit.	CDH13	Glucose metabolism; Lipid metabolism	CDH13 rs385618 was significantly associated with MetS. The AT genotype increased MetS risk	[34]
Puspasari et al, 2021	Case control	Indonesia	168 subjects aged 20–66 years diagnosed with MetS	Blood sample buffy-coat solid-phase	Genotyping using PCR-RFLP	NAMPT rs4730153	Glucose metabolism; Lipid metabolism; Immune response; Oxidative stress; Apoptosis induction; Energy metabolism	The rs4730153 GG genotype was most frequent and a risk factor for MetS. In individuals ≤45 years, GA, GG genotypes, and the G allele increased MetS risk, while no significant associations were seen in >45 years	[35]
Zhan et al, 2021	Case control	China	560 participants aged 19–87 years old	Blood sample	DNA Extraction and Estimation of the CNs of AMY1/2A/2B Using ddPCR	AMY1, AMY2A, AMY2B	Glucose metabolism; Energy metabolism	Low amylase activity in young individuals increased risk of metabolic abnormalities, suggesting amylase activity as a potential biomarker for MetS	[36]

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Table 1 (Continued).

Author, Year	Study Design	Country/ Population	Subjects	Sample	Method used for Genetic/Epigenetic Analysis	Gene(s) Analyzed	Biological Function(s) Related with Corresponding Genes	Outcome/Result	Ref.
Wang et al, 2021	Case control	China	106 overweight/obese and 86 healthy (control) children aged 6–14 years	Blood sample	Genotyping	VDR	Vitamin D receptor	The VDR ApaI AA genotype was linked to higher risk of obesity and elevated plasma glucose. VDR ApaI SNP may also affect obesity and glucose metabolism in children	[37]
Abaj et al, 2021	Cross sectional	Iran	404 obese or overweight women aged 18–55 years. No history of smoking and alcohol consumption	Blood sample	Genotyping	CAV1	Glucose metabolism; Lipid metabolism	CAV1 rs3807992 is associated with elevated blood pressure and dyslipidemia.	[38]
Tong et al, 2021	Case control	China	1018 MetS cases and 1029 controls	Blood sample	Genotyping	ANGPTL4	Glucose metabolism; Insulin metabolism; Lipid metabolism	ANGPTL4 SNP rs1044250 is an independent risk factor for MetS through increased WC and BP.	[39]
Fernández-Carrión et al, 2021	Cross sectional	Spain	425 subjects aged 55–75 years with MetS	Blood sample	GWAS	PTPRN2	Glucose metabolism; Insulin metabolism; Lipid metabolism	Minor allele of PTPRN2 was associated with a lower sweet taste preference. T2D subjects shows higher preference for sweet taste but lower overall taste perception.	[40]
Žák et al, 2022	Cross sectional	Czech Republic	166 MetS and 188 control patients	Blood sample	PCR-RFLP and Direct DNA Sequencing	FADS1, FADS2	Glucose metabolism; Lipid metabolism	FADS1 (rs174537, rs174545, rs174546) and FADS2 (rs174570, rs174602) polymorphism along with haplotypes GGGCC and TCACT were significantly associated with two MetS phenotypes. MetS1 showed a more adverse profile with greater WC, insulin resistance, and oxidative stress compared to MetS2	[41]
Zhao et al, 2022	Case control	China	445 MetS cases with 445 controls aged 20–90 years	Blood sample	Real-time PCR technology using TaqMan assays	GC gene	Vitamin D receptor	GC gene polymorphism (rs4588 CA/AA, rs2282679 AC) were inversely associated with MetS risk (lower TG and higher HDL-C)	[42]
Carrasco-Luna et al, 2023	Cross sectional and analytical study	Spain	178 children diagnosed of comorbidities in the context of obesity	Blood sample	Genotyping and allelic discrimination, RT-qPCR	MC4R	Adipogenesis; Energy metabolism; Eating behavior	Carrying minor C allele in MC4R variants (rs17782313, rs17773430, rs34114122) is linked to a higher obesity risk and altered carbohydrate metabolism, highlighting MC4R role in genetic predisposition to obesity, even in childhood.	[43]

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Kim et al, 2023	Cohort	Republic of Korea	15,869 male and 31,693 female aged 41-85	Genomic DNA samples	Genotyping, GWAS, and GRS calculation	APOA5	Lipid metabolism	Sex-specific SNPs (rs662799 in male, rs651821 in female) influences dyslipidemia risk which is modified by diet. Carriers of minor alleles and those with higher GRS showed increased risk, with elevated LDL-C and TG	[44]
Kolb et al, 2023	Case control	Brazil	112 MetS and 237 healthy subjects	Blood sample	Genotyping, pyrosequencing, RT-qPCR	NR3C1	Glucose metabolism; Lipid metabolism; Immune response; Apoptosis induction; Adipogenesis; Protein metabolism	NR3C1 polymorphisms (rs10482605*C homozygosity and TTCGTTGATT/CCT haplotypes) were linked to higher MetS risk, most likely via HPA axis dysregulation.	[45]
Andrzejczak et al, 2023	Case control	Polandia	95 adult diagnosed with MetS	Blood sample	NGS	UCP1	Energy metabolism; Oxidative stress	12 novel UCP1 variants were identified. Only rs3811787 had been previously studied. These variants may be associated with MetS and T2D risk	[46]
Zhao et al, 2023	Case control	China	590 NAFLD patients and 463 controls aged 66.75–75	Blood sample	Genotyping	SAMM50 gene: rs2073082 G and rs738491 T alleles	Mitochondrial biogenesis; Lipid metabolism	SAMM50 variants rs2073082 G and rs738491 T increased NAFLD risk. rs738491 T and rs3761472 G linked to higher liver stiffness. Combined, the three SNPs doubled NAFLD risk and showed strongest predictive power	[47]
Sanguino Otero et al, 2024	Cross sectional	Spain	409 unrelated patients with suspected familial hypercholesterolemia	Blood sample	NGS	LDLR, PCSK9	Lipid metabolism	Genetic analysis of LDLR and PCSK9 3'UTRs in familial hypercholesterolemia identified rare variants (7%): 13 in LDL5 and 8 in PCSK9. LDLR variants may raise cholesterol by disrupting miRNA binding, while PCSK9 variants may boost expression by creating new binding sites	[48]

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de Toro-Martín et al, 2016	Cross sectional	Canada	1720 patients (537 men and 1183 women) who had severe obesity and underwent biliopancreatic diversion	Visceral adipose tissue	Methylation profiling, SNP genotyping	TOMM20	Lipid metabolism	TOMM20 SNPs influence methylation at cg16490124. rs4567344/rs11301 rare alleles linked to lower methylation and higher TG, while rs4551650/ rs17523127 rare alleles linked to higher methylation and lower total cholesterol	[49]
Dayeh et al, 2016	Cohort	Finland	129 participants who developed T2D over a mean follow up time and 129 controls who did not develop T2D over the same follow up time	Blood sample, visceral adipose tissue, and liver biopsy	Pyrosequencing	PHOSPHO1, ABCG1	Lipid metabolism; Glucose metabolism	ABCG1 cg06500161 methylation rises T2D risk by 9% (OR=1.09); PHOSPHO1 cg02650017 methylation lower T2D risk by 15% (OR=0.85), adjusted for age, gender, and fasting glucose	[50]
van Otterdjik et al, 2017	Case control	Germany	45 subjects aged between 45–85 diagnosed with T2D and central obesity plus at least one factors which defines MetS	Blood sample	Pyrosequencing	PEG3, FTO, KCNJ11, PPARγ, PDK4	Cell cycle; Insulin metabolism; Eating behavior; Glucose metabolism; Lipid metabolism; Adipogenesis	No significant gene-specific methylation differences were observed between patients and control, although a trend for PEG3 was observed towards a positive correlation for HDL level. Differential methylation were observed at 4 CpG sites in FTO, KCNJ11, PPARγ, and PDK4 promoters	[51]
Yao et al, 2018	Case control	China	8 phlegm-dampness constitution and 4 balance constitution volunteers aged between 30–60 and had no diagnosed diseases	Blood sample	Genome-wide DNA methylation analysis	SQSTM1, FBXO9, GRWD1, ATP10A, CTBP1	Adipogenesis; Adipogenesis; Oxidative stress; Ribosome biogenesis; Glucose metabolism	Ingenuity Pathway Analysis (IPA) shows that hypomethylated SQSTM1 and FBXO9 were linked to diabetes, GRWD1 and ATP10A to insulin resistance, and ATP10A and CTBP1 to obesity	[52]
Castellano-Castillo et al, 2018	Case control	Spain	64 subjects with MetS and 70 non-MetS controls	Visceral adipose tissue	RT-qPCR, Pyrosequencing, Western blot, ELISA	LPL	Lipid metabolism	LPL promoter methylation in adipose tissue was higher in MetS subjects compared to non-MetS.	[53]
Krause et al, 2019	Cohort	Germany	176 healthy subjects without T2D and 100 obese non-diabetic and obese diabetic subjects	Blood sample, visceral adipose tissue, and liver biopsy	Bisulfite pyrosequencing	SREBF1, ABCG1	Lipid metabolism; Insulin metabolism	Methylation at ABCG1 cg06500161 and SREBF1 cg11024682 correlated with blood glucose	[54]

Das et al, 2016	Cross sectional	USA	365 subjects with MetS and 481 controls aged ≥ 30 years	Frozen buffy coat sample	Illumina Infinium HumanMethylation450 BeadChip was used to quantify methylation	CPT1A	Lipid metabolism	Methylation at intronic CPT1A loci inversely associated with MetS and its components, suggesting a role in MetS susceptibility.	[55]
Nuotio et al, 2020	Cross sectional	Finland	1187 individuals	Blood sample	HM450K DNA methylation assay	TXNIP, ABCG1	Glucose metabolism; Lipid metabolism; Oxidative stress; Apoptosis induction; Adipogenesis	Methylation site cg19693031 in gene TXNIP associated with FBG and cg06500161 in gene ABCG1 associated both with serum TG and WC.	[56]
Urashima et al, 2021	Cross sectional	USA	110 non-MetS and 74 MetS participants	Blood sample	Pyrosequencing	COX6C and RPL9	Energy metabolism	Decreased methylation were found at COX6C (2CpGs) and RPL9 (3 CpGs) in MetS with no differences in ATP5E. RPL9 showed inverse methylation-expression correlation.	[57]
Sasaki et al, 2022	Case control	Canada	20 neonatal dried blood spots from infants born to obese mothers and 20 neonatal dried blood spots to normal weight mothers	Dried blood spots	Bisulfite sequencing	PTPRN2, MAD1L1, IGF1R	Glucose metabolism; Insulin metabolism; Eating behaviour	PTPRN2 (important in insulin secretion) and MAD1L1 (has roles in cell cycle/tumor suppression) had DMRs in both sexes. In males, KEGG pathway analysis revealed a significant presence of endocytosis and cancer genes, including IGF1R, linked to diet-induced metabolic stress and childhood obesity	[58]
Seo et al, 2023	Case control	Republic of Korea	887 T2DM and 247 normal subjects, aged 40–69	Blood sample	DNA methylome analysis	TXNIP, PDE1C, TDRD9, DIP2C, FLJ90757, PRSS50	Oxidative stress; Insulin metabolism; Cell cycle; Lipid metabolism; Apoptosis induction; Protein metabolism	Differential methylation analysis identified 106 DMPs (top hits in TXNIP, PDK4, NBPF20, ARRDC4, UFM1, PFKFB2, C7orf50, ABCG1) linked to FBG and HbA1c. Methylation levels on PDE1C DIP2C, FLJ90757, PRSS50, and TDRD9 also changed.	[59]
Ma et al, 2023	Case control	China	15 obese and 15 extremely thin children	Blood sample	miRNA microarrays and TaqMan qPCR	hsa-miR-15b-5p, hsa-miR-223-3p	Lipid metabolism; Glucose metabolism	hsa-miR-15b-5p and hsa-miR-223-3p were upregulated in obesity.	[60]

(*Continued*)

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Table 1 (Continued).

Author, Year	Study Design	Country/ Population	Subjects	Sample	Method used for Genetic/Epigenetic Analysis	Gene(s) Analyzed	Biological Function(s) Related with Corresponding Genes	Outcome/Result	Ref.
McAllan et al, 2023	Case control	United Kingdom	190 samples (consisting of obesity and healthy subjects): 691 loci in subcutaneous and 173 loci in visceral adipocytes	Subcutaneous and visceral adipose tissues	Epigenome-wide association study with Illumina 450K and EPIC; whole transcriptome by RNA-seq	PRRC2A, LIMD2	Lipid metabolism; Adipogenesis; Insulin metabolism	PRRC2A is linked to central adiposity, insulin resistance, and T2D; LIMD2 linked to obesity, adiposity, and T2D. In obesity, hypomethylation at cg15809217 promote insulin resistance and T2D by reducing PRRC2A expression; hypomethylation at cg05941027 in obese visceral adipocytes may upregulates LIMD2 expression.	[61]
Si et al, 2023	Cohort	USA	903 mother-child pairs (urban, low-income, minority)	Cord blood	Infinium Methylation EPIC BeadChip	AKAP7, CAMK2B	Energy metabolism; Glucose metabolism; Insulin metabolism	Maternal overweight or obesity linked to DNA methylation changes in cord blood; 14 CpGs were found to mediate maternal BMI and child overweight or obesity; some gene involved were associated with energy balance and metabolism (AKAP7) and development of metabolic syndrome in adulthood (CAMK2B)	[62]
Zahedani et al, 2023	Randomized double-blind placebo-controlled trial	Iran	50 overweight and obese subjects (25 participants in each intervention and control group)	Blood sample	Serum homocysteine measurement	Methyl donor	Energy metabolism; Protein metabolism	Methyl donor supplementation improved weight, BMI, body fat, and waist/hip size; improved skeletal muscle, fat-free mass, and body cell mass; reduced visceral fat and serum homocysteine	[63]
Gutowska et al, 2023	Cohort	Poland	62 obese patients before weight loss, 15 obese patients after weight loss, and 20 normal weight controls	Visceral and subcutaneous adipose tissues	RT-qPCR for lncRNA measurement; ELISA	AGER	Immune response; Oxidative stress	In women, obesity increased AGER expression in SAT; AGER-driven inflammation mainly affected VAT, raising insulin resistance and T2DM risk	[64]
Bao et al, 2015	Case control	Mongolia	34 T2DM patients, 27 patients with IGT, and 30 controls with normal glucose tolerance	Blood sample	RT-qPCR, Western blot, ELISA, luciferase reporter assay	SOCS3	Lipid metabolism; Immune response; Insulin metabolism	miR-185 are reduced in plasma of diabetic patients and pancreatic islets of diabetic mice. miR-185 stimulates insulin secretion and targets SOCS3. PCR and Western blot analysis consistently shows that the mRNA and protein levels of SOCS3 were upregulated in miR-185 knocked-down cells	[65]

Lischka et al, 2021	Cohort	Austria	109 pediatric patients with severe obesity	Blood sample	RT-qPCR for miRNA quantification	miR-34a, miR-93, miR-122, miR-192	Immune response; Lipid metabolism; Glucose metabolism	The levels of miRNAs 34a, 93, 122, and 192 in patients with prediabetes, impaired glucose tolerance, MetS, or NAFLD were significantly different compared to controls.	[66]
Cerda et al, 2021	Case control	Brazil	Initial study: 6 MetS and 6 non-MetS individuals. Further study: 80 obese patients (48 MetS and 32 non-MetS)	Blood sample	Small-RNA sequencing, RT-qPCR	miR-155	Insulin metabolism; Glucose metabolism	miR-155 is downregulated in obese patients with MetS, especially those with hyperglycemia and insulin resistance.	[67]
Liu et al, 2016	Case control	China	60 MetS patients and 30 healthy controls	Blood sample	RT-qPCR, Western blot	MEG3, miR-140-5p	Cell cycle	lncRNA MEG3 was found downregulated while miR-140-5p expression was upregulated in MetS patients without pioglitazone treatment.	[68]
Zhao et al, 2022	Case control	China	39 patients diagnosed with Mets and 42 healthy individuals without any MetS components	Blood sample	RT-qPCR	lncRNA SRA, lncRNA GAS5	Immune response; Cell cycle; Adipogenesis stimulation; Glucose metabolism	Levels of SRA in MetS patients was significantly lower than in control individuals. No significant differences were observed in GAS5 levels.	[69]
Liu et al, 2014	Case control	USA	284 healthy African-American or Caucasian individuals aged 18-45	Blood sample and adipose tissue	RNA-sequencing, RT-qPCR	linc-DMRT2, linc-TP53I13	Immune response; Cell cycle	lincRNA DMRT2 and TP53I13 were downregulated in adipose tissue of obese subjects.	[70]
Qi et al, 2021	Case control	China	75 PCOS women and 72 healthy controls	Blood sample	RT-qPCR	lncRNA ENST00000550337.1	Glucose metabolism	lncRNA ENST00000550337.1 expression level was significantly higher and independently correlated with insulin resistance in PCOS women compared to healthy controls.	[71]
Abd-Elmawla et al, 2018	Case control	Egypt	65 patients with SLE (7 males and 58 females) aged from 18 to 55 years and 35 normolipidemic healthy volunteers.	Blood sample	ELISA, RT-qPCR	ANRIL, NOS3-AS, APOA1-AS	Immune response; Cell cycle; Lipid metabolism	ANRIL, NOS3-AS, and APOA1-AS were found significantly upregulated among atherosclerotic SLE patients compared to non-atherosclerotic SLE patients and normal control subjects.	[72]
Zhu et al, 2019	Case control	China	50 MetS patients and 50 healthy controls	Blood sample	RT-qPCR, Western blot	hsa_circH19	Adipogenesis inhibition; Lipid metabolism	Expression of circulating hsa_circH19 was found upregulated in MetS patients and correlates with lipid-related parameters.	[73]

Abbreviations: BMI, body mass index; BP, blood pressure; DMPs, differentially methylated positions; DMRs, differentially methylated regions; ELISA, enzyme-linked immunosorbent assay; FBG, fasting blood glucose; GRS, genetic risk score; GWAS, genome-wide association study; H-ORAC, hydrophilic oxygen radical absorbance capacity; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; HPA, hypothalamic-pituitary-adrenal; L-ORAC, lipophilic oxygen radical absorbance capacity; LDL-C, low-density lipoprotein cholesterol; lncRNA, long non-coding RNA; lincRNA, long intergenic non-coding RNA; MetS, metabolic syndrome; miRNA, microRNA; NAFLD, non-alcoholic fatty liver disease; NCEP ATP III, national cholesterol education program adult treatment panel III; NGS, next-generation sequencing; PCOS, polycystic ovarian syndrome; RT-qPCR, reverse transcription quantitative polymerase chain reaction; SAT, subcutaneous adipose tissue; SLE, systemic lupus erythematosus; T2DM, type 2 diabetes mellitus; TG, triglyceride; VAT, visceral adipose tissue; WC, waist circumference.

(SBP), suggesting a strong genetic contribution of *KCNQ1* to metabolic dysfunction.[25] Similarly, a study on 690 Chinese Han adults (40–65 years) examined the association of sirtuin 1 (*SIRT1*) and nuclear factor erythroid 2-related factor 2 (*NRF2*) gene variants with MetS, reporting that the SIRT1 rs7895833 variant was associated with an increased MetS risk, as well as elevated low-density lipoprotein cholesterol (LDL-C), homeostatic model assessment for insulin resistance (HOMA-IR), and total cholesterol levels, reinforcing the role of these genetic factors in lipid metabolism and insulin resistance.[26] The interaction between genetic variation at the 9p21.3 locus and dietary antioxidants in relation to MetS risk was explored in an Iranian population, revealing that the rs1333048 polymorphism was linked to a higher risk of MetS.[27] However, individuals with a high intake of hydrophilic and lipophilic antioxidants exhibited a reduced risk, suggesting that dietary modifications could modulate genetic susceptibility to MetS. A GWAS was conducted in a Korean population to identify genetic factors associated with MetS, identifying a significant association between MetS and an SNP pair (rs7107152 and rs1242229) in the SID1 transmembrane family member 2 (*SIDT2*) gene at 11q23.3. These SNPs were linked to *SIDT2* and transgelin (*TAGLN*) expression, genes involved in insulin secretion and lipid metabolism, highlighting a potential genetic mechanism underlying MetS.[28]

The genetic landscape of metabolic disorders was expanded by investigating loci associated with type 2 diabetes (T2D) across four cohorts: METSIM (487 participants), Ashkenazi (509 participants), Partners Biobank (2,065 participants), and UK Biobank (14,813 participants).[29] Five major genetic clusters contributing to T2D risk were identified through Bayesian Nonnegative Matrix Factorization (bNMF) and GWAS: the Beta Cell Cluster (*MTNR1B, HHEX, TCF7L2*), the Proinsulin Cluster (*ARAP1, SPRY2*), the Obesity Cluster (*FTO, MC4R*), the Lipodystrophy Cluster (*PPARG, ANKRD55, ARL15*), and the Liver/Lipid Cluster (*GCKR, CILP2*/*TM6SF2, PNPLA3*). The study emphasized the heterogeneity of genetic risk factors for T2D and the need for phenotype-specific approaches in metabolic disease research. Genetic and environmental factors significantly influence methylation heritability in MetS-associated CpG sites in carnitine palmitoyltransferase 1A (*CPT1A*), supressor of cytokine signaling 3 (*SOCS3*), and ATP-binding cassette sub-family G member 1 (*ABCG1*), highlighting the complex interplay between genetics and environment in MetS-related epigenetic regulation.[30]

Other studies have also explored the genetic factors associated with MetS. A study on 203 women (16–40 years) examined the association of paraoxonase-1 (PON1) L55M and Q192R polymorphisms with PCOS and atherosclerosis risk using polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) analysis.[31] The Q192R polymorphism significantly distinguished PCOS patients, with R allele carriers being at a higher risk. Additionally, when combined with BMI, this polymorphism became a stronger predictor for PCOS and its associated risk of atherosclerosis, highlighting the interplay between genetic and metabolic factors. Female-specific genetic variants associated with MetS and its components have also been identified in an attempt to improve prediction accuracy in women. GWAS and genetic risk score (GRS) methodologies identified 14 moderate genetic signals specific to females with MetS. Notably, two significant genome-wide associations were found: rs455489 in the down syndrome cell adhesion molecule (*DSCAM*) gene, linked to fasting plasma glucose, and rs7115583 in the salt-inducible kinase 3 (*SIK3*) gene, associated with high-density lipoprotein cholesterol (HDL-C). The GRS demonstrated strong predictive power for MetS in females (AUC = 0.85) but not in males (AUC = 0.57), emphasizing the importance of gender-specific genetic risk factors in MetS.[32] A case-control study examined candidate gene polymorphisms associated with MetS in 304 Mongolian subjects, revealing that ADIPOQ +45T>G, LPL PvII, and PGC-1α Gly482Ser polymorphisms may contribute to MetS risk.[33]

Various studies have explored the genetic underpinnings of MetS across diverse populations, highlighting the complex interplay between genetic variants and metabolic traits. A study of 136 Gambian adults with at least three generations of African ancestry investigated the association between the cadherin 13 (CDH13) rs385618 polymorphism and MetS using polymerase chain reaction (PCR) analysis, revealing a significant association between this polymorphism and MetS, with the AT genotype linked to an increased risk. However, no correlation was found between rs385618 and individual MetS traits.[34] Another study of Javanese individuals (20–66 years) from Yogyakarta examined the association of rs4730153 with MetS risk, indicating that the GG genotype was significantly linked to a higher MetS risk, particularly in individuals aged ≤45 years (OR: 3.88–16.14), suggesting potential age-related genetic influences on MetS susceptibility.[35]

Meanwhile, a study conducted on 560 Chinese adults (19–87 years) investigated the relationship between serum amylase activity, amylase (*AMY*) gene copy numbers, and MetS risk using droplet digital polymerase chain reaction (ddPCR) analysis. While the copy numbers of *AMY1, AMY2A*, and *AMY2B* were not significantly associated with MetS,

individuals with higher serum amylase activity appeared to have a lower MetS risk. Notably, younger individuals with low amylase activity and reduced AMY1 copy numbers exhibited increased metabolic risks, indicating the potential role of amylase activity as a MetS biomarker.[36] Similarly, another study in China focused on 192 children (6–14 years) to explore the relationship between vitamin D receptor (*VDR*) gene polymorphisms and MetS, revealing that ApaI SNPs were associated with obesity and glucose metabolism, whereas *FOKI* SNPs were linked to MetS susceptibility.[37] Interestingly, these genetic associations were independent of serum vitamin D levels, although vitamin D deficiency was more prevalent in overweight and obese children. In addition, a study involving 404 overweight and obese women (18–55 years) examined the interaction between genetics, dietary factors, and MetS risk, focusing on the caveolin 1 (CAV-1) rs3807992 polymorphism and its association with dietary fatty acid intake.[38] The rs3807992 variant was significantly associated with elevated blood pressure, dyslipidemia, low HDL-C, and high triglyceride (TG) levels. Moreover, dietary intake of saturated fatty acids and polyunsaturated fatty acids appeared to interact with rs3807992 genotypes, suggesting that dietary modifications could influence MetS risk in genetically susceptible individuals. The angiopoietin-like 4 (ANGPTL4) rs1044250 SNP is an independent risk factor for increased waist circumference and elevated blood pressure in MetS in the Han population in Shandong, China.[39] Additionally, individuals carrying the wild-type variant had a higher likelihood of developing MetS in association with weight gain, primarily due to increased blood pressure, highlighting the genetic contribution to weight management and MetS risk. An exploration of the genetic basis of taste preferences in 425 white Caucasian individuals with MetS from the PREDIMED Plus-Valencia cohort (aged 55–75 years) indicated that individuals with T2D had a stronger preference for sweet tastes compared to non-diabetic participants ($p = 0.021$). Furthermore, T2D participants exhibited reduced overall taste perception, particularly for bitterness ($p = 0.023$). These findings suggest that metabolic disorders, such as T2D, may influence taste perception, potentially affecting dietary behaviors and MetS progression.[40]

The fatty acid desaturase (*FADS*) gene polymorphisms, *FADS1* (rs174537, rs174545, rs174546) and FADS2 (rs174570, rs174602), along with haplotypes GGGCC and TCACT, are significantly associated with two distinct MetS phenotypes (MetS1 and MetS2).[41] Notably, MetS1 was linked to a more adverse metabolic profile, including increased waist circumference, insulin resistance, and oxidative stress, highlighting the role of *FADS* polymorphisms in MetS heterogeneity and clinical variability. Furthermore, the CA and AA genotypes of rs4588 and the AC genotype of rs2282679 were inversely associated with MetS risk in Chinese Han adults, showing links to improved lipid profiles, including lower triglycerides and higher HDL-C levels.[42] However, there was no association between vitamin D-binding protein levels and MetS risk. These findings suggest that while *FADS* gene variants may contribute to metabolic dysfunction and oxidative stress, GC gene polymorphisms could play a protective role, particularly in lipid metabolism.

The role of various gene polymorphisms in disease susceptibility, metabolic regulation, and genetic predisposition has been highlighted in diverse populations. A study of 178 Spanish pediatric outpatients (80 girls, 98 boys) investigated the association of *MC4R* gene polymorphisms (rs17782313, rs17773430, rs34114122) with obesity and its comorbidities, revealing that the minor C allele was linked to an increased risk of obesity and carbohydrate metabolism alterations.[43] These findings emphasize the importance of *MC4R* gene polymorphisms in assessing genetic susceptibility to childhood obesity and related metabolic disorders. A large-scale study of 47,562 Korean adults (41–85 years) examined the genetic heritability of dyslipidemia and its interaction with dietary patterns, with a focus on sex differences.[44] GWAS and genotyping analyses showed that individuals carrying minor alleles of SNPs rs662799 (males) and rs651821 (females) had a higher risk of dyslipidemia. Additionally, a higher GRS was associated with elevated LDL-C and triglyceride levels in both sexes, underscoring the interaction between genetics, lipid metabolism, and dietary factors in dyslipidemia development. Another study investigated the relationship between nuclear receptor subfamily 3 group C member 1 (*NR3C1*) gene polymorphisms and MetS in a Mennonite population from southern Brazil, showing that specific *NR3C1* polymorphisms, including homozygosity for the rs10482605*C allele and certain haplotypes, were associated with an increased MetS risk, likely due to hypothalamic-pituitary-adrenal (HPA) axis dysregulation. However, there was no significant correlation between *NR3C1* methylation or gene expression and MetS, highlighting the genetic rather than epigenetic contribution of *NR3C1* to MetS susceptibility.[45] Additionally, twelve novel uncoupling protein 1 (UCP1) gene variants associated with MetS and T2D were identified in a Polish population, suggesting that UCP1 gene variations may contribute to MetS and T2D risk, emphasizing its potential role in metabolic regulation.[46] Finally, Zhao et al investigated

sorting and assembly machinery component (*SAMM50*) genetic variants in relation to non-alcoholic fatty acid liver disease (NAFLD) susceptibility among elderly individuals (590 with NAFLD and 463 controls) in Beijing, revealing that carriers of the SAMM50-rs2073082 G allele and rs738491 T allele had a significantly higher risk of NAFLD (odds ratios of 1.962 and 1.532, respectively).[47] Moreover, a combination of three SNPs, rs2073082 G, rs738491 T, and rs3761472 G, was identified as a strong predictor of NAFLD, nearly doubling the risk. These findings suggest that SAMM50 variants could serve as genetic markers for assessing NAFLD risk in older populations.

Recent research has provided fresh insights into the genetic factors underlying familial hypercholesterolemia (FH). A study explored the role of *LDLR* and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) 3′UTR variants in FH patients, identifying 13 variants in LDLR-3'UTR and 8 variants in PCSK9-3'UTR, which were found in 7% of the participants.[48] The findings suggest that LDLR-3'UTR variants may contribute to hypercholesterolemia by disrupting miRNA binding sites, potentially impairing post-transcriptional regulation. Meanwhile, PCSK9-3'UTR variants appeared to increase PCSK9 expression by creating illegitimate binding sites, which could lead to higher LDL-C levels. This study highlights the significance of analyzing 3′UTR regions in FH genetics, emphasizing their potential role in refining genetic diagnoses and improving risk assessment for hypercholesterolemia.

DNA Methylation

The relationship between methylation quantitative trait loci (meQTLs) in the translocase of outer mitochondrial membrane 20 (*TOMM20*) gene and lipid changes was examined in 1,717 severely obese individuals, including 1,402 with MetS and 315 without MetS, identifying four SNPs as meQTLs for the CpG site cg16490124, revealing distinct methylation-lipid associations.[49] Rare alleles of rs4567344 and rs11301 were linked to lower methylation and higher triglyceride levels, while rs4551650 and rs17523127 were associated with higher methylation and lower cholesterol levels. These findings suggest that genetic variations in *TOMM20* may influence lipid metabolism in MetS via epigenetic mechanisms. Another study investigated the potential of DNA methylation at the *ABCG1* and phosphoethanolamine/phosphocholine phosphatase 1 (*PHOSPHO1*) loci as biomarkers for predicting future T2D risk, following 258 individuals for 8.1 years, including 129 who later developed T2D and 129 controls.[50] Methylation analysis revealed that higher *ABCG1* methylation was associated with a 9% increased risk of T2D, while higher *PHOSPHO1* methylation was linked to a 15% reduced risk. These results highlight DNA methylation as a possible predictive marker for metabolic disorders, emphasizing its role in disease progression.

A later study analyzed DNA methylation in peripheral blood from 34 metabolic patients (including T2D and MetS) and 11 controls (aged 45–85), showing no significant gene-specific methylation differences in potassium inwardly rectifying channel subfamily J member 11 (*KCNJ11), PPARG*, pyruvatt dehydrogenase kinase 4 (*PDK4), KCNQ1*, stearoyl-CoA desaturase-1 (*SCD1*), pancreatic and duodenal homeobox 1 (*PDX1), FTO*, and paternally expressed 3 (*PEG3*).[51] However, trends were noted for *PEG3* and four CpG loci in *FTO, KCNJ11, PPARG*, and *PDK4*. A positive correlation between *PEG3* methylation and HDL-C levels was also observed, emphasizing the complexity of DNA methylation in T2D and MetS.

A genome-wide DNA methylation study based on Traditional Chinese Medicine (TCM) Constitution Classification found that sequestosome 1 (*SQSTM1*) and F-box protein 9 (*FBXO9*) hypomethylation was associated with diabetes, while glutamate rich WD repeat containing 1 (*GRWD1*) and ATPase phospholipid transporting 10A (*ATP10A*) were linked to insulin resistance. Additionally, *ATP10A* and C-terminal binding protein 1 (*CTBP1*) were hypomethylated and associated with obesity, suggesting a potential role of DNA methylation in the TCM-based metabolic constitution and its metabolic implications.[52] Another study investigated lipoprotein lipase (*LPL*) promoter methylation in visceral adipose tissue from MetS patients undergoing laparoscopic surgery, reporting that *LPL* promoter methylation was higher in MetS patients compared to non-MetS subjects, suggesting that metabolic conditions and oxidative stress may contribute to this hypermethylation.[53]

DNA methylation markers, *ABCG1* and sterol regulatory element-binding transcription factor 1 (*SREBF1*), were evaluated for T2D stratification, showing that methylation at *ABCG1* and *SREBF* correlated with blood glucose levels, distinguishing insulin-resistant from insulin-sensitive individuals. However, whole blood was not suitable for reflecting obesity-related metabolic changes. A metabolic risk score based on these markers successfully stratified participants. The

study suggests these markers may help with T2D stratification but emphasizes the need for metabolically active tissues for more accurate assessment.[54]

The inverse association between DNA methylation at the carnitine palmitoyltransferase 1A (*CPT1A*) locus and MetS in 1,718 participants from the GOLDN and Bogalusa Heart Studies suggests a potential role of *CPT1A* methylation in MetS predisposition.[55] Another epigenome-wide association study (EWAS) of samples from the FINRISK, DILGOM, and Northern Finland Birth Cohort 1966 studies identified cg08309687 (linked to lipid metabolism), cg17901584 (associated with HDL-C), and cg19693031 in thioredoxin-interacting protein (*TXNIP*) as strong candidates for MetS, highlighting key epigenetic markers potentially involved in MetS pathogenesis.[56]

In another study, epigenetic biomarkers of MetS were explored in 184 Latino participants, finding decreased methylation at two CpG sites in the cytochrome c oxidase subunit 6c (*COX6C*) gene and three CpG sites in the ribosomal protein L9 (*RPL9*) gene in MetS participants, with no changes observed in ATP synthase F1 subunit epsilon (*ATP5E*) methylation.[57] Logistic regression confirmed an inverse correlation between *RPL9* gene expression and methylation levels, supporting the role of *COX6C* and *RPL9* methylation as potential epigenetic biomarkers for MetS.[57] Sasaki et al examined DNA methylation profiles in 40 neonates (20 born to mothers with obesity, 20 to mothers with normal weight), matched for parity, maternal age, and neonatal sex, reporting that differentially methylated regions (DMRs) were mainly found in intergenic regions and gene bodies (9% in promoters).[58] Comparison with the ALSPAC cohort showed overlapping genes, including protein tyrosine phosphatase receptor type N2 (*PTPRN2*) (insulin secretion) and mitotic arrest deficient 1 like 1 (*MAD1L1*) (cell cycle, tumor suppression). In male neonates, KEGG pathway analysis revealed enrichment in endocytosis and cancer pathways, including insuling-like growth factor 1 receptor (*IGF1R*), linked to diet-induced metabolic stress. These findings suggest that maternal obesity influences neonatal epigenetic regulation and metabolic pathways.

An EWAS on T2D using data from the KoGES AS–AS cohort in Korea identified 106 differentially methylated probes (DMPs), with key genes including *TXNIP, PDK4*, neuroblastoma breakpoint family member 20 (*NBPF20*), arrestin domain containing 4 (*ARRDC4*), ubiquitin fold modifier 1 (*UFM1*), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 (*PFKFB2*), chromosome 7, open reading frame 50 (*C7orf50*), and *ABCG1*.[59] Notably, cg19693031 and cg26974062 (*TXNIP*) correlated with fasting glucose and HbA1c levels. Additionally, 62 differentially methylated regions (DMRs) across 61 genes were identified, with phosphodiesterase 1C (*PDE1C*) showing hypermethylation, while disco-interacting protein 2 homolog c (*DIP2C), FLJ90757, PRSS50*, and tudor domain containing 9 (*TDRD9*) were hypomethylated. These findings highlight epigenetic alterations as key contributors to T2D pathophysiology and potential biomarkers for disease progression. In another study investigating circulating miRNA biomarkers for obesity in children, hsa-miR-15b-5p and hsa-miR-223-3p were strongly correlated with obesity, suggesting their potential use as predictive biomarkers for distinguishing between healthy and obese individuals.[60] Additionally, decreased methylation at cg15809217 in obese subcutaneous adipocytes reduced proline rich coiled-coil 2A (*PRRC2A*) expression, promoting insulin resistance and T2D.[61] Similarly, reduced methylation at cg05941027 in visceral adipocytes increased LIM domain containing 2 (*LIMD2*) expression, contributing to obesity and T2D. Thus, DNA methylation is a key regulator of gene expression in adipocytes, influencing metabolic disorders.

Si et al reported that excess maternal weight induced DNA methylation changes in newborn cord blood, particularly in genes related to metabolism and energy balance, such as A-kinase anchor protein 7 (*AKAP7*) and calcium/calmodulin dependent protein kinase II beta (*CAMK2B*).[62] These epigenetic changes may contribute to transgenerational obesity risk, highlighting the influence of maternal BMI on offspring metabolic health. A randomized placebo-controlled trial investigated the effects of methyl donor supplementation on body composition and metabolic markers in 50 overweight and obese adults from Shiraz, Iran.[63] The intervention group showed significant reductions in weight, BMI, body fat percentage, and waist/hip circumference, along with improved skeletal muscle mass, fat-free mass, and visceral fat levels. Additionally, serum homocysteine levels were significantly lower in the intervention group. These findings suggest that methyl donor supplementation may enhance body composition and metabolic health. A 2023 study examined advanced glycation end product receptor 1 (*AGER-1*) long non-coding RNA (lncRNA) levels and *AGER* expression in adipose tissue samples collected from 97 obese women (BMI >40 kg/m^2) during bariatric and abdominoplasty surgeries, demonstrating that *AGER* expression was

increased in subcutaneous adipose tissue, while metabolic inflammation driven by *AGER* mainly affected visceral adipose tissue, contributing to insulin resistance and T2D.[64]

Non-Coding RNAs (ncRNAs)

Other studies offer interesting insights by examining MetS through miRNAs elaboration. The role of microRNA-185 (miR-185) in β-cell dysfunction was explored in 34 T2D patients, 27 individuals with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), and 30 healthy controls, demonstrating significantly lower miR-185 expression in diabetic patients compared to controls, and that miR-185 overexpression reduced *SOCS3*, an inhibitor of insulin signaling.[65] These results suggest that miR-185 plays a key role in enhancing insulin secretion and inhibiting beta-cell dysfunction by targeting *SOCS3*.

An unfavorable miRNA (34a, 93, 122, 192) profile was shown to be associated with obesity-related inflammation and metabolic disease, suggesting these miRNAs as potential biomarkers for risk stratification and early intervention in pediatric obesity.[66] Furthermore, analysis of the miRNome in peripheral blood to identify potential biomarkers for MetS and cardiometabolic risk in obese patients revealed that ten miRNAs, including miR-155, miR-181a, and let-7a, were involved in insulin receptor signaling.[67] Notably, miR-155 expression was significantly downregulated in patients with MetS, particularly those with hyperglycemia and insulin resistance, suggesting that miR-155 could serve as a promising biomarker for MetS and cardiometabolic risk.

Beyond miRNAs, accumulating evidence suggests that lncRNAs contribute to multiple aspects of MetS pathophysiology, ranging from insulin resistance and endothelial dysfunction to obesity-associated inflammation and vascular complications. Analysis of circulating endothelial progenitor cells (EPCs) from patients with MetS demonstrated a significantly reduced expression of the lncRNA maternally expressed gene 3 (MEG3) accompanied by an increase in miR-140-5p levels.[68] This pattern was accompanied by decreased expression of histone deacetylase 7 (HDAC7) as a target gene of miR-140-5p. Interestingly, treatment with pioglitazone reversed these alterations by restoring MEG3 and HDAC7 expression while supressing miR-140-5p levels, indicating a potential involvement of the MEG3/miR-140-5p/HDAC7 regulatory axis in endothelial dysfunction associated with MetS. Similarly, steroid receptor RNA activator (SRA) expression was significantly reduced in individuals with MetS, whereas growth arrest-specific transcript 5 (GAS5) expression remained unchanged.[69] In addition, patients with MetS were also exhibited significantly higher plasma cortisol and interleukin-6 (IL-6) levels relative to healthy controls. Although SRA expression alone was not independently associated with MetS after adjustment for potential cofounders, inflammatory cell-to-SRA ratios, particularly peripheral blood mononuclear (PBMC)-to-SRA, emerged as independent risk factors for MetS.[69]

Several lncRNAs have also been linked to obesity-related metabolic disturbances. In adipose tissue, linc-DMRT2 and linc-TP53I13 were significantly downregulated in obese individuals compared to lean controls.[70] Expression of these long intergenic non-coding RNAs (lincRNAs) in both adipocytes and immune cell populations suggests a potential involvement in the crosstalk between metabolic and immune regulatory pathways within adipose tissue. A similar association with metabolic dysfunction was observed in women with polycystic ovarian syndrome (PCOS). Elevated expression of lncRNA ENST00000550337.1 in women with PCOS was positively correlated with waist circumference, waist-to-hip ratio, fasting glucose, fasting insulin, and HOMA-IR.[71] Moreover, ENST00000550337.1 remained independently associated with both PCOS and insulin resistance after adjustment for potential confounders, further supporting a role for lncRNAs in obesity-associated metabolic dysfunction.

Beyond obesity-related metabolic dysfunction, lncRNA dysregulation has also been observed in vascular manifestations relevant to cardiometabolic diseases. Expression levels of antisense non-coding RNA in the INK4 locus (ANRIL), nitric oxide synthase 3 antisense (NOS3-AS), and apolipoprotein A1 antisense (APOA1-AS) were significantly elevated in patients with systemic lupus erythematosus (SLE) compared to healthy controls.[72] Notably, all three lncRNAs exhibited further upregulation among SLE patients with atherosclerosis relative to those without atherosclerosis. These findings suggest a potential association between lncRNA dysregulation and atherosclerotic burden.

Expanding beyond miRNAs and lncRNAs, emerging evidence also highlights the involvement of circular RNAs (circRNAs) in MetS. Serum expression of hsa_circH19 was significantly elevated in individuals with MetS compared to healthy controls and was closely associated with lipid metabolism abnormalities.[73] Functional analysis further

demonstrated that silencing hsa_circH19 promoted adipocyte differentiation and lipid accumulation, whereas its overexpression suppressed these processes.[73] These effects were accompanied by alterations in the expression of polypyrimidine tract-binding protein 1 (PTBP1) and sterol regulatory element-binding protein 1 (SREBP1), suggesting a potential role of hsa_circH19 in regulating adipogenesis and lipid homeostasis in MetS.

Discussion

This systematic review of relevant articles suggests that multiple interrelated molecular pathways contribute to MetS pathogenesis. These pathways include central regulatory networks and peripheral metabolic pathways, emphasizing the multifactorial nature of this condition. The following discussion is structured into four sections for a comprehensive study of how distinct yet overlapping mechanisms collectively influence the development and progression of MetS.

Neuroendocrine

The neuroendocrine pathways maintain energy homeostasis by integrating peripheral metabolic signals with the central nervous system of feeding behavior and satiety. Among these, the central melanocortin system constitutes a key regulatory network composed of extensive neuronal circuits that mediate the balance between energy intake and expenditure.[74] The melanocortin-4 receptor (MC4R) is a receptor involved in the central melanocortin system and functions as a key component of the body's anti-obesity mechanisms.[75] Widely expressed in brain regions involved in feeding control, this receptor integrates two opposing signals from distinct neuropeptides. MC4R is activated by its agonist, α-melanocyte-stimulating hormone (α-MSH), which inhibits food intake and increases energy expenditure,[76] thereby acting as an anti-obesity mechanism.[77] Conversely, agouti-related protein (AGRP) acts as a competitive antagonist to promote food intake and decrease energy expenditure.[74] The physiological balance between these ligands determines the net output of the melanocortin pathway;[78] therefore, inactivation or dysfunction of this receptor has been strongly associated with hyperphagia and obesity.[78,79] The clinical relevance of MC4R's role in MetS pathogenesis is further supported by population-based studies. Several polymorphisms have been identified in pediatric patients, with specific variants such as rs17782313 and rs34114122 associated with increased obesity risk and impaired carbohydrate metabolism, suggesting that MC4R dysfunction may manifest early in life.[43] These results emphasize MC4R as a potential genetic marker for metabolic risk in children.

The dopaminergic pathway also emerged as a critical modulator of energy intake. The dopamine D2 receptor (DRD2) plays a central role in modulating the motivational and emotional aspects of food intake.[80] Reduced expression of dopamine receptor in the mesolimbic reward system can alter activity motivation and reduce behavioral energy expenditure, thus inducing obesity in rodent models.[81] Conversely, an increase in DRD2 expression is linked to a bodyweight reduction through diminished food intake in rats fed a high-fat diet.[82] While in human studies, *DRD2* variants have also been linked to longitudinal weight gain trajectories.[20] These findings suggest that DRD2 alteration contributes to the interplay between the central reward system and metabolic homeostasis in promoting metabolic syndrome.

Another key neuroendocrine modulator associated with metabolic syndrome is the *FTO* gene. Its role in obesity extends beyond its effect on appetite regulation, implicating a broader metabolic sensor pathway such as mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK).[83] Emerging evidence shows that FTO may function as an amino acid sensor that regulates mechanistic/mammalian target of rapamycin complex 1 (mTORC1),[84] potentially modulating insulin signaling via downstream mediators, affecting energy utilization.[84] Although not included in our review, this mechanistic insight is supported by clinical findings that show that the *FTO* rs9939609 polymorphism is associated with T2D progression in an obese population.[85] Other than *FTO* rs9939609, an additional intronic variants within the FTO locus further highlight its role as a regulatory node. The *FTO* rs9930506 recently has been shown to influence long-range chromatin interactions that modulate iroquois homeobox 3 (*IRX3*) expression. This gene involved in hypothalamic neurodevelopment and energy balance regulation.[86] Aligned with this, a study has also shown that a knockout of *IRX3* in brain correlates to a decrease in body weight through loss of fat mass and increase in basal metabolic rate.[87] Moreover, mTORC1 signaling in the hypothalamus is also involved in regulating food intake and controlling body weight,[83] consistent with *FTO* being associated with weight gain during the transition from adolescence to early adulthood.[20] This regulatory mechanism provides a neurodevelopmental basis for feeding behaviour modulation and metabolic phenotypes associated with *FTO* variants.

Adipogenesis and Insulin Signaling

Adipogenesis and insulin signaling are closely interconnected mechanisms that contribute to MetS pathophysiology. These processes are controlled by a complex network of tightly regulated genetic and epigenetic systems. Although tightly regulated, certain genetic and epigenetic variations may disrupt the metabolic network, specifically affecting insulin sensitivity and adipocyte proliferation.

Among the key genetic contributors to these processes is *KCNQ1*, a gene that encodes a voltage-gated potassium channel widely expressed in pancreatic β-cells and cardiomyocytes.[25,88] Normally, the closure of this channel following an increased ATP/ADP ratio leads to the opening of a voltage-dependent calcium channel, triggering exocytosis of insulin-containing granules.[89] Inhibition or alterations of this voltage-gated potassium channel prolong depolarization and increase insulin secretion.[88]

While many GWASs have confirmed that *KCNQ1* is linked to diabetes in both Asian and European populations,[90] Liu et al reported an interesting exception. They found that the rs163182 variant did not significantly alter fasting plasma glucose concentration in their cohort.[25] Nevertheless, their findings indicated an association with elevated BMI and systolic blood pressure, suggesting that *KCNQ1* may influence MetS pathogenesis through a mechanism beyond glucose control.[25,91] Such findings emphasize the need to consider *KCNQ1* as part of a wide cardiometabolic risk profile rather than as an isolated diabetes susceptibility-related gene.

Downstream of glucose sensing, inflammatory mediators represent another level of control over insulin signaling. The SOCS3 has emerged as a physiological inhibitor of the JAK/STAT pathway and insulin receptor substrate (IRS) phosphorylation. Driven by inflammatory cytokines, their expression is elevated in obesity and in individuals with chronic low-grade inflammation.[92] SOCS3 contributes to insulin resistance through multiple mechanisms, including inhibition of IRS phosphorylation, promotion of proteasomal degradation of IRS, and inhibition of insulin receptor kinases.[92–94] These changes may disrupt PI3K/Akt pathway signaling, thereby limiting GLUT4 translocation and glucose uptake. Notably, Bao et al identified a miRNA that exhibits an inhibitory effect on *SOCS3* expression. From an epigenetic standpoint, they demonstrated that miR-185 upregulation enhanced insulin sensitivity, whereas its knockdown increased *SOCS3* expression.[49] This aligns with an earlier discussion that SOCS3 acts as a mediator between inflammatory signaling and impaired insulin function.[94,95]

The regulatory network underlying insulin resistance extends beyond protein-coding genes to include ncRNAs. Supporting this concept, evidence from women with PCOS, a disorder sharing key metabolic features with MetS, demonstrated an elevated expression of lncRNA ENST00000550337.1.[71] This overexpression was independently associated with insulin resistance and positively correlated with fasting glucose, fasting insulin, HOMA-IR, waist circumference, and waist-to-hip ratio.[71] Supporting this, Sathishkumar et al observed that higher ENST00000550337.1 expression was significantly associated with type 2 diabetes.[96] Although the precise biological function of ENST00000550337.1 remains to be fully elucidated, the consistent association of this lncRNA with insulin-resistant phenotypes across independent studies strengthens its potential relevance to insulin resistance and glucose metabolism.

Peroxisome proliferator-activated receptor gamma (PPARG) plays a crucial role in metabolic homeostasis as a master regulator of adipocyte differentiation and lipid storage. It influences adipogenesis, fatty acid uptake, and insulin sensitivity, multiple components of MetS.[97] Epigenetic modulation of PPARG has emerged as a critical determinant of its expression in individuals with obesity and insulin resistance. It has been revealed that hypomethylation of the *PPARG* promoter to increase gene expression is frequently observed in individuals with MetS.[13,14] While this upregulation may initially facilitate adipogenesis as a storage buffer for circulating fatty acids, chronic overexpression in obesity leads to adipocyte hypertrophy and systemic insulin resistance.[13,97,98]

Beyond adipocyte differentiation and insulin signaling, emerging evidence suggests that ncRNAs networks have also contribute to endothelial homeostasis, thereby linking metabolic dysfunction to vascular injury. One such pathway involves the lncRNA MEG3 which was found to be downregulated in circulating endothelial progenitor cells from patients with MetS.[68] Reduced MEG3 expression was accompanied by increased miR-140-5p levels and decreased HDAC7 expression.[68] Although the interaction between MEG3, miR-140-5p, and HDAC7 has not been fully elucidated in MetS, previous studies have identified HDAC7 as a downstream target of miR-140-5p, whereby increased miR-140-5p suppresses HDAC7 expression.[99] Given that HDAC7 appears to represent the principal downstream effector of this axis,

its physiological role provides important insight into the potential consequences of MEG3 dysregulation. Previous studies have demonstrated that HDAC7 silencing impairs angiogenesis through disruption of pro- and anti-angiogenic factors, ultimately compromises endothelial repair.[100] Therefore, the reduced HDAC7 expression observed in MetS may represent a mechanistic link through which dysregulation of the MEG3/miR-140-5p axis contributes to endothelial dysfunction.

Protein Regulators in Glucose and Lipid Metabolism

SIRT1 is a major nutrient-sensing protein that integrates glucose and lipid metabolism through controlled transcriptional activity.[101] The observed association between the SIRT1 rs7895833 variant and increased LDL-C, HOMA-IR, and total cholesterol levels in the Han population underscores the importance of this gene as a key regulator of metabolic processes.[26] Physiologically, SIRT1 transcription is tightly regulated by nutritional status. During low food intake, the CREB/CRTC2 complex binds to the *SIRT1* promoter to initiate transcription. At the same time, attenuation of the insulin signaling pathway in nutritional depletion allows FOXO factors to translocate to the nucleus and further enhance SIRT1 expression, establishing a natural positive feedback loop to sustain activity.[102] Once activated, SIRT1 inhibits PPARG activity, thus repressing adipogenesis.[103] In addition, SIRT1 releases free fatty acids into circulation through lipolysis upregulation,[104] as evidenced by *SIRT1* knockdown leading to a significant triglyceride accumulation and increased PPARG in a 3T3-L1 model.[105] However, while this study shows a mechanistically promising target for lipid-associated disease,[106] the clinical trials for SIRT1 modulation and its related pathway remain limited. Beyond its role as a nutrient-sensitive transcriptional regulator, emerging evidence suggests that epigenetic regulators also participate in lipid homeostasis. Among these, circular RNAs have recently gained attention as post-transcriptional modulators of adipocyte differentiation and lipogenesis.

CircRNAs regulate gene expression primarily through post-transcriptional mechanisms, including its function as molecular sponges for microRNAs or by interacting with RNA-binding proteins, thereby modulating downstream transcriptional networks.[73] One circRNA that has recently attracted attention in MetS is has_circH19. In the study by Zhu et al, serum hsa_circH19 expression was significantly elevated in individuals with MetS and correlated with multiple indices of adiposity, including BMI, waist circumference, body fat percentage, HDL-C, and visceral fat area.[73] Interestingly, despite its elevated circulating expression in individuals with MetS, functional study conducted by Wen et al demonstrated that has_circH19 was instead found to be overexpressed and exerted protection against obesity whereas its deletion promoting adipogenic differentiation and enhancing lipid storage.[107] Knockdown of hsa_circH19 resulted in the upregulation of several lipogenic regulators, including CCAAT/enhancer-binding protein alpha (*C/EBPα), PPARG*, sterol regulatory element-binding protein 1c (*SREBP1c), FABP4*, and acetyl-CoA carboxylase 1 (*ACC1*).[73] Notably, visceral fat area remained the only independent predictor of circulating hsa_circH19 levels, suggesting a closer relationship between hsa_circH19 dysregulation and visceral adiposity than with generalized obesity.[73]

While circH19 appears to regulate lipid metabolism at the level of adipocyte differentiation and lipogenesis, efficient systemic lipid homeostasis also depends on proteins governing lipid transport and clearance. Among these, *ANGPTL4* has emerged as a central regulator of triglyceride and fatty acid metabolism. The *ANGPTL* family, particularly *ANGPTL4*, is a central regulator of triglyceride and fatty acid metabolism. The release of fatty acids from triglyceride-rich lipoprotein into the circulation is regulated by LPL,[108] which is highly expressed in cells that store fat, including adipose tissue.[109,110] Inhibition of LPL by ANGPTL4 leads to elevated plasma triglyceride and free fatty acid levels.[111] Moreover, ANGPTL4 dysfunction in humans is associated with lower plasma triglyceride levels and CAD risk.[112,113] In nutrient-depleted conditions, PPARs upregulate ANGPTL4 expression to promote the mobilization of free fatty acids from the adipose tissue into the circulation while preventing lipid uptake.[108] The observed association between the ANGPTL4 rs1044250 variant and increased waist circumference and blood pressure in the Han population supports these mechanistic insights, indicating that ANGPTL4 dysregulation not only contributes to impaired lipid clearance but also to the exacerbation of central adiposity and hypertension. Taken together, this indicates that ANGPTL4 is a common node in the intersection between lipid metabolism and cardiovascular regulation, with significant implications for the development of MetS and obesity-related complications.

While ANGPTL4 primarily regulates triglyceride hydrolysis and fatty acid mobilization, cholesterol homeostasis is also under substantial epigenetic control. Among the emerging ncRNAs involved in this process, APOA1-AS has attracted attention because of its close relationship with HDL metabolism and atherosclerotic risk. Abd-Elmawa et al reported that APOA1-AS plasma expression was significantly higher in atherosclerotic SLE patients compared with both healthy controls and non-atherosclerotic SLE patients.[72] Moreover, APOA1-AS expression was also positively associated with total cholesterol and LDL-C, while it was negatively associated with HDL-C.[72] Mechanistically, APOA1-AS functions as an antisense lncRNA that epigenetically capable of repressing APOA1 expression. Reduced APOA1 expression consequently impairs HDL-C biogenesis and reverse cholesterol transport, thereby facilitating cholesterol accumulation within the vascular wall and accelerating atherogenesis.[114] Consistent with this mechanism, elevated APOA1-AS expression was also observed in individuals with MetS, obesity, and hypertension,[72] further supporting its potential role as an epigenetic mediator linking dyslipidemia with cardiovascular complications in MetS.

Several epigenome-wide analyses have revealed that MetS is accompanied by widespread alterations in DNA methylation across multiple genes involved in glucose metabolism. TXNIP has consistently emerged as a major regulator linking epigenetic markers with glycemic imbalance, with cg19693031 and cg26974062 located within *TXNIP* being significantly associated with diabetes.[62] Mechanistically, TXNIP suppresses glucose uptake through downregulation of the surface expression and lysosomal degradation of glucose transporters (GLUTs),[115] while enhancing oxidative stress via thioredoxin binding.[116] *TXNIP* expression is upregulated in chronic hyperglycemia, thus triggering NLR family pyrin domain-containing 3 (NLRP3) inflammasome activation and inducing inflammatory signaling cascades.[117,118] Thus, the epigenetic modulation of TXNIP may contribute to MetS, particularly diabetes, so TXNIP is a promising biomarker for disease progression and potentially a therapeutic target.

Immune Response and Inflammatory Signaling

Chronic low-grade inflammation is a hallmark of the MetS. This condition arises from complex interactions between metabolic stressors, adipose tissue dysfunction, and immune cell activation. Among the key genetic mediators involved in this process, the receptor for advanced glycation end-products (AGER) has gained particular attention and is considered a major junctional node between adipose tissue expansion and inflammatory signaling.[67] The physiological role of AGER is mediated through its product, the receptor for advanced glycation end-products (RAGE), which activates intracellular signaling cascades to promote proinflammatory cytokine transcription on binding to its ligands such as advanced glycation end-products (AGEs), HMGB1, and S100 proteins.[119,120]

Recently, AGER has been shown to be overexpressed in the subcutaneous adipose tissue of obese women.[67] Interestingly, its proinflammatory properties appear to be more pronounced in visceral adipose tissue, suggesting that AGER overexpression cannot be interpreted as uniformly unfavorable.[120] While it amplifies ligand-derived inflammatory cascade in visceral adipose tissue, its upregulation in subcutaneous adipose tissue may serve as a buffer against excess metabolic stress, consistent with the idea of it being a metabolically safer depot.[119,121] These depot-specific differences may be due to lower ligand availability in subcutaneous adipose tissue and a predominance of anti-inflammatory macrophages that attenuate RAGE-induced signaling, whereas more ligand availability and pro-inflammatory immune cells amplify the inflammatory cascade, directly linking RAGE activity to metabolic dysfunction. However, this protective capacity seems limited to some extent, with the protective mechanism transitioning toward promoting chronic inflammation under a chronic metabolic overload.[122]

Beyond protein-coding inflammatory mediators such as AGER, emerging evidence suggests that non-coding RNAs may also contribute to immune dysregulation in MetS. Zhao et al reported significantly reduced plasma expression of the lncRNA SRA in individuals with MetS, accompanied by elevated circulating IL-6 and cortisol levels.[69] However, SRA expression alone was not independently associated with MetS. The PBMC-to-SRA ratio has emerged as an independent risk factor for MetS. Interestingly, Liu et al developed an SRA-deficient mouse model and observed an insulin sensitivity improvement, fatty liver reduction, and diet-induced obesity resistance,[123] rather than metabolic deterioration that would be expected if reduced SRA expression were directly pathogenic. Experimental evidence suggests that SRA functions as a coactivator of steroid hormone receptors and promotes adipocyte differentiation,[124] while also regulating inflammatory pathways involving tumor necrosis factor alpha (TNF-α) and chemokine (C-C motif) ligand 2 (CCL2).[123] Thus, the attenuation of these inflammatory

pathways in SRA-deficient mice further supports that SRA may contribute to obesity-associated inflammation and insulin resistance. Nevertheless, the reduced circulating SRA expression observed by Zhao et al contrasts with these experimental findings. This apparent discrepancy suggests that the role of SRA in metabolic dysfunction may be highly tissue-dependent and may differ substantially between circulating immune compartments and metabolically active tissues. Supporting this, other experimental studies have also demonstrated that SRA is predominantly expressed in adipose tissue, particularly within mature adipocytes.[125] Given its established role in promoting adipocyte differentiation, SRA may exert distinct biological effects across tissues that may potentially contribute to adipose tissue expansion and local inflammatory responses, whereas circulating SRA levels may reflect systemic immune response and metabolic alterations. Adipose tissue inflammation is increasingly recognized as a consequence of disrupted communication between metabolic and immune cell populations. Supporting this concept, the lincRNAs linc-DMRT2 and linc-TP53I13 were significantly downregulated in obese individuals and were detected in both adipocytes and immune cells.[70] Their distribution across these cellular compartments suggests a potential role in coordinating immune-metabolic axis within adipose tissue. Although their downstream molecular targets remain poorly characterized, the reduced expression of both transcripts in obesity raises the possibility that they contribute to the maintenance of adipose tissue homeostasis. Dysregulation of these lincRNAs may therefore facilitate the inflammatory remodeling of adipose tissue and promotes immune cells infiltration, chronic low-grade inflammation, and subsequently metabolic dysfunction.

In contrast to lncRNAs implicated in adipose tissue inflammation and metabolic dysfunction, ANRIL appears to be more closely related to vascular complications associated with cardiometabolic disease. Although Abd-Elmawa et al found no significant associations between ANRIL expression and conventional metabolic syndrome components such as obesity, dyslipidemia, diabetes, and hypertension,[71] ANRIL expression was markedly elevated among patients with atherosclerosis and was further increased in atherosclerotic SLE patients.[71] Mechanistically, ANRIL is induced by pro-inflammatory mediators such as TNF-α and NF-κB, subsequently regulates the expression of downstream cytokines such as IL-6 and IL-8.[126] Furthermore, increased ANRIL activity has been associated with enhanced endothelial cell proliferation and survival and subsequently leads to vascular remodelling and plaque progression.[126] Contrarily, suppression of ANRIL attenuate endothelial activation, reduce local inflammatory responses, and promote features associated with plaque stabilization, including increased fibrous cap integrity.,[126,127] Notably, emerging evidence suggests that the biological effects of ANRIL may differ according to its transcript isoforms, with distinct roles reported for circular and linear ANRIL in atherosclerotic plaque development.[126] Collectively, these findings may explain why ANRIL demonstrates a stronger association with atherosclerotic burden than with metabolic risk factors themselves, suggesting that its contribution to metabolic diseases may be more relevant to vascular complications than to the initiation of metabolic dysfunction.

Conclusion

Genetic and epigenetic factors are central to the pathogenesis of MetS, acting through interconnected pathways that regulate neuroendocrine signaling, adipogenesis, insulin signaling, metabolism, energy balance, and inflammation. While polymorphisms in several key genes predispose individuals to cardiometabolic traits, epigenetic modification, including DNA methylation, miRNAs, lncRNAs, and circRNAs regulation, mediate the influence of environmental and lifestyle exposures on disease risk. Despite substantial advances, the precise molecular mechanisms underlying these interactions remain incompletely understood and inter-population variability further underscores the complexity of gene-environment interactions. In addition, many candidate epigenetic biomarkers have primarily been validated in circulating blood samples without sufficient confirmation in metabolically active tissues such as adipose, liver, and skeletal muscle tissue, causing limitation in their translational applicability. Most current available studies are also cross-sectional, making it rather difficult to establish a time-bound causal relationships between lifestyle-related exposures and epigenetic dysregulation.

Future study should therefore integrate genomics, epigenomics, transcriptomics, and metabolomics, with longitudinal assessments of lifestyle-related factors including dietary patterns, physical activities, sleep behaviours, circadian rhythm disruptions, and psychosocial stressors. Prospective cohort studies incorporating biomarker-specific profiling and dynamic lifestyle monitoring may be an option to better characterize the evolution of each epigenetic alteration during MetS progression. Furthermore, tissue-specific validation using models or in vivo experimental approaches may help clarify

whether circulating epigenetic biomarkers reflect clinically relevant alterations in metabolically active tissues since biomarker discovery alone does not necessarily establish causal or tissue-specific involvement in metabolic dysregulation.

Collectively, these approaches may facilitate the development of robust biomarkers and a specific therapeutic strategy to further construct a population or sex-specific genetic risk model and ultimately enable more personalized risk stratification, prevention, therapy, and management of MetS.

Abbreviations

ABCG1, ATP-binding cassette sub-family G member 1; ACC1, acetyl-CoA carboxylase 1; AGER, advanced glycation end-products; AGER-1, advanced glycation end product receptor 1; AGEs, advanced glycation end-products; AGRP, agouti-related protein; AKAP7, A-kinase anchor protein 7; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; AMY, amylase activity, amylase; ANGPTL4, angiopoietin-like 4; ANRIL, antisense non-coding RNA in the INK4 locus; APOA1-AS, apolipoprotein A1 antisense; APOA5, apolipoprotein A5; APOC3, apolipoprotein C3; ARRDC4, arrestin domain containing 4; AT1aR, angiotensin type 1A receptors; ATP, adenosine triphosphate; ATP10A, ATPase phospholipid transporting 10A; ATP5E, ATP synthase F1 subunit epsilon; AUC, area under curve; BMI, body mass index; bNMF, bayesian nonnegative matrix factorization; CAD, coronary artery disease; CAMK2B, calcium/calmodulin dependent protein kinase II beta; CAV-1, caveolin 1; CCL2, chemokine (C-C motif) ligand 2; CDH13, cadherin 13; CGK, cGMP-dependent Protein Kinase; CircRNAs, circular RNAs; COX6C, cytochrome c oxidase subunit 6c; CPT1A, carnitine palmitoyltransferase 1A; CTBP1, C-terminal binding protein 1; CVD, cardiovascular diseases; DIP2C, disco-interacting protein 2 homolog c; DM, diabetes mellitus; DMPs, differentially methylated probes; DMRs, differentially methylated regions; DNA, deoxyribose nucleic acid; DRD2, dopamine receptor D2; DSCAM, down syndrome cell adhesion molecule; eNOS3, endothelial nitric oxide synthase; EPCs, endothelial progenitor cells; ERK5, extracellular signal-regulated kinase 5; EWAS, epigenome-wide association study; FABP1, fatty acid-binding protein 1; FADS, fatty acid desaturase; FBXO9, F-box protein 9; FH, familial hypercholesterolemia; FTO, fat mass and obesity-associated; GALNT2, polypeptide N-acetylgalactosaminyltransferase 2; GAS5, growth arrest-specific transcript 5; GLUTs, glucose transporters; GRS, genetic risk score; GRWD1, glutamate rich WD repeat containing 1; GWAS, genome-wide association study; HbA1c, hemoglobin A1c; HDAC7, histone deacetylase 7; HDL-C, high-density lipoprotein cholesterol; HMGCR, hydroxy-3-methylglutaryl-CoA reductase; HOMA-IR, homeostatic model assessment for insulin resistance; HPA, hypothalamic-pituitary-adrenal; IFG, impaired fasting glucose; IGF1R, insuling-like growth factor 1 receptor; IGT, impaired glucose tolerance; IL-1, interleukin-1; IL-1Ra, interleukin-1 receptor antagonist; IL6, interleukin-6; IL-6, interleukin-6; IRS, insulin receptor substrate; IRX3, iroquois homeobox 3; KCNJ11, potassium inwardly rectifying channel subfamily J member 11; KCNQ1, potassium voltage-gated channel, subfamily Q, member 1; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LIMD2, LIM domain containing 2; LPL, lipoprotein lipase; MAD1L1, mitotic arrest deficient 1 like 1; MAP2K5, mitogen-activated protein kinase kinase 5; MAPK7, mitogen-activated protein kinase 7; MC4R, melanocortin-4 receptor; MCT3, monocarboxylate transporter 3; MEG3, maternally expressed gene 3; MetS, metabolic syndrome; mRNA, messenger RNA; MTHFR, methylenetetrahydrofolate; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic/mammalian target of rapamycin complex 1; MTRR, methionine synthase reductase; NAFLD, non-alcoholic fatty acid liver disease; NBPF20, neuroblastoma breakpoint family member 20; NLRP3, NLR family pyrin domain-containing 3; NOS3-AS, nitric oxide synthase 3 antisense; NR3C1, nuclear receptor subfamily 3 group C member 1; NRF2, nuclear factor erythroid 2-related factor 2; PBMC, peripheral blood mononuclear; PCOS, polycystic ovarian syndrome; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction – restriction fragment length polymorphism; PCSK9, proprotein convertase subtilisin/kexin type 9; PDE1C, phosphodiesterase 1C; PDK4, pyruvatt dehydrogenase kinase 4; PDX1, pancreatic and duodenal homeobox 1; PEG3, paternally expressed 3; PFKFB2, phosphofructo-2-kinase/fructose-2,6-biphosphatase 2; PHOSPHO1, phosphoethanolamine/phosphocholine phosphatase; PON1, paraoxonase-1; PPARG, peroxisome proliferator-activated receptor Gamma; PRRC2A, proline rich coiled-coil 2A; PTBP1, polypyrimidine tract-binding protein 1; PTPRN2, protein tyrosine phosphatase receptor type N2; RAGE, receptor for advanced glycation end-products; RNA, ribonucleic acid; RPL9, ribosomal protein L9; SAMM50, sorting and assembly machinery component; SBP, systolic blood pressure; SCD1, stearoyl-CoA desaturase-1; SIDT2, SID1 transmembrane family member 2; SIK3, salt-inducible

kinase 3; SIRT1, sirtuin 1; SLE, systemic lupus erythematosus; SNPs, single-nucleotide polymorphisms; SOCS3, supressor of cytokine signaling 3; SQSTM1, sequestosome 1; SRA, steroid receptor RNA activator; SREBF1, sterol regulatory element-binding transcription factor 1; SREBP1, sterol regulatory element-binding protein 1; SREBP1c, sterol regulatory element-binding protein 1c; T2D, type 2 diabetes; TAGLN, transgelin; TCF7L2, transcription factor 7 Like 2; TCM, traditional chinese medicine; TDRD9, tudor domain containing 9; TG, triglyceride; TNF-α, tumor necrosis factor alpha; TOMM20, translocase of outer mitochondrial membrane 20; TXNIP, thioredoxin-interacting protein; UCP1, uncoupling protein 1; UFM1, ubiquitin fold modifier 1; VDR, vitamin D receptor; WHO, world health organization.

Data Sharing Statement

Data of this study can be accessed through corresponding author by request.

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Author Contributions

EFA contributed in conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing - original draft, and writing - review and editing and led these processes. MPL, DNF, SAA, AKF, GSJS, and MPAW contributed in data curation, formal analysis, investigation, methodology, software, validation, visualization, writing - original draft, and writing - review and editing. NSR, PPS, YSP, GIN, MG, MRAAS, YS, and THA contributed in data curation, methodology, supervision, validation, visualization, and writing - review and editing. YM contributed in data curation, methodology, validation, visualization, and writing - review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest.

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