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Genetics and epigenetics in the obesity phenotyping scenario

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Abstract

Obesity is a common complex trait that elevates the risk for various diseases, including type 2 diabetes and cardiovascular disease. A combination of environmental and genetic factors influences the pathogenesis of obesity. Advances in genomic technologies have driven the identification of multiple genetic loci associated with this disease, ranging from studying severe onset cases to investigating common multifactorial polygenic forms. Additionally, findings from epigenetic analyses of modifications to the genome that do not involve changes to the underlying DNA sequence have emerged as key signatures in the development of obesity. Such modifications can mediate the effects of environmental factors, including diet and lifestyle, on gene expression and clinical presentation. This review outlines what is known about the genetic and epigenetic contributors to obesity susceptibility, along with the albeit limited therapeutic options currently available. Furthermore, we delineate the potential mechanisms of actions through which epigenetic changes can mediate environmental influences and the related opportunities they present for future interventions in the management of obesity.

Keywords Genetics · Genomics · Obesity · Monogenic · Polygenic · GWAS · Epigenetics

Abbreviations

ACTH	Adrenocorticotropic Hormone
ADCY3	Adenylate Cyclase 3
ADORA2A	Adenosine A2a Receptor
Agouti	Agouti
AI	Artificial Intelligence
AKR1CL1	Aldo-Keto Reductase Family 1 Member C8
ALDH1L2	Aldehyde Dehydrogenase 1 Family Member L2
ALDH2	Aldehyde Dehydrogenase 2 Family Member
ALMS1	ALMS1 Centrosome and Basal Body Associated Protein
AMP	Adenosine Monophosphate
AMPKA2	Protein Kinase AMP-Activated Catalytic Subunit Alpha 2
ATP	Adenosine Triphosphate
BBS	Bardet-Biedl Syndrome
BDNF	Brain-Derived Neurotrophic Factor
BIA	Bioimpedance Analysis
BMAL1	Brain and Muscle Aryl Hydrocarbon Receptor Nuclear Translocator–Like 1
BMI	Body Mass Index
BRD2	Bromodomain-Containing Protein 2
CAMKK2	Calcium/Calmodulin-Dependent Protein Kinase 2
CART	Cocaine- and Amphetamine-Regulated Transcript
CBP	Sarcoplasmic Calcium-Binding Protein
CCDC112	Coiled-Coil Domain-Containing 112
CCL2	C-C Motif Chemokine Ligand 2
CD36	Cd36 Molecule / Fatty Acid Translocase
CHST8	Carbohydrate Sulfotransferase 8

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CLOCK	Clock Circadian Regulator
CNV	Copy Number Variants
CPE	Carboxypeptidase
CPT1	Carnitine Palmitoyltransferase-1
CPT1A	Carnitine Palmitoyltransferase 1 A
CR1	Cannabinoid Receptor Type 1
CREBRF	CAMP Responsive Element Binding Protein 3 Regulatory Factor
CRISP2	Cysteine-Rich Secretory Protein 2
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRY1	Cryptochrome Circadian Regulator 1
CRY2	Cryptochrome Circadian Regulator 2
CS	Citrate Synthase
CT	Computerized Tomography
CYCSP30	CYCS Pseudogene 30
DA	Dopamine
DBH	Dopamine Beta-Hydroxylase
DNMT	DNA Methyltransferases
DXA	Dual-Energy X-Ray Absorptiometry
EBF1	EBF Transcription Factor 1
C/EBPA	CCAAT Enhancer Binding Protein Alpha
C/EBPB	CCAAT Enhancer Binding Protein Beta
EGG	Early Growth Genetics
ENSA	Endosulfine Alpha
ETS	V-Ets Avian Erythroblastosis Virus E26 Oncogene Homolog 1
FASN	Fatty Acid Synthase
FDA	U.S. Food and Drug Administration
FGFR1	Fibroblast Growth Factor Receptor 1
FOXP2	Forkhead Box P2
FTO	Fat Mass and Obesity Associated
GABRP	Gamma-Aminobutyric Acid Type A Receptor Subunit Pi
GAD1	Glutamate-Decarboxylase
GFI1	Growth Factor Independent 1 Transcriptional Repressor
GLIS3	GLIS Family Zinc Finger 3
GLUT4	Glucose Transporter 4
GO	Gene Ontology
GSK3A	Glycogen Synthase Kinase 3 Alpha
GWAS	Genome-Wide Association Studies
GYG2P1	Glycogenin 2 Pseudogene 1
H3K4me3	Tri-Methylation at the 4th Lysine Residue of the Histone H3 Protein
HDAC	Histone Deacetylase
HDAC4	Histone Deacetylase 4
HDM	Histone Demethylase
HHEX	Haematopoietically Expressed Homeobox
HIF3A	Hypoxia Inducible Factor 3 Subunit Alpha
HOXA2	Homeobox A2
IGF2	Insulin Growth Factor 2
IGF2BP2	Insulin-Like Growth Factor 2 mRNA Binding Protein 2
IGF2R	Insulin Growth Factor 2 Receptor
IL-1B	Interleukin 1B
IL-6	Interleukin 6
INS	Insulin
INSM1	Insulinoma Associated Repression Factor 1
IRS1	Insulin Receptor Substrate 1
IRS2	Insulin Receptor Substrate 2
JAZF1	JAZF Zinc Finger 1
KAL1	(ANOS1) Anosmin 1
KCNA3	Potassium Voltage-Gated Channel Subfamily A Member 3 Gene
KCNQ1	Potassium Voltage-Gated Channel Subfamily Q Member 1 Gene
KSR2	Kinase Suppressor of Ras 2
LD	Linkage Disequilibrium
LEP	Leptin
LEPR	Leptin Receptor
LINE-1	Long Interspersed Nucleotide Element-1
LRRC27	Leucine-Rich Repeat-Containing 27
LYPLAL1	Lysophospholipase Like 1
MAF	Minor Allele Frequency
MAP2K4	Mitogen-Activated Protein Kinase 4
MC4R	Melanocortin 4 Receptor
MCOLN3	Mucolipin TRP Cation Channel 3
MIST	Macrophage Inflammation-Suppressing Transcript
MOMO	Macrocephaly, Obesity, Mental Disability, Ocular Abnormalities
MRAP2	Melanocortin 2 Receptor Accessory Protein 2
MRI	Magnetic Resonance Imaging
MSH	Melanocyte-Stimulating Hormone
NAMPT	Nicotinamide Phosphoribosyltransferase
NCOR2	Nuclear Receptor Corepressor 2
NFIX	Nuclear Factor I X
NIPBL	NIPBL Cohesin Loading Factor
NPY	Neuropeptide Y
NR2B	Ionotropic Glutamate Receptor Subunit
NRF1	Nuclear Respiratory Factor 1
NTRK2	Neurotrophic Receptor Tyrosine Kinase 2
NUDT3	Nudix Hydrolase 3
PC1/3	Proprotein Convertase-1/3
PCSK1	Proprotein Convertase Subtilisin/Kexin Type 1
PDK4	Pyruvate Dehydrogenase Kinase 4

PDX1	Pancreatic Homeobox Transcription Factor
PER1	Period Circadian Protein Homolog 1
PER2	Period Circadian Regulator 2
PFKFB3	6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3
PGC1A	Peroxisome Proliferator-Activated Receptor Γ Coactivator 1 Alpha
PHIP	Pleckstrin Homology Domain Interacting Protein
PIK3R1	Phosphoinositide-3-Kinase Regulatory Subunit 1
PKD4	(PKHD1) Polycystic Kidney and Hepatic Disease 1
PNPLA3	Patatin Like Phospholipase Domain Containing 3
POMC	Proopiomelanocortin
PPARD	Peroxisome Proliferator-Activated Receptor Delta
PPARG	Peroxisome Proliferator-Activated Receptor Gamma
PPARGC	PPARG Coactivator 1 Alpha
PROK2	Prokineticin 2
PROKR2	Prokineticin Receptor 2
PWS	Prader-Willi Syndrome
QTL	Quantitative Trait Locus
RAI1	Retinoic Acid Induced 1
RAMP3	Receptor Activity Modifying Protein 3
ROHHAD	Rapid Onset obesity, Hypothalamic dysfunction, Hypoventilation, and Autonomic Dysregulation
ROHHADNET	Rapid Onset obesity, Hypothalamic dysfunction, Hypoventilation, Autonomic Dysregulation, and Neuro Endocrine Tumor
RORA	RAR Related Orphan Receptor A
RWAS	Regulome-Wide Association Studies
SARS	Severe Acute Respiratory Syndrome
SCD1	Stearoyl-CoA Desaturase 1
SERPINE-1	Serpin Family E Member 1
SH2B1	Src Homology 2 B Adapter Protein
SIM1	Single-Minded Homologue of Drosophila
SLC2A4	Solute Carrier Family 2
SLFN12	Schlafen Family Member 12
SNCA	Alpha-Synuclein
SNP	Single-Nucleotide Polymorphism
SOCS2	Suppressor of Cytokine Signaling 2
SREBF1	Sterol Regulatory Element-Binding Transcription Factor 1
SREBPs	Sterol Regulatory Element-Binding Proteins
SUGP	SURP and G-Patch Domain Containing 1
TCF7L2	Transcription Factor 7 Like 2
TET	Tet Methylcytosine Dioxygenase
TFAM	Transcription Factor A, Mitochondrial
THNSL2	Threonine Synthase Like 2
TMEM18	Transmembrane Protein 18
TNF	Tumor Necrosis Factor
TRIB2	Tribbles Pseudokinase 2
TRIM2	Tripartite Motif-Containing 2
TUB	TUB Bipartite Transcription Factor
TWAS	Transcriptome-Wide Association Studies
UBE2E2	Ubiquitin Conjugating Enzyme E2 E2
UCP1	Uncoupling Protein 1
UGT1A	UDP Glucuronosyltransferase Family 1 Member A Complex Locus
US	Ultrasound
VAT	Visceral Adipose Tissue
WAGR	Wilms-Tumor-Aniridia-Syndrome
WAGRO	Wilms Tumor, Aniridia, Genitourinary Anomalies, Mental Retardation, and Obesity
WC	Waist Circumference
WES	Whole Exome Sequencing
WHO	World Health Organization
WHR	Waist-Hip Ratio

1 Introduction

Obesity is a phenotype in which the percentage of body fat is increased to the point where health and well-being are impaired. The World Health Organization has declared obesity a "global epidemic" given its alarming prevalence both in developed and developing countries. In the US, the prevalence of obesity between 2017 and 2020 was 41.9% for adults over 20 years old, with 19.7% being approximately 14.7 million children and adolescents aged 2–19 years [1]. Obesity is a driver of a wide range of chronic cardio-metabolic diseases, including type 2 diabetes and cardiovascular disease, along with numerous non-metabolic co-morbidities such as several types of cancer [2]. The mechanical issues resulting from increased body weight can drive risk for osteoarthritis [3] and sleep apnea [4]. The recent COVID-19 pandemic revealed that individuals living with obesity were at increased risk of severe illness and hospitalization [5–7], highlighting its impact on communicable diseases, particularly viral infection [8]. Altogether, obesity represents a significant health burden on society, shortening life expectancy and reducing life quality.

While there is clear evidence that environmental factors contribute substantially to obesity risk, including a

sedentary lifestyle, high-calorie/nutrient-poor food intake and reduced energy expenditure, it is also widely known that genetics contribute substantially to determining an individual's response to an 'obesogenic environment' [9]. Early evidence from family [10–12], twin [13–15], and adoption [16] studies has estimated the heritability of obesity/BMI at 70–80%. It is now feasible to characterize underlying genetic mechanisms that influence variation in BMI.

The genetics community typically places obesity into two broad categories: monogenic and polygenic. The monogenic form is generally inherited through Mendelian inheritance; the related rare traits present as relatively severe and early age of onset, and caused by genomic deletions or deleterious variants in specific genes. On the other hand, the common polygenic form of obesity results from hundreds of independent variants across the genome, each conferring a small effect. Since the first 2007 report, genome wide association studies (GWAS) have revealed multiple new insights into obesity and BMI genetics. However, they have fallen short of defining the entire repertoire of genetic contributors to date; meta-analysis studies of multiple GWAS datasets have shown that the identified variants to date collectively only explain less than 6% of the observed variability in BMI [17, 18], indicating that much of the "missing heritability" [19] still needs to be found. Indeed, a recent GWAS of height that reached saturation for discovered loci revealed more than 12,000 signals [20]; as such, one would expect that many additional BMI loci remain to be uncovered. Even if one could account for the missing heritability, there is a substantial proportion of variability between individuals driven by gene-environment interactions contributing to the etiology of obesity. Non-genetic/behavioral factors, such as diet and exercise, can alter epigenetic signatures, and consequently influence gene expression. Clinical variables relevant to obesity strongly correlate with epigenetic changes in cell types, such as those from skeletal muscle, liver, and adipose [21–24]. Moreover, such epigenetic modifications can be reversed, making them amenable for perturbation via therapeutics. Indeed, a broad range of study designs, ranging from cell-based systems, rodent models to human systems, have revealed multiple factors that correlate with the etiology of human obesity. And with these expanding biometric indicators of obesity, the phenotyping and subtyping of obesity has become even more complex.

To achieve precision medicine for obesity treatment, it is crucial to identify risk profiles for individuals through assessing multiple contributing factors. This will not only help predict obesity risk and related diseases for a given individual, but will also aid in determining treatment response. This review summarizes the current understanding of genetic factors, gene-environment interactions and epigenetic alterations that lead to the derailed metabolism observed for obesity, which in turn can be harnessed to aid precision therapies for this disease in the future.

2 Anthropometric parameters of obesity

2.1 BMI – a classic with limitations

Body mass index (BMI) is commonly used to measure excess body weight and obesity. Adult BMI between 18.5 and 25 kg/m^2 is considered average weight, 25–30 kg/m^2 overweight, and over 30 kg/m^2 is defined as obese. But despite its widespread use, BMI as a measure of adiposity has limitations. Most notably BMI does not differentiate fat-free and fat mass nor consider body fat distribution, which can lead to misleading interpretations about an individual's health risks. Indeed, extensive research has shown that fat distribution has a greater correlation with certain health risks, including cardiovascular disease and cancer [25, 26].

2.2 Other measurements

To establish the presence of obesity and its relation to potential associated diseases, other indices – waist and neck circumference, waist-to-hip ratio (WHR) and waist-to-height ratio – have shown to independently serve as better indicators of central obesity, predictors of cardiometabolic disease [26, 27] and more accurately associated with overall mortality [28–30]. However, differences between individuals in the same apparent categories persist with respect to the percentage of fat and lean body mass observed across different ancestral groups [31]; specifically, differences in gynoid subcutaneous adipose tissue between age groups in females [32]. Stratifying anthropometric measurements by BMI, sex and ethnicity have improved health risk assessment accuracy [33, 34].

2.3 Measuring methods

Advances in technology have enabled assessment of an individual's anthropometric classification based on body fat using more accurate measurement methods, including magnetic dual-energy X-ray absorptiometry (DXA), air-displacement plethysmography (BodPod), bioimpedance analysis (BIA), computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US). MRI, CT, DXA, and ultrasounds were previously used as reference standards in decade-apart meta-analysis studies, which consistently rendered low sensitivities and relatively high specificities for anthropometric measures. Despite the cost, invasiveness and sparse accessibility, these imaging techniques triumphed over traditional anthropometric measurements such

as BMI, WC, and WHR in predicting obesity-related health risks.

3 Genetic determinants of obesity

Monogenic obesity is the consequence of a mutation in a given gene and can present as either syndromic or non-syndromic; indeed, this setting has blazed the trail with respect to the first obesity genes discovered. The most common form of obesity is the polygenic version, driven by hundreds to possibly thousands of independent single nucleotide polymorphisms (SNPs) distributed across the human genome and therefore has a complex mode of inheritance typical of common traits. The expression of mutations driving the pathogenesis of monogenic obesity can be partly impacted by polygenic obesity susceptibility in a given subject [35].

3.1 Syndromic and monogenic obesity

This rare form of obesity typically presents with various comorbidities, such as cognitive delay [36]. Currently, of the almost eighty obesity syndromes that have been identified to date, only a minority have been either fully or partially defined, with the remainder just mapped to an approximate genomic location or not characterized at all [36]. The best-known syndromes include Prader-Willi syndrome (PWS) caused by an imprinting change on chromosome 15, the related Prader-Willi-like syndrome driven by deletion events on chromosome 16 impacting genes such as *SIM1* (which encodes a crucial transcription factor for hypothalamus paraventricular and supraoptic nuclei development) [37], Fragile X syndrome, Bardet-Biedl syndrome (BBS, caused by multiple different genes), Albright's hereditary osteodystrophy caused by mutations in *GNAS*, and Wilms-Tumor-Aniridia-Syndrome (WAGR) driven by deletion events on chromosome 11) [38]. Given how rare these presentations are, they remain challenging to be distinguished from conventional obesity [39].

3.1.1 Heterogeneity of clinical features

Twenty three obesity syndromes display wide phenotypic heterogeneity [36]. Studying such heterogeneity in syndromic obesity is challenging due to limited cases worldwide. Some contributing factors include genetic or allelic heterogeneity, the impact of the environment, including diet and medication, ancestral differences, gene-gene interactions and gene-environment interactions affecting epigenetic patterning.

Genetic heterogeneity includes structural variants like deletions, insertions, inversions and complex rearrangements. Bardet–Biedl syndrome (BBS) is one such example, with in excess of twenty genes implicated to date [40–42] but with the clinical presentation being relatively homogeneous. Likewise, Kallmann syndrome is due to mutations in *PROK2, KAL1 and FGFR1*, and similarly presents homogeneously. In contrast, Cornelia de Lange syndrome (CdLS) behaves quite the opposite; for instance, an *NIPBL* c.2827delA mosaic can present with either severe or milder forms [43]. The ciliopathy, Alström syndrome, is driven by a range of missense and frameshift causal mutations in *ALMS1*, differing almost at the individual level [44].

Differences in ethnicity can lead to variation in clinical presentation. Phenotypic differences for PWS have been reported in African American patients and can result in underdiagnosis in this population. Treatment can also modify clinical presentation of obesity syndromes; for instance, growth hormone treatment for PWAS can improve symptoms [45]. The role of epigenetics in human diseases, including obesity, is still being actively investigated, e.g., monozygotic twins have shown discordancy for the ROHHAD phenotype ('Rapid Onset obesity with Hypothalamic dysfunction, Hypoventilation, and Autonomic Dysregulation'), with just one of the twins presenting with the syndrome [46].

3.1.2 Diagnostic challenges due to phenotypic similarities

The clinical presentation of identified obesity syndromes is frequently similar, making diagnosis/phenotyping challenging. For example, the majority of such syndromes present with mental retardation, while microcephaly and macrocephaly are also a common feature [36]. Both clinical differences and commonalities features lead to diagnostic challenges. An eight-year-old patient was first diagnosed with BBS but later correctly diagnosed with Alström syndrome at fourteen years old after updated clinical and genetic analysis. Indeed both these syndromes are ciliopathies, and have similar presentations including obesity and retinal degeneration, but their respective genetic etiologies are distinct [47].

3.1.3 Evolving clinical picture of syndromes

Studies of patients with specific obesity syndromes can help refine diagnosis and treatment options but are limited by small sample sizes and overlap of symptoms between syndromes. For instances, an investigation of seven Kabuki syndrome patients identified ocular anomalies from three cases as novel features for diagnosis and treatment options [48]. Macrosomia was suggested to be excluded from the MOMO syndrome ('Macrocephaly, Obesity, Mental disability, Ocular abnormalities') after two additional reported

cases [49]. The endocrine manifestations of ROHHADNET syndrome were studied in six patients and varied hypothalamic-pituitary endocrine dysregulation was found, deeming it crucial to be considered during the diagnosis process for all obesity cases with early onset [50]. Such characterization, which does not just entail medical records, is expensive with respect expertise and time required.

3.1.4 Combining and separating syndromes

Advances in genetics have led to the reclassification of syndromes to aid improved understanding and diagnostic approaches. Prior to genetic testing, diagnoses were based principally on physical characteristics. For example, Carpenter, Goodman, and Summit syndromes were proposed to be combined into one due to their similarities in symptoms including obesity features; however, variation in these given symptoms have now be attributed to genetic differences [51]. Recently, genetic evidence has been used to subdivide WAGR syndrome into two separate disorders, WAGR and WAGRO (WARG with Obesity), with the latter characterized by obesity and molecular testing confirmation of *BDNF* deletions [52, 53].

3.1.5 Advances in genetic elucidation

Genetic elucidation of syndromes is critical for understanding the underlying molecular mechanisms and improving diagnosis, treatment, and care. Techniques such as whole-exome sequencing (WES), linkage mapping, candidate gene assessments and cytogenetics have been leveraged to reveal critical chromosomal regions and genes associated with syndromic obesity. For example, the multiple genes causal for BBS have been determined using various methods [40–42].

3.1.6 Complex patterns of genetic inheritance

With an expanding genetic picture of obesity syndrome drivers, complexities of inheritance are being observed. Kallmann syndrome can be caused by mutations in autosomal genes *PROK2, KAL1 and FGFR1*, or *KAL1* on the X chromosome, each presenting with different heterozygous, homozygous and compound states [54]. Studies have also suggested that BBS may be a complex disorder caused by a combination of three mutant alleles [55, 56], though this is considered a rare phenomenon. Genetic factors that influence the manifestation of a syndrome include mosaicism [57], skewed X inactivation [58] and deletion/duplication of multiple adjacent genes [59].

The current classification of syndromes was developed principally based on cardinal features, which may need to be updated or already is. Leveraging genetic testing to define syndromic obesity should aid efficiency, enhance classification and improve the diagnosis process, management and treatment.

3.2 Monogenic (non-syndromic) obesity

Some causal genes for obesity exert substantial effects and are inherited in a Mendelian pattern, whose predominant trait is excess adiposity. Endocrine disorders and hyperphagia typically characterize them. Most genes and pathways causal for monogenic obesity were first discovered in transgenic mice presenting with spontaneous obesity and hyperphagia. 'Reverse genetics' could identify causal mutations in the *ob* (encoding leptin), and *db* (encoding the leptin receptor) genes [60, 61]. These discoveries in mice were quickly followed with multiple human genes encoding components of the leptin–melanocortin pathway, crucial for control of appetite. Figure 1 summarizes the known genes and factors involved in this key circuit.

3.2.1 LEP

Congenital leptin deficiency is inherited recessively and was initially characterized in two Pakistani cousins presenting with obesity due to a frameshift mutation in *LEP* [62]. Since then, ten other mutations in *LEP* have been described [63–73]. Symptoms include rapid weight gain, severe early-onset obesity and intense hyperphagia [74]. Recombinant leptin can be used to improve adiposity and restore related functions [73, 75]. Myalept (metreleptin) is an FDA-approved therapeutic for treatment of congenital leptin deficiency [76].

3.2.2 LEPR

Subjects with leptin receptor *(LEPR)* mutations present with comparable symptoms to those with leptin deficiency, but lack the signature of serum hormone deficiency [77]. Advances in DNA sequencing have enabled detections of mutations in *LEPR*, which can affect 2–3% of a given population. Some patients also develop growth hormone and thyroid function deficiency; however, homozygous carriers of *LEPR* mutations do not respond to recombinant leptin.

3.2.3 POMC

Autosomal recessive inheritance of deficiency in POMC leads to a lack of ACTH, α-MSH and β-endorphins [78]. This can cause red hair and severe obesity via an α-MSH influence on both pigmentation and appetite. A rare deficiency of ACTH causes adrenal insufficiency. Early diagnosis combined with glucocorticoid replacement therapy

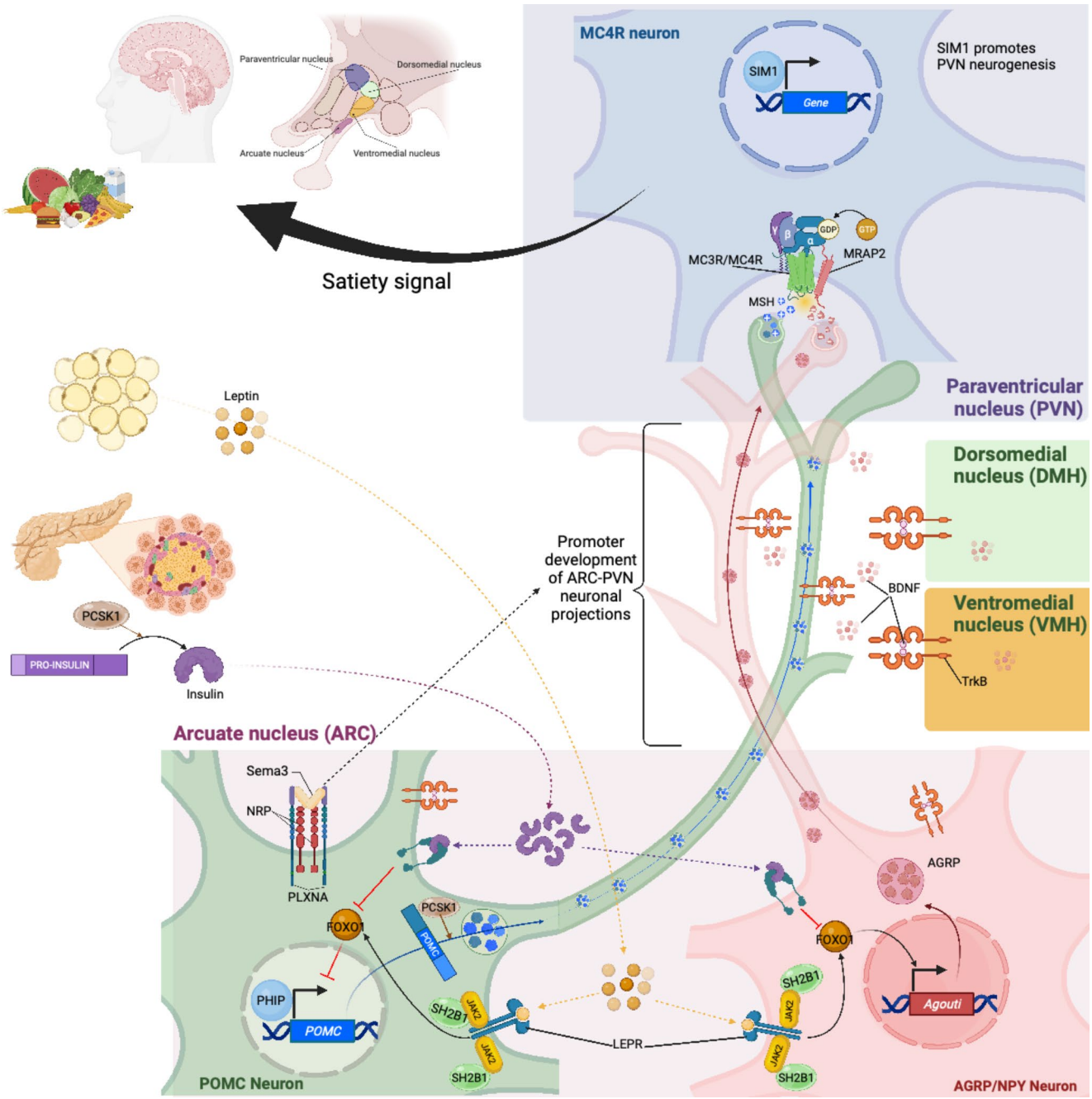

Fig. 1 Leptin-melanocortin pathway. Leptin is an anorexigenic hormone produced by white adipocytes, with its levels driven by the degree of fat mass present, and influences food consumption together with energy balance [112]. When its circulating levels become lower in the fasting state and rise when feeding takes place, leptin influences appetite via the hypothalamus [113, 114]. The arcuate nucleus is a component of the hypothalamus, where a key isoform of leptin receptor resides in two types of neurons, one expressing POMC and the other expressing agouti-related protein (AGRP) [115]. Leptin stimulates neurons expressing POMC, which is subsequently processed to various active melanocortin peptides [116]. The POMC-expressing neurons contact MC4R neurons in the paraventricular nucleus (PVN) where these melanocortin peptides influence a reduction in intake of food [115], whereas AGRP antagonizes MC4R to do the opposite [115, 117]; as such representing a finely tuned balance in the regulation of appetite

is vital for efficient treatment. A few studies have found *POMC* mutations in individuals with obesity, but with no other symptoms [79, 80]. Setmelanotide, which activates the melanocortin-4 receptor, has the potential as a treatment for POMC deficiency [81].

3.2.4 MC4R

Mutations in *MC4R*, both autosomal dominant [82] and recessive, drive increased appetite and feeding behavior in children, along with additional co-morbidities principally related to growth [83, 84].

MC4R heterozygous mutations are the most frequent drivers of monogenic childhood obesity, being observed in as many as 5% of pediatric patients [83, 85, 86] and caused by an array of nonsynonymous variants across the gene [87–89]. Furthermore, the impact of such mutations can be influenced by polygenic risk scores for common obesity [35]. Researchers are currently exploring ways to perturb MC4R to improve satiety circuits, given that no such treatments are currently available [90–92].

3.2.5 ADCY3

A WES study on consanguineous families from Pakistan identified four children suffered from severe obesity with extremely rare homozygous *ADCY3* mutations. The encoded cyclase catalyzes the synthesis of cyclic AMP from ATP. Such loss-of-function mutations are hypothesized to interfere with several anorexigenic signaling cascades [93]. The main clinical features are early onset hyperphagia and obesity.

3.2.6 SIM1

Loss-of-function mutations in the gene encoding the transcription factor 'Single-minded homolog of *drosophila*' (SIM1) lead to changes in feeding behavior and extreme obesity [37, 94]. Furthermore, a novel *SIM1* variant, p.D134N, has been recently implicated in monogenic pediatric obesity [95].

3.2.7 NTRK2

Neurotrophins contribute to the development, maintenance and function of nerves in the peripheral and central nervous system. Studies on animals have shown that the tropomyosin receptor kinase B (TrkB, encoded by *NTRK2*), and its ligand BDNF, play a role in regulating food intake and body weight. A dominantly inherited mutation that results in loss of function of *NTRK2* was reported in one subject with severe obesity but no other related symptoms [96].

3.2.8 BDNF

Brain-derived neurotrophic factor (BDNF) exerts its influence in the hypothalamus. It plays a key role in controlling feeding behavior and energy balance, partly due to its influence on leptin signaling [97]. Deletions in *BDNF* as part of the WAGRO syndrome have been linked to early-onset obesity [53]. Furthermore, multiple missense mutations within *BDNF* drive the pathogenesis of severe obesity [98–101].

3.2.9 SH2B1

'Src homology 2 B adapter protein' (SH2B1) helps regulate sensitivity to leptin [102]. Autosomal dominantly inherited *SH2B1* mutations are known to lead to severe childhood obesity [103], along with features of developmental delay. It has been shown that the effects of each mutation can vary [104].

3.2.10 Other genes

Kinase suppressor of Ras 2 (*KSR2*) mutations can cause hyperphagia, low heart rate, and insulin resistance, with metformin being used as treatment [105]. Mutations in the genes *PCSK1* encoding proprotein convertase-1/3 (PC1/3) result in a range of diabetes-related traits and extreme childhood obesity [106]. The gene products represent attractive therapeutic targets, but no treatments have been developed to date. A homozygous frameshift mutation in *TUB* was found in a subject with obesity and vision disorders [107]. A truncating mutation in the carboxypeptidase (*CPE*) gene was found in one subject with severe obesity [108]. A truncating mutation in the retinoic acid induced 1 (*RAI1*) gene was linked to hypoventilation, developmental disability and severe obesity [109]. Melanocortin receptor accessory protein 2 (*MRAP2*) variants have been reported to increase obesity risk [110]. And *PHIP* mutations correlate with developmental delay, intellectual disability and being overweight. The mechanism by which these genes contribute to obesity is principally through repression of *POMC* expression or interference with leptin-melanocortin signaling [111].

3.2.11 Whole exome sequencing and the future

Newer comprehensive sequencing methods can aid new genetic insights into obesity, and new discoveries are happening nearly every day. For instance, twenty-two *GNAS* mutations (encoding the Gαs protein, and involved in signaling through G protein-coupled receptors) have been found with WES, resulting in children with severe obesity, reduced growth and developmental delay [118].

And like syndromic, non-syndromic monogenic obesity is approaching the era where diseases are better classified by genetic profiles rather than the underlying cardinal symptoms.

3.3 Polygenic obesity

Most individuals with obesity develop the common/multifactorial form, caused by a combination of multiple genetic variations (polygenic), each with modest effects. The discovery of genes contributing to this type of obesity has been a slow process, starting with candidate gene studies in the 1990s, then family-based linkage studies leading up to genome-wide association studies (GWAS).

3.3.1 GWAS

The discovery of genes contributing to common diseases accelerated with the advent of GWAS. The first GWAS for BMI was published in 2007, where it reported the *FTO* locus as being strongest association signal [119]. To date, GWAS has identified more than a thousand loci associated with BMI/obesity and its related comorbidities. However, despite the identification of a myriad of loci, in combination, these signals only explain approximately 5% of the variance in BMI [18]. Given the limitation of BMI as a proxy for overall adiposity, as discussed above, GWAS has also been performed on more specifically-defined obesity phenotypes, including WHR [120], body fat percentage [121, 122] and circulating leptin and leptin receptor levels [123, 124]. These more specific studies are often smaller in size, and therefore lacking in relative statistical power, but reveal more direct biological relevance underpinning obesity.

3.3.2 GWAS and fat distribution

Genetic components characterize 30–55% of fat distribution. Three major studies have shown that the WHR has a significant genetic component [120, 125, 126]. With their increasing sample sizes, a growing number of significant loci have been reported, with a subset exhibiting sex dimorphism. Furthermore, it has been reported recently that the genetics of sexually dimorphism influence human adipose distribution, where genetic-mediated process were found to underpin adipose distribution specifically in females leading to metabolic dysfunction in women [127].

A study of subjects from five different ancestries found protein-coding variants influencing variations in fat distribution. Fifty-six significant coding variants were identified, with forty-three being common, and twenty-five also associated with BMI. The remaining thirty-one influenced adipose tissue topography. Nineteen had sex-specific effects, where sixteen were more strongly associated with WHR in women [128]. Unlike BMI loci, there was no evidence that genetic variants near genes related to central nervous system regulation had any impact on the distribution of fat [129].

Associations with abdominal visceral adipose tissue (VAT) and WC were found near *THNSL2* only in women [130], near *BBS9* and *CYCSP30* [131]. A more recent study found the *UBE2E2* locus associated with the VAT:subcutaneous fat ratio [132], with loss of function mutations in a mouse model impacting differentiation of adipocytes.

The genetics of ectopic fat deposition has also been investigated. A previous study found moderate genetic correlations among six ectopic fat depots, where *ENSA, TRIB2*, and *EBF1* were associated with heart deposition specifically, suggesting common and depot-specific genetic determinants [132]. Another study found several genetic variants associated with liver fat levels, including at *UGT1A, SOCS2, RAMP3, PNPLA3* and *SUGP1* [133].

3.3.3 Childhood obesity loci

GWAS has been conducted to study the genetics of obesity by integrating demographic factors such as sex and age. The Early Growth Genetics (EGG) consortium and other investigative teams have studied birth weight, pediatric BMI and childhood obesity. Most of the identified loci are also associated with obesity and/or BMI in adults, including at the *FTO* locus across multiple ancestries, highlighting that the genetics of obesity is relatively consistent over the lifecycle. However, a distinct genetic signature for peak BMI during infancy has also been reported [134].

3.3.4 Sex as confounding factor

A number of loci have been reported for waist-related traits, such as waist-to-hip ratio, that are stronger or exclusive to women [120, 135, 136]. No interaction was found between sex and BMI loci in those studies. By contrast, another study in subjects of Asian ancestry found that four BMI loci were more strongly associated in males [137]. A targeted analysis of BMI, WC, and WHR variants in Chinese subjects found that specific loci like *MC4R* and *LYPLAL1* were associated with female visceral fat area, and *ALDH2* in males [138]. Several BMI and waist-hip ratio loci revealed sexual dimorphism in subjects of African ancestry [139]. As such, obesity genetic associations can be impacted by sex in an ethnicity/population-dependent manner.

3.3.5 Ethnicity as cofounding factor

Most GWAS for obesity have been conducted in populations of European ancestry. However, additional loci have been uncovered in other ethnicities [139–142], albeit with much smaller sample sizes. These loci often demonstrate good transferability across other ancestries, but the allele

frequencies and effect sizes are often substantially different. Genetic correlation assessments across populations point to yet-to-be-discovered loci for BMI in specific ancestral groups. To address this point, increasing statistical power by including additional subjects in GWAS of specific ancestries have been conducted, along with searching for specific high-impact variants conferring effects specifically in population isolates. Examples include *CREBRF* discovered in Samoans and *ADCY3* first detected in Greenlanders [143–145].

3.3.6 Low frequency and rare variants

Microarray arrays leveraged for GWAS initially provided strong coverage for common variation (MAF > 5%), but as the technology has developed and informed by more fully sequenced human genomes, detection of lower frequency variation (MAF = 1–5%) and even rare variants (MAF < 1%) has become increasingly feasible; indeed, such variants are more likely to reside in coding and regulatory elements and therefore plausibly pathogenic. Furthermore, such genotyping data can be leveraged to detect copy number variants (CNVs) contributing to obesity risk, with a number reported to date. Rare (MAF < 1%) and low frequency (MAF = 1–5%) variants generally impact coding and regulatory elements more frequently [146]. An effort conducted in approximately 700,000 subjects to uncover rare variants contributing to variation in BMI, revealed coding mutations across 13 genes [147]. Despite these successes, the haul of variants at this scale of sample size is considered modest, with more expected to be found as collections increase in number even further.

3.3.7 Target genes and functional annotation

Although GWAS has been very successful in detecting common variants associated with complex traits, understanding the underlying mechanisms of action has remained elusive. GWAS makes no inference of either the causal variant(s) or the corresponding effector gene(s) at a given locus. These variants typically reside in non-coding genomic regions, which are important for gene regulation, and these regulatory elements in turn can provide clues about potential mechanisms via pathway-based analyses. Besides the hypothalamus and pituitary gland being key players within the brain in appetite regulation, the limbic system, hippocampus and substantia nigra likely play a role in the genetic etiology of obesity [17, 140, 148, 149].

Only a relative handful of GWAS-implicated obesity loci have been functionally followed up to date. Figure 2 outlines four different mechanistic examples of how loci can contribute to obesity etiology.

As such, a full functional appraisal of such GWAS loci can reveal novel understanding of the genetic etiology of obesity; however, the vast majority of BMI/obesity loci remain to be fully characterized with respect to precise mechanism of action. Determining the causal variant(s) at each of these loci, and then connecting them to the causal effector gene(s) remains challenging. Various methods have been used to achieve this, including SNP enrichment analysis, molecular trait profiling, colocalization analysis, transcriptome-wide association studies (TWAS), regulome-wide association studies (RWAS), integrating polygenic risk scores with functional annotations, and the use of different types of quantitative traits (eQTLs, sQTLs, 3′aQTLs) and tissue types. More recently, machine learning and AI networks have also been used to predict effector genes. These findings then require further functional validation, such as with CRISPR-based approaches. Furthermore, using gene ontology to analyze gene overlap across co-morbidities for obesity, including diabetes and hypertension, new insights into key pathways can be revealed [160].

Emerging high-throughput methods to aid mapping of regulatory elements, multi-omics databases and advanced computational techniques are expected to accelerate the process of understanding the biology behind GWAS loci.

3.3.8 The genetic architecture of monogenic versus polygenic obesity

Recent GWAS have identified loci harboring genes that were initially uncovered in studies of extreme and early-onset obesity, including *MC4R* [161, 162] and *POMC* [163]. Many of these gene products operate in the BDNF–TrkB and leptin–melanocortin signaling pathways. Severe obesity can present when these pathways are disrupted, while common susceptibility variants colocalized nearby the same genes can influence an individual's BMI. While many genes were initially identified in studies of extreme obesity, some, like *ADCY3*, were first found in studies of common obesity [147], and later linked to extreme obesity [143]. Given larger GWAS efforts for BMI and obesity are expected in the future, one would expect this list of converging genes to continue to grow.

4 Gene-environment interaction: emerging role of epigenetics

Studies suggest that people with genetic susceptibility to obesity are also more susceptible to adverse environments. This is known as gene-by-environment interaction, transmitted via epigenetic processes. The agouti mouse model demonstrates the influence of epigenetics on obesity

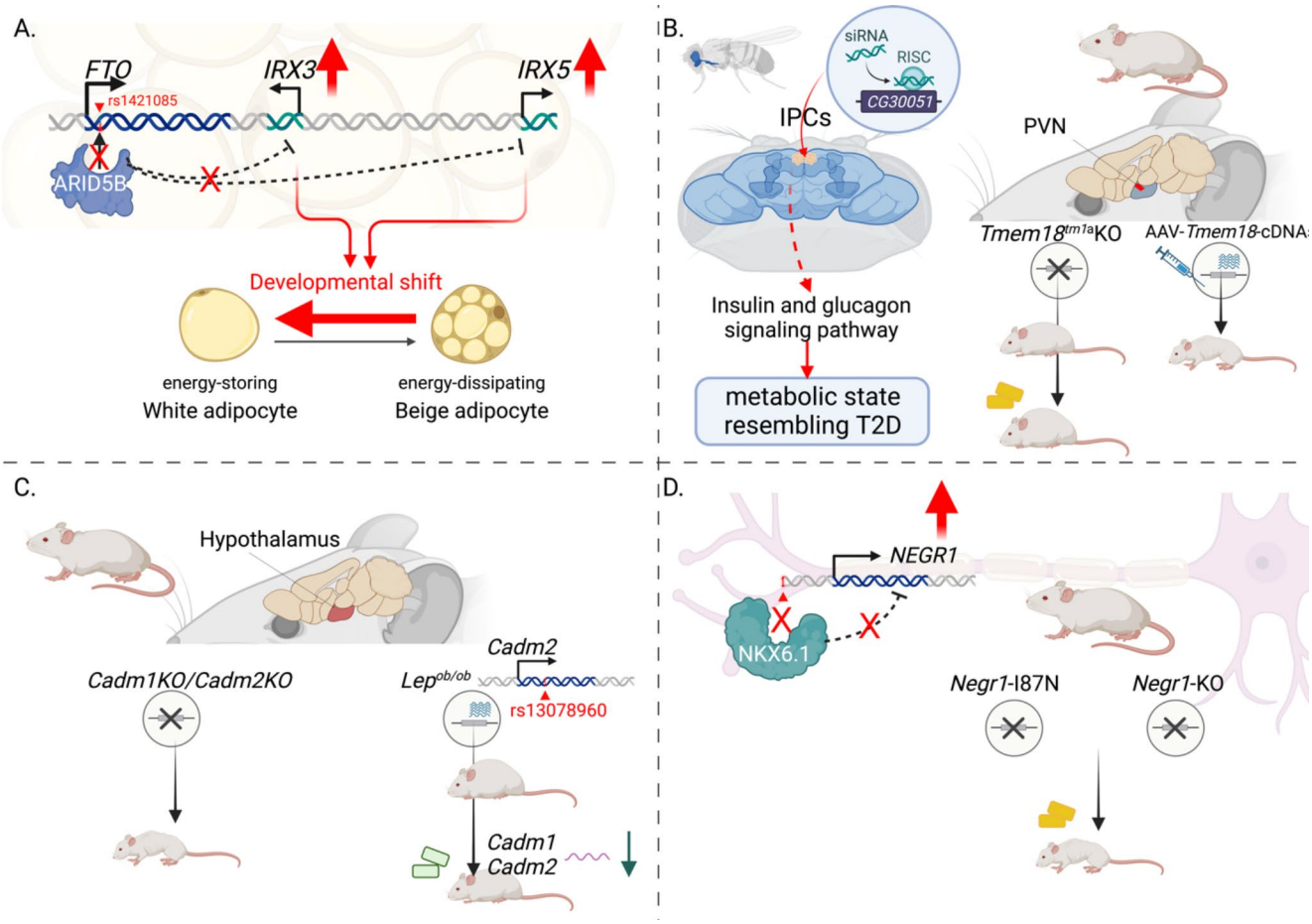

Fig. 2 Four functional follow-up strategies of different GWAS-implicated obesity loci. (**A**). A specific variant embedded within the *FTO* gene is located in an ARID5B regulatory element, which in turn impacts the expression of the neighboring genes, IRX3 and IRX5, which play a role in adipose biology [150]. (**B**). One of the strongest obesity loci coincides with the *TMEM18* gene [151, 152], which encodes a poorly characterized transmembrane protein. Work with a Drosophila melanogaster knock-out model implicates *TMEM18* in influencing lipid and carbohydrate levels via disruption of insulin and glucagon signaling [153], while knock-out in a mouse model leads to increased body weight due to elevated food intake, with over-expression of the gene showing an opposite effect [154]. (**C**). *CADM1* and *CADM2* encode cell-adhesion proteins in the brain. The associated variants influence the expression of the respective genes in the hypothalamus, leading to increased body weight, insulin sensitivity and energy expenditure. Loss of function of these genes promotes weight loss. Keto diet ("green" food cube) showed lower expression of these genes and promoted weight loss [155, 156]. (**D**). Deletion variants located just upstream of *NEGR1* impacts a binding site for the strong transcriptional repressor NKX6.1. When NKX6.1 binding is lost, increased *NEGR1* expression is observed. *NEGR1* is expressed in the brain. Studies in mice have found that NEGR1 deficiency lowers body weight via a reduction in lean mass [157], although other studies have found opposite results [158, 159]. High-fat diet seemed to accelerate weight loss.

through an *Avy* mutation. The mutation leads to the disruption of MC4R and triggers obesity, but can be reversed by feeding the mice with food rich in methyl donors. This establishes a link between obesity and epigenetic alterations driven by environmental factors [164]. DNA methylation, histone modifications and non-coding RNAs represent the most frequent and well-studied epigenetic changes.

4.1 Epigenetic and obesity

4.1.1 DNA methylation

DNA methylation is an epigenetic feature that contributes to obesity pathogenesis. This process involves adding a methyl group to a cytosine residue in DNA, specifically at CpG sites. This chemical modification can prevent transcription factors interacting with DNA, thereby interfering with gene transcription.

Studies have found mixed results for global DNA hypomethylation in obesity, but more consistent findings for

specific candidate genes methylation. For example, a negative association has been found between body weight in adults with obesity [165] and BMI in subjects with obesity and methylation at the *LEP* promoter and adiponectin gene [166–168]. Positive association was found for methylation status of members of the insulin signaling pathway, including *INS, IRS1* and *PIK3R1* [23, 169, 170], with obesity and metabolic disease. Increased *POMC* and lower *NPY* methylation has been reported for subjects presenting with resistance to weight loss [171]. *TNF, IL6* and *TFAM* exhibit changes in DNA methylation in subjects presenting with obesity.

Collectively, DNA methylation differences are observed in obesity and may offer new avenues for diagnostic approaches and therapeutic interventions. Imbalances in the activity of enzymes responsible for methylation and demethylation, such as DNA Methyltransferases (DNMTs) and Tet methylcytosine dioxygenases (TETs) may cause these changes. However, more studies are required to fully understand the mechanisms behind such changes.

4.1.2 Histone modifications

Histones help to compact DNA into chromatin. Histone alterations by mechanisms such as methylation and acetylation can impact how compact DNA becomes and subsequently influence gene expression. Enzymes that modify histones include histone methyltransferases, histone demethylases, histone deacetylases (HDACs) and histone acetyltransferases. Changes in the levels of these enzymes have been linked to obesity, and specific enzymes, such as HDACs and Jhdm2a, have been shown to accelerate the progression of obesity in clinical studies [172–174].

Histone modifications have been shown to regulate gene expression related to adipogenesis, including *C/EBPB, C/EBPA, Pref-1, aP2* and *PPARG*, appetite control, including *NPY* and *POMC* [175]. Changes in histone acetylation caused by high-fat diets have been linked to obesity.

4.1.3 Non-coding RNAs

Non-coding RNAs do not encode proteins but can have a crucial impact on gene expression. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have both been implicated in the pathogenesis of obesity.

Several miRNAs involved in adipogenesis have been shown to be expressed both in subjects and mice with obesity that were placed on a high fat diet. Additionally, specific miRNAs have been reported to be expressed at higher levels in visceral fat tissue derived from subjects with obesity [176]. miR21 and miR221 have been reported to have higher expression in the white adipose of subjects with obesity, while upregulation of miR221 has been observed in diet-induced obese mice. Silencing these miRNAs can lead to reductions in adipogenesis, triglyceride accumulation and alterations to BMI. Multiple miRNAs have now been uncovered that show differences in expression in subjects with obesity, including those operating within adipogenesis, insulin signaling and hypoxia [177].

Several lncRNAs, including GYG2P1, lncRNAp21015 and lncRNA-p5549, have reduced expression levels in obesity [178, 179]. RP11-20G13.3, lnc-dPrm16 and MIST are among the lncRNAs that impact metrics of adipogenesis [180, 181]. As such there is increasing evidence that lncRNAs place a specific role in conferring obesity risk [182].

4.2 Environment and Lifestyle impact epigenetics

Epigenetic processes are nimble in responding to lifestyle and the environment, enabling a subject to respond to external factors and to then return to the original state once that factor is no longer present. This includes endocrine disrupting chemicals exposures, dietary including high-fat, high/low-carb, sugar/oil-rich and micronutrients, physical activity including short/long-term training, sleep disturbance and deprivation, alcohol intake, weight loss interventions and the use of epigenetic drugs [183]. Figure 3 summarizes the identified genes affected by different environmental factors.

The following section will look at two environmental exposures that take place before an individual is born.

4.2.1 Inheritance of epigenetic susceptibility to obesity

A birth cohort study in the Netherlands reported a relationship between parental nutrition prior to conception and inherited epigenetic patterns [184]. This can be potentially exacerbated by assortative mating, which can increase predisposition to obesity in offspring [185]. Recent studies have shown that obesity can influence modifications of DNA, histones and ncRNAs in both sperm and the oocyte [186]. The negative effect of obesity on oocytes has been studied mainly in model organisms for obesity, where alterations in histone modifications and DNA methylation in this setting are observed [186–188].

Research is growing on how epigenetics can be passed down via the sperm of men and affect the next generation. Studies have shown high-fat, low-protein diets and bariatric surgery can cause changes in the expression of certain types of RNA and DNA methylation patterns in the sperm, leading to insulin resistance and weight changes in the offspring [189, 190].

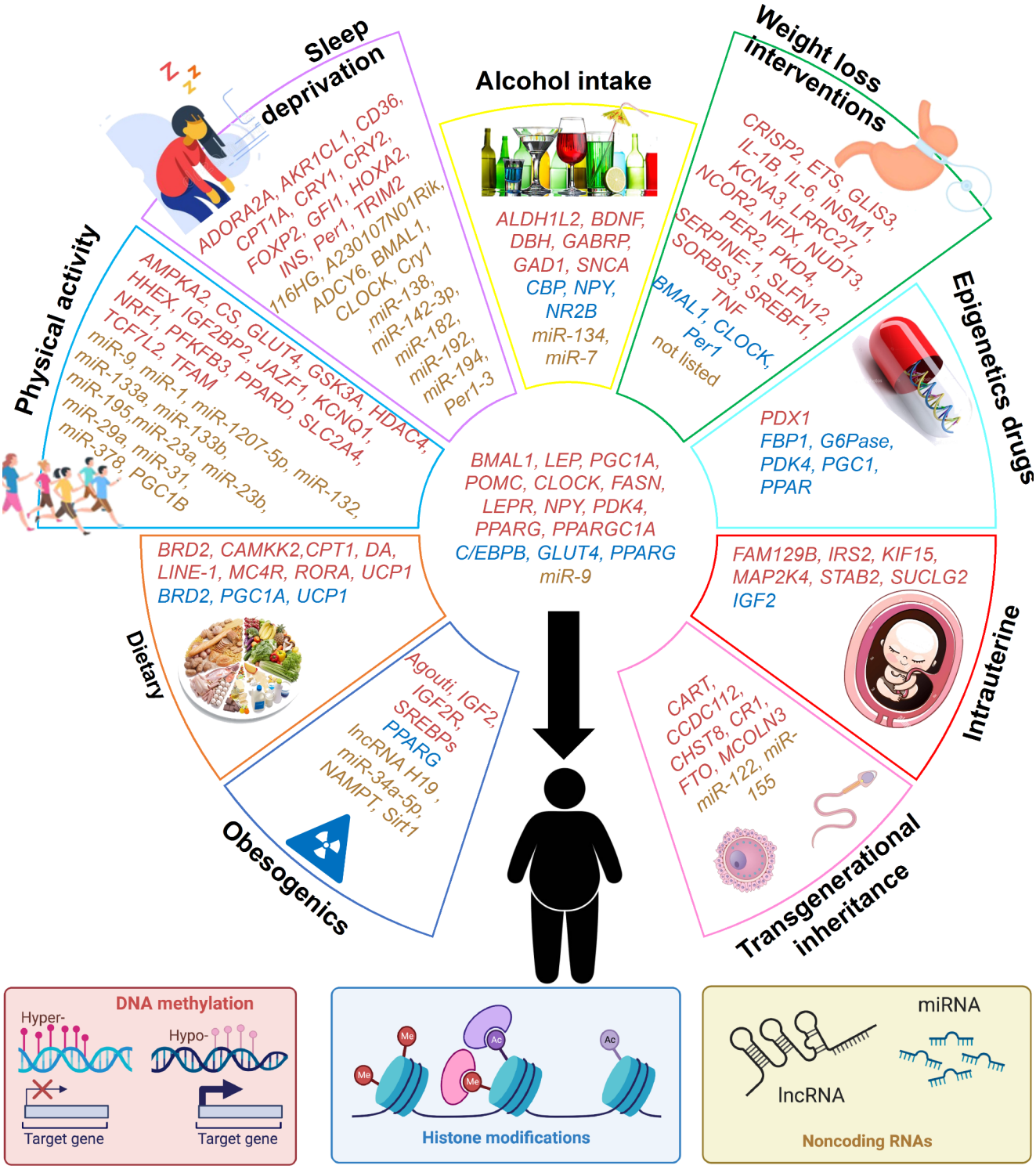

Fig. 3 Genes affected by environmental factors through epigenetic mechanisms. Genes are color-coded by mechanism. The genes within each section are specific for each factor, and genes placed in the middle space are common between at least two factors

4.2.2 Epigenetic changes during pregnancy

The placenta regulates nutrients, oxygen and hormonal supply between the mother and fetus. Any abnormalities in this process can lead to issues with fetal growth, causing hepato-metabolic and cardiovascular diseases [191, 192].

Increased *LEPR* methylation is linked to poor maternal weight gain during pregnancy, affecting newborns' protein

expression in umbilical veins [193]. Humans and animal studies have both found that diets high in fat and low in protein during pregnancy lead to alterations in epigenetics across specific genes and leads to obesity and related comorbidities in the offspring, lasting into adulthood. Conversely a healthy diet has been shown to have beneficial epigenetic impact [194].

Inadequate diets can cause epigenetic changes in certain genes, including *PPARG, IGF2, GLUT4*, and *C/EBPB*, resulting in eating disorders and the presentation of obesity that persists into adulthood [195, 196].

5 From genetics to the clinic

Advances in genetic technology can lead to better identification of disease genes for forms of obesity that are not yet fully understood. Furthermore, knowing a patient's genotype could allow for precise diagnosis of obesity type, and inform subsequent precision medicine approaches.

The social burden of obesity is significant, with increased healthcare costs, decreased productivity, and decreased quality of life. This challenge is gradually alleviated by the decreasing cost of advanced genomic technologies, making it increasingly feasible for precision medicine to improve health outcomes. By understanding a patient's genotype, it is possible to make a more accurate diagnosis of obesity, which in turn leads to more tailored treatment and prevention methods. Additionally, early detection of a subject's genetic predisposition to obesity has implications for weight control in later life.

Leveraging recombinant human leptin as a treatment serves as a key example of a genetically-informed therapeutic strategy, as described above, which showed responses in some of the cases depending on their genetic makeup. The second treatment for obesity based on patient genotype is setmelanotide, a drug that selectively activates MC4R and has been FDA approved to specifically treat monogenic obesity caused by mutations in *LEPR, PCSK1* and *POMC* [197]. These two treatments demonstrate how understanding the genetic causes of obesity can inform the development of targeted therapies that address specific deficiencies in monogenic forms. However, challenges remain to fully transition to a precision medicine approach for monogenic obesity, such as implementing widespread genetic testing.

Epigenetics is also a rapidly growing field of research, and progress is being made in identifying such biomarkers for obesity. To elucidate how epigenetics impact obesity risk, further research is required to explore the impact of factors such as hypoxia, inflammation, oxidative stress and hormonal imbalances on epigenetics. Additionally, large scale prospective efforts are required to determine the relationship between changes in environmental factors such as diet, physical activity, sleep and alcohol consumption with epigenetic changes. The modifiable nature of epigenetics makes it a promising avenue for obesity prevention and treatment.

Insights from genetic and epigenetic discovery efforts represent exciting advances toward precision medicine, and which should directly affect health outcomes in the decades to follow.

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Declarations

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