

Genetics and epigenetics in obesity

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ABSTRACT

Obesity is among the most threatening health burdens worldwide and its prevalence has markedly increased over the last decades. Obesity maybe considered a heritable trait. Identifications of rare cases of monogenic obesity unveiled that hypothalamic circuits and the brain-adipose axis play an important role in the regulation of energy homeostasis, appetite, hunger and satiety. For example, mutations in the leptin gene cause obesity through almost unsuppressed overeating. Common (multifactorial) obesity, most likely resulting from a concerted interplay of genetic, epigenetic and environmental factors, is clearly linked to genetic predisposition by multiple risk variants, which, however only account for a minor part of the general BMI variability. Although GWAS opened new avenues in elucidating the complex genetics behind common obesity, understanding the biological mechanisms relative to the specific risk contributing to obesity remains poorly understood. Non-genetic factors such as eating behavior or physical activity strongly modulate the individual risk for developing obesity. These factors may interact with genetic predisposition for obesity through epigenetic mechanisms. Thus, here, we review the current knowledge about monogenic and common (multifactorial) obesity highlighting the important recent advances in our knowledge on how epigenetic regulation is involved in the etiology of obesity.

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Abbreviations: ABCG1, ATP-binding-cassette-sub-family-G member 1 gene; ABCA1, ATP-binding-cassette-sub-family-A member 1 gene; ADRB3, beta-3-adrenergic receptor gene; ADCY3, adenylate cyclase-3 gene; BDNF, brain-derived-neurotrophic-factor-gene; BMAL1, aryl hydrocarbon receptor nuclear translocator-like 1 gene; BMI, body mass index; CEPT, cholesteryl ester transfer protein gene; CLOCK, clock-circadian-regulator gene; CT, computed tomography; DNMT3B, DNA-methylase-3B gene; DXA, dual-energy X-ray absorption; FOXO2, forkhead-box-protein-P2 gene; FTO, fat-mass-and-obesity-associated gene; GWAS, genome-wide association studies; HbA1c, glycated hemoglobin (A1c); HDAC4, histone-deacetylase-4 gene; HDL-c, high density lipoprotein cholesterol; HIF3A, hypoxia induced factor 3A gene; HLA-C, major histocompatibility complex, class C; HSD2, 11 beta-hydroxysteroid dehydrogenase type 2 gene; IL17RA, interleukin-17 receptor-A gene; IL1B, interleukin-1B gene; IL6, interleukin-6 gene; IGF2/H19, insulin-like growth factor2/H19 imprinting control region; IRS1, insulin-receptor 1 gene; IRX3, iroquois-homeobox 3 gene; IRX5, iroquois-homeobox 5 gene; KCNQ1, potassium voltage-gated channel subfamily q member 1 gene; LDL-c, low density lipoprotein cholesterol; LEP, leptin gene; LEPR, leptin receptor gene; LY86, lymphocyte antigen-86 gene; MAP2K5, mitogen-activated protein kinase kinase 5 gene; MCHR1, melanin-concentrating hormone receptor 1 gene; MC4R, melanocortin-4-receptor gene; MRI, magnet resonance imaging; NEGR, neurogranin gene; NPY, neuropeptide-Y gene; PCSK1, pro-hormone-convertase-1 gene; PDK4, pyruvate dehydrogenase kinase-4 gene; PER2 and 3, period circadian 2 and 3 genes; PHGDH, phosphoglycerate dehydrogenase gene; POMC, pro-opio-melanocortin gene; PPARG, peroxisome-proliferator-activated receptor gamma gene; PPARGC1A, PPARG coactivator-1-alpha gene; RPTOR, regulatory associated protein of mTOR complex 1 gene; RYGB, Roux-en Y gastric bypass; T2D, type 2 diabetes; TMEM18, transmembrane protein-18 gene; TNFA, tumor necrosis factor-alpha gene; SIM1, single-minded homolog-1 gene; SNP, single nucleotide polymorphism; SORBS3, sorbin and sh3 domain containing-3 gene; SRBF1, sterol-regulatory element binding transcription factor-1 gene; TCF7L2, transcription factor-7-like-2 gene; TOMM20, translocase of outer mitochondrial membrane-20 gene; WHR, waist to hip ratio.

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1. Introduction

The prevalence of obesity is increasing dramatically globally not only in well-developed countries but also in developing countries [1] impacting on public health around the globe and causing a formidable socioeconomic challenge. Obesity significantly shortens the life expectancy [2] and contributes to multiple cardio-metabolic diseases such as T2D, dyslipidemia, coronary artery disease, stroke, hypertension and numerous non-metabolic co-morbidities (e.g. reflux disease, several types of cancer including esophageal adenocarcinoma, non-alcoholic steatohepatitis, liver cirrhosis and hepatocellular carcinoma, sleeping problems, depression, or musculoskeletal diseases) [3–5]. While a very small proportion of obesity cases result from monogenic alterations, the increasing prevalence of common (multifactorial) obesity during the last 50 years is most likely due to a complex interplay of environmental changes (“obesogenic environment”) and the individual genetic predisposition. Despite major evidence for an important role of environmental factors such as sedentary lifestyle combined with intake of energy dense nutrition and reduced energy expenditure there is no doubt for a strong genetic basis of common obesity. Early evidence stemming from family [6–9], twin [10–12] and adoption [13] studies revealed heritability estimates for BMI of up to 70–80% and recent studies in ethnically diverse populations underline the relevance of genetic contribution [14]. Over the past decade, GWAS, based on their hypothesis free nature, has emerged as an excellent tool for identifying novel and unexpected genes as well as loci contributing to obesity [15,16]. Most of these studies have been conducted in individuals of Caucasian ancestry [15,16], while fewer reports describe the genetic architecture of obesity in other populations e.g. Africans or apply transethnic analyses in ancestrally diverse populations [17,18]. GWAS revealed important novel insights into genetics of obesity, however, a major limitation in understanding the genetic contribution is owed to the large proportion of unexplained variability of BMI, as identified SNP markers collectively explain less than 3%–5% of the observed variability [15,19]. A more recent study however, estimated a lower genetic heritability for BMI (30–40%) compared to early studies by using millions of imputed genetic variants in ten-thousands of individuals [20]. It suggested that the missing heritability for obesity is rather negligible, which may point towards a potential limitation of heritability estimates with the use of incomplete genetic information [20]. Still, the undoubtedly important influence of environmental factors contributes to the variability evident in the etiology of obesity as a large body of evidence has emerged for substantial individual variability induced by gene-environment interactions. Furthermore, non-genetic factors (e.g. nutrition, exercise or weight loss interventions) induce dynamic alterations in the epigenetic signatures, which in turn modulate gene activity. Indeed, strong correlations were observed between clinical variables relevant for obesity and epigenetic patterns from whole blood, adipose tissue, liver or skeletal muscle, while however, cause and consequence of these relationships are still not well understood [21–24].

One ultimate goal for future clinical obesity treatment and intervention is to define individual risk profiles based on a combination of genetic and non-genetic factors that may be helpful in both predicting personal risk for obesity and its accompanying diseases and estimating response to treatment and interventions. This review aims at summarizing the current knowledge of genetics of obesity including monogenic (syndromic and non-syndromic) and common (polygenic) forms of obesity, gene-environment interaction in obesity, and current advancements in the study of epigenetic alterations that are related to (or potentially causative for) obesity. We put this into context of potential future precision medicine efforts.

2. Genetic Background of Obesity

2.1. Monogenic Syndromic and Non-syndromic Obesity

Monogenic obesity results from a single gene mutation. It can be syndromic, or non-syndromic. Despite in accordance to Mendelian inheritance, syndromic monogenic obesity is co-presented with other characteristics, such as cognitive delay, dysmorphic features and organ-specific abnormalities [25]. To date, 79 different syndromes have been identified, among which, only 19 have been completely characterized genetically; 11 have been partially elucidated; 27 are mapped to a chromosomal region: and the remaining 22 remain elusive, with neither the gene(s) nor the chromosomal location(s) identified [25]. The best characterized syndromes with obesity are Prader-Willi syndrome (imprinting defect in the region on chromosome 15q11–13), Prader-Willi like syndrome (several deletions on chromosome 16, including *SIM1* [26]), Fragile X syndrome (with features of Prader-Willi syndrome), Bardet-Biedl syndrome (19 genes reported to date), Albright's hereditary osteodystrophy (*GNAS1* mutation) and WAGR (Wilms-Tumour-Aniridia-Syndrom) syndrome (chromosome 11p14 deletions) (reviewed in [27]).

As for non-syndromic monogenic obesity, there are well-recognized genes, each playing a role in the regulation of energy homeostasis mediated by the leptin-melanocortin pathway [28,29]. Although extremely rare, homozygous loss-of-function mutations in genes such as *MC4R*, *LEP*, *LEPR*, *PCSK1*, *ADCY3* and *POMC* result in fully penetrant monogenic obesity. In contrast, 2–3% of common (oligogenic) obesity in adults and children is mostly attributed to heterozygous coding mutations in these genes [30] and is characterized by a variable severity of obesity partly dependent on environmental factors [31].

Discovery of the leptin gene mutation in severely obese *ob/ob* mice [32] and mutations in rare cases of extremely obese children paved a path for identifying rare genetic mutations in obesity. Leptin signaling modulates energy balance through a combination of melanocortin-dependent/independent pathways [33]. Through leptin and its receptor, the hypothalamus receives signals from adipose tissue indicating sufficient energy stores in the body. Mutations in leptin result in hyperphagia, lower locomotor activity, reduced sympathetic tone, mild hypothyroidism, hypogonadism, and impaired T-cell-mediated immunity.

Treatment with recombinant human leptin can relieve the symptoms resulting from impaired leptin signaling [34–37]. At molecular level, leptin stimulates neurons expressing POMC, whose gene product promotes production of alpha-melanocyte-stimulating hormone (α -MSH) binding to MC4R. Given their physiologic relevance in energy homeostasis, it is not surprising that mutations in *POMC* [38] and *MC4R* also result in severe obesity [39]. Human loss-of-function mutations in *MC4R* result in increased food intake, increased lean mass and linear growth [39]. It is of note that heterozygous *MC4R* mutations are observed in up to 5% of people with childhood obesity, making this the commonest gene in monogenic obesity [40,41]. Melanocortin peptides are processed by enzymes such as prohormone convertase 1 (*PCSK1*) [42]. Patients with homozygous and compound heterozygous mutations in *PCSK1* have altered POMC processing and manifest obesity accompanied by glucocorticoid deficiency, hypogonadotropic hypogonadism, and postprandial hypoglycemia [43,44]. Finally, *SIM1*, a transcription factor involved in the development of the paraventricular and supraoptic nuclei of the hypothalamus has to be acknowledged. *Sim1* may be involved in signaling downstream of Mc4r [45] and *SIM1* loss-of-function mutations cause severe obesity in humans [26,46,47].

2.2. Common Obesity

Despite the significant contribution of monogenic obesity to our general knowledge on genetics and physiology of body weight regulation, the majority of the individuals with obesity develop “common (multifactorial) obesity” which is attributed to the interplay between multiple loci (polygenic), though each with rather small effects on BMI and the “obesogenic” environment. While candidate gene and genome-wide linkage approaches have not been tremendously successful in identifying relevant genetic contributors to obesity, the advent of GWAS has led to the discovery of novel genetic factors associated with obesity, e.g. *FTO* [48]. So far, more than 870 SNPs strongly associated with BMI have been identified in large scale GWAS within international consortia such as (the Genetic Investigation of ANthropometric Traits) GIANT [15,19] or other well-powered studies [49]. The GWAS findings indicate that despite identification of hundreds of loci associated with obesity, they only explain 5% of the variance of BMI [19]. Thus, explaining the remaining variability appears to be highly challenging and will definitely influence future research focus in this field. Nevertheless, recent advances in genome-wide strategies have clearly demonstrated that loci associated with obesity carry genes involved in pathways affecting neuro-circuits of appetite and satiety regulation (*BDNF*, *MC4R*, and *NEGR*) [15,50–52], insulin secretion and action (*TCF7L2*, *IRS1*) [15,53], adipogenesis [16] and energy and lipid metabolism (*FTO*, *RPTOR*, *MAP2K5*) [15,48,53]. Further, gene ontology analyses in genes overlapping with obesity-related diseases (e.g. diabetes, hypertension, coronary artery disease) have revealed “gene modules” that provide common shared gene ontology (GO) pathways for these diseases [54]. It is also of note, that in addition to rare loss of function variants resulting in non-syndromic monogenic obesity, several common polymorphisms in *PCSK1* [55–57], *MC4R* [58] and *POMC* have been strongly associated with polygenic obesity in ethnically diverse population. Without doubts, GWAS are a powerful tool to reveal common variants contributing to common polygenic traits and diseases, but the interpretation of these findings is challenging. Most of the “obesity” SNPs map within non-coding regions carrying regulatory elements that are essential for gene regulation. However, the respective target genes of these variants are not necessarily the genes for which they have been attributed (simply based on the location within the gene). For instance, it took ~7 years to clarify the regulatory circuitry and mechanistic basis of the associations between *FTO* variants and obesity. Ultimately, Claussnitzer et al. demonstrated that an intronic *FTO* SNP associated with BMI resides within an enhancer element for *ARID5B* which regulated the expression of *IRX3* and *IRX5*, which in turn affect thermogenesis, lipid accumulation and adipogenesis [59].

Sophisticated functional studies are required to understand the underlying molecular mechanisms of obesity-associated genes unveiled by GWAS and their contribution to obesity and its related traits.

2.3. Gene-Environment Interaction in Obesity

The role of genetic and environmental factors (particularly physical activity and dietary) has been addressed in numerous genetic and epidemiological studies. Although studies targeting gene - environment interactions (GxE) have emerged rapidly in the last decade, the results are still rather inconclusive. The main focus has been placed on the interactions between polymorphisms associated with obesity and environmental modulators of obesity risk such as age, sex, physical activity, diet, socioeconomic and educational status and ethnicity. For instance, physical activity has been shown to reduce the genetic predisposition to obesity for *FTO* [60,61], but also for a combination of 12 obesity-associated SNPs [62]. In addition, dietary habits have been extensively studied in the context of GxE. It has been shown in the Nurses' Health Study (NHS), the Health Professionals Follow-up Study (HPFS), and the Women's Genome Health Study (WGHS) that genetic associations with obesity based on 32 BMI variants were stronger among subjects with higher intake of sugar-sweetened beverages than among those with lower intake [63]. Similarly, in the same cohorts, genetic association with adiposity seemed to be more pronounced with higher consumption of fried foods [63]. In line with the described interaction with physical activity, this study demonstrated that the genetic association with BMI was strengthened by sedentary lifestyle as represented by increased hours of TV watching but weakened in participants with increased physical activity [63]. Individual variants in *FTO* have been shown to interact with dietary habits. A high-protein diet had beneficial effects on weight loss and improvement of body composition in carriers of the *FTO* obesity risk allele rs1558902 [64]. Moreover, subjects with the *FTO* rs9939609 A allele achieved a better metabolic outcome in response to weight loss after on a low-fat hypocaloric diet [65].

One of the major lessons we have learned so far is that unfavorable effects of obesity variants can be compensated by behavioral changes such as improving diet and physical activity [66]. Despite the challenges in the understanding of GxE, there is strong evidence to progress and to intensify research in this field. Investments in the respective research will not only provide deeper insights into molecular mechanisms behind GxE, essential for improvement of treatment, but also help to identify individuals for more efficient targeted anti-obesity interventions.

Admittedly, GxE interactions are unlikely to contribute significantly to risk prediction [67]. However, GxE interactions seem to account for some of the missing heritability underlining the importance of epigenetic signatures as potential mediator for GxE [68]. Considering the metabolic diversity of obesity, epigenetic modifications such as DNA methylation are very likely representing one of the determining factors and may constitute another level of regulation in mediating disease risk.

3. Epigenetic Signatures in Obesity: Fine Tuning the Genome - Beyond Genetic Factors

Epigenetic mechanisms are modifications prior to or post translation regulating gene activity without changing the genomic sequence [69,70]. In this review we focus on DNA cytosine (C) methylation (CpG) which is the best studied and most stable epigenetic mechanism [71,72].

3.1. Genome Wide DNA Methylation Analysis in Obesity and Associated Traits

In the recent years multiple studies analyzed DNA methylation at CpG sites on a genome wide level and its potential relationship with common obesity and clinical variables related to obesity and adipose tissue distribution [24,73].

Table 1

Summary of studies that performed genome wide DNA methylation analysis in obesity and associated traits.

Clinical variable	Study reference	Population size, gender equality (y/n)	Tissue type	Analysis technique	Top gene(s)	Main findings
Genome-wide DNA methylation studies						
BMI	Dick et al. <i>Lancet</i> , 2014 [73]	479/n	WB, SAT, skin	Infinium Human Methylation 450 BeadChip	<i>HIF3A</i>	5 CpGs mapping for 3 genes showed significant association to BMI, association for one of the genes could be replicated in adipose tissue.
BMI	Dahlmann et al. <i>Int J Obesity</i> , 2015 [81]	30/n	abdominal subcutaneous fat cells	Infinium Human Methylation 450 BeadChip	<i>IGF1R, IRS2, FASN, RGS3, TGFB2</i>	248 genes showed significant methylation differences between post obese and never obese subjects.
BMI/ waist (cm)	Aslibekyan et al. <i>Obesity</i> , 2015 [140]	991/y	CD4+ cells from PB	Infinium Human Methylation 450 BeadChip	<i>CPT1A, PHGDH, CD38</i> ; long intergenic non-coding RNA 00263	8 CpGs showed significant association with BMI and 5 CpGs with waist circumference.
MetS	Guénard et al. <i>Physiol Genomics</i> , 2014 [84]	14/n	VAT	Infinium Human Methylation 450 BeadChip	MetS+ vs. MetS-: <i>TBL1X MYADML2, UVSSA, GMCL1L, MAPK10, LOC150935</i>	3258 annotated genes showed significant methylation differences between MetS+ and MetS- subjects. Most overrepresented pathways relate to structural components of the cell membrane, inflammation and immunity and cell cycle regulation.
MetS/ metabolic traits	Allum et al. <i>Nat Commun</i> , 2015 [86]	72/?	VAT	MCC-seq	CD36	Identified novel variation within enhancers strongly correlated to plasma triglyceride and HDL-cholesterol, MCC-Seq provides comparable accuracy to alternative approaches but enables more efficient cataloguing of functional and disease-relevant epigenetic and genetic variants for large-scale EWAS.
meQTL studies						
BMI	Voisin et al. <i>Genome Med</i> , 2015 [83]	355/y	WB	Infinium Human Methylation 450 BeadChip, Illumina Golden Gate Assay	<i>MIR148A, BDNF, PTPMT1, NR1H3, MGAT1, SCGB3A1, HOXC12, PMAIP1, PSIP1, RPS10-NUDT3, RPS10, SKOR1, MAP2K5, SIX5, AGRN, IMMP1L, ELP4, ITIH4, SEMA3G, POMC, ADCY3, SSPN, LGR4, TUFM, MIR4721, SULT1A1, SULT1A2, APOBR, CLN3, SPNS1, SH2B1, ATXN2L, IL27</i>	28 obesity associated SNPs associate with methylation levels at 107 proximal CpG sites, 38 are located in the promoter including obesity relevant genes.
BMI/ metabolic traits	Grundberg et al. <i>Am J Hum Genet</i> , 2013 [80]	648/n	SAT	Infinium Human Methylation 450 BeadChip, Illumina HT12 BeadChip, HumanHap300, HumanHap610Q, 1 M-Duo, and 1.2MDuo 1 M	ADCY3	DNA methylation variation was highly heritable and shared environmental effects correlated with metabolic phenotype-associated CpGs. Analysis of meQTLs revealed that 28% of CpGs were associated with nearby SNPs.
MetS	Guénard et al. <i>Transl Res</i> , 2017 [85]	31/n	VAT	Infinium Human Methylation 450 BeadChip, Affymetrix HG-U133 plus 2 arrays, Illumina HumanOmni-5-Quad BeadChip	<i>COL11A2</i>	Identification of 17,800 differing CpG sites between MetS+ and MetS-, 2182 unique meQTLs associate with methylation levels at variable CpG sites.
BMI/ metabolic traits	Volkov et al. <i>PLoS ONE</i> , 2016 [91]	119/n	SAT	Infinium Human Methylation 450 BeadChip, whole-transcript GeneChip® Human Gene 1.0 ST Array, Illumina HumanOmniExpress BeadChip	<i>meQTL of known obesity, lipid, T2D loci: ADCY3/POMC, APOA5, CETP, FADS2, GCKR, SORT1, LEPR</i> <i>meQTL newly identified: CHRNA5, G6PC2, GPX7, RPL27A, THNSL2, ZFP57</i>	101,911 SNP-CpG pairs in <i>cis</i> and 5342 SNP-CpG pairs in <i>trans</i> were identified in SAT. Of those meQTL, 635 SNPs associate with expression of 86 genes in SAT and further with BMI, lipid, glucose and insulin traits. CIT showed that SNPs in meQTL impact metabolic traits through changes in DNA methylation.

BMI/age/ HbA1c	Rönn et al. Hum Mol Genet, 2015 [78]	190/y	SAT, WB	Infinium Human Methylation 450 BeadChip, whole-transcript GeneChip® (Affymetrix)	BMI: FTO , ITIH5 , CCL18 , MTCH2 , IRS1 , SPP1	Identification of 2825 genes where methylation and expression correlated with BMI
BMI	Keller et al. Mol Met, 2016 [22]	77/y	SAT and OVAT	MeDIP on Chip, GeneChip Human Promoter 1.0R Arrays, Illumina human HT-12 expression chips	obesity state specific: ETV6 ; tissue specific: HAND2 , HOXC6 , PPARG , SORBS2 , CD36 , CLDN1	Identification of 56 adipose depot specific genes and 90 obesity state specific genes which showed significant promoter methylation differences and contrary changes of mRNA expression 5529 differentially methylated CpGs were associated with 2223 differentially expressed genes between obese cases and never-obese controls, candidate genes overrepresented in pathways for adipogenesis, insulin signaling and lipolysis.
BMI	Arner et al. Clin. Epigenetics, 2015 [82]	29/n	abdominal subcutaneous fat cells	Infinium Human Methylation 450 BeadChip, Illumina Infinium 27 K Human Methylation Beadchip v1.2, Gene 1.1 ST Arrays (Affymetrix)	Adipogenesis: KLF15 , KLF5 , PLIN2 , PPARG , PPARGC1A ; Insulin signaling: AKT2 , INSR , IRS1 , IRS2	BMI is associated with widespread changes in DNA methylation (187 genetic). Alterations in DNA methylation are predominantly the consequence of adiposity. Methylation loci are enriched for functional genomic features in multiple tissues and show that sentinel methylation markers identify gene expression signatures (38 loci). Loci identify genes involved in lipid and lipoprotein metabolism, substrate transport and inflammatory pathways.
BMI	Wahl et al. Nature, 2017 [24]	5387/y	WB	Infinium Human Methylation 450 BeadChip, Illumina HumanHT-12 v3 and v4 BeadChip array.	ABCG1 , LPINI , HOXA5 , LMNA , CPT1A , SOC3 , SREBF1 , PHGDH	BMI is associated with widespread changes in DNA methylation (187 genetic). Alterations in DNA methylation are predominantly the consequence of adiposity. Methylation loci are enriched for functional genomic features in multiple tissues and show that sentinel methylation markers identify gene expression signatures (38 loci). Loci identify genes involved in lipid and lipoprotein metabolism, substrate transport and inflammatory pathways.

This table summarizes genome wide DNA methylation studies in Caucasian populations for obesity that formed the research field during the last five years. Bold genes were repeatedly identified in several studies. AT = adipose tissue; SAT = subcutaneous AT; OVAT = omental visceral AT; PB = peripheral blood; WB = whole blood; PI = pancreatic islets; MCC-seq = methylation capture sequencing; MeDIP-seq = methylated DNA immunoprecipitation based sequencing; BMI = body mass index; HbA1c = glycosylated hemoglobin; MetS = metabolic syndrome; y = yes; n = no; HDL-c = high density lipoprotein-cholesterol; CIT = causal inference test; HOMA-IR = Homeostasis Model Assessment based insulin resistance score; FDR = false discovery rate; DMR = differentially methylated regions; meQTL = methylation quantitative trait loci; SNPs = single nucleotide polymorphism; EWAS = epigenome wide association studies.

Here, we review studies analyzing DNA methylation profiles mainly in human adipose tissue, and whole blood in Caucasian populations that formed the research field during the last 5 years (Table 1). For instance, Dick et al. [73] showed that increased methylation at *HIF3A* was linked to higher BMI and this relationship was present in both subcutaneous adipose tissue (SAT) and whole blood which was successfully replicated by others [74–77]. Other studies identified significant correlations of multiple genes (either involved in insulin and glucose metabolism, adipogenesis or early development) with BMI or other clinical variables related to obesity and adipose tissue distribution (e.g. waist circumference, WHR, summarized in Table 1). Most of these studies used adipose tissue (SAT) [73,78–82] and/or whole blood samples [24,73,78,83]. Others reported strong methylation differences between individuals with and without metabolic syndrome (MetS+ vs. MetS–) which were measured in visceral adipose tissue (VAT) [84–86]. VAT might represent an ideal target tissue for detecting potential biomarkers for MetS since increased abdominal fat accumulation is known to be associated with impaired insulin sensitivity and altered lipid profiles [87]. The majority of studies investigated, in addition to DNA methylation changes, mRNA expression differences underlining the close relationship between methylation changes and transcriptome levels. However, it is noteworthy that far from all observed methylation differences translate into changes in gene activity, an observation that is poorly understood so far [22,88]. In conclusion, genome wide DNA methylation analyses provided evidence for a strong correlation of epigenetic patterns with clinical variables. However, despite indications from whole blood derived epigenetic changes being secondary to metabolic changes [24], no final conclusions can yet be drawn whether alterations in clinical variables related to common obesity are cause or consequence of epigenetic modifications, particularly for other tissue specific epigenetic profiles.

3.2. Studies Analyzing the Correlation Between Genetic Variants and DNA Methylation

Despite evidence for a clear relationship between epigenetic patterns and clinical traits, the interpretation of the causal relationship between the observed alterations in DNA methylation and obesity is still challenging. Genetic variants can introduce or delete methylation sites in CG context, thereby induce changes in DNA methylation at the SNP site. Moreover, SNPs located in cis or trans of the CpG site can alter action of methylation enzymes. To further test for potential interactions between epigenetic profiles and genetic factors several studies (Table 1) performed correlation analyses of DNA methylation and SNP genotypes. These methylation quantitative trait locus (meQTLs) analyses are valuable tools to understand whether DNA methylation changes represent a) a mediator between genetic predisposition and clinical variables, b) consequences of the interaction between genotype and phenotype or c) the effects between genotype and methylation are independent from the genotype-phenotype associations. One recent study used Mendelian randomization and a weighted genetic risk score, generated by SNPs known to affect BMI, in order to elucidate whether DNA methylation changes in blood are cause or consequence of adiposity [24]. The authors found a strong correlation between predicted and observed effects of BMI genetic risk score on methylation ($R^2 = 0.65$; $P = 4.7 \times 10^{-44}$) [24]. They further showed an association between the risk score and DNA methylation of *ABCG1* which is in line with other reports suggesting that weight loss influences *ABCG1* methylation, expression and protein activity [89,90]. Finally, Wahl et al. suggested that DNA methylation changes in blood represented most likely the consequence of obesity rather than the cause [24]. However, it is still under debate whether and if so, to which extent evidence stemming from whole blood can be transferred to the potential target tissue. In contrast, Volkov et al. demonstrated by using a causal inference test (CIT), that genetic variants interfere with different metabolic traits such as BMI, HbA1c, and HDL-cholesterol (HDL-c) via altered DNA methylation in human adipose tissue [91]. Others reported

Table 2

Summary of studies that performed candidate gene approaches for DNA methylation in obesity and associated traits.

Associated clinical variable	Genes	Involved pathways (related to obesity)	Study reference	Tissue type	Analysis technique	Population ancestry (replicated by)	Main findings
overall obesity	POMC	Eating behavior	Kühnen P. et al. <i>Cell Metab.</i> 2016 [96] Kuehnen P. et al. <i>PLoS Genet.</i> 2012 [95] Volkov P. et al. <i>PLoS One.</i> 2016 [91] Crujeiras AB. et al. <i>Regul Pept.</i> 2013 [97]	PBS PBS AT PBL	Pyroseq. bisulfite seq. Illumina 450 K MALDI-TOF mass spec.	Caucasians, m and w Caucasians Caucasians, m and w Caucasians, m	Meth* of <i>POMC</i> VMR is associated with BMI; higher meth in obese vs normal weight adults and children. Replication in post-mortem MSH-positive neurons of obese subjects vs lean. Rs713587 represents meQTL for <i>POMC/ADCY3</i> in AT. Weight regain associates with increased meth in PBL.
overall obesity	NPY	Eating behavior	Crujeiras AB. et al. <i>Regul Pept.</i> 2013 [97]	PBL	MALDI-TOF mass spec.	Caucasians, m	Low methylation of <i>NPY</i> promoter associates with risk of weight regain
overall obesity	SLC6A4	Reward	Zhao J. et al. <i>Int J Obes (Lond).</i> 2013 [141] Drabe M. et al. <i>Transl. Psychiatry.</i> 2017 [142]	PBL PBL	Pyroseq. Pyroseq.	Emory Twin Studies, m Caucasians, m and w	Positive correlation with BMI, waist and weight; differences in monozygotic twin pairs discordant for obesity. Meth of <i>SLC6A4</i> coding region (<i>5-HTTLPR</i>) correlates negatively with 5-HTT level in PFC and sensitivity to reward in obese subjects
overall obesity	MCHR1	Eating behavior	Stepanow S. et al. <i>PLoS One.</i> 2011 [143] Perfilyev A. et al. <i>Am J Clin Nutr.</i> 2017 [104]	WB SAT	bisulfite seq. Illumina 450 K	Caucasians, m Caucasians, LIPOGAIN cohort	<i>MCHR1</i> exon1 GT-haplotype specific meth is decreased with a higher BMI. DNA meth is associated with weight gain due to increased energy intake during HFD
overall obesity	FTO	m6A methyltransferase Glucose/Energy metabolism	Bell CG. et al. <i>PLoS One</i> 2010 [144]	WB	MeDIP-chip; Pyroseq.	Caucasians	Increased DNA meth for obesity susceptibility haplotype tagged by rs8050136
overall obesity	ADIPOQ	Eating behavior	Houde AA. et al. <i>BMC Med Genet.</i> 2015 [92]	WB, SAT, VAT	Pyroseq. MassArray Epityper	Caucasians, m and w (French)	Meth in SAT is positively associated to BMI, waist circumference and LDL-C.
fat distribution			Hjort L. et al. <i>Clin Epigenetics</i> 2017 [93]	SAT biopsies		Caucasian m	In NBW: DNA meth increases during fasting; positive association of meth level with BF%
fat distribution	LPL	Lipid metabolism	Drogan D. et al. <i>Nutr Diabetes.</i> 2015 [145]	SAT	Illumina 450 K	Caucasians, m and w; EPIC-cohort	Meth of one CpG site correlates with BMI, waist girth, WHR, total %BF, SAT and VAT mass and also to changes of waist, BMI and weight over 5 years; further inverse association to <i>LPL</i> gene expr in SAT
fat distribution	IRS1	Glucose metabolism	Rohde K. et al. <i>Sci Rep.</i> 2017 [115]	SAT, OVAT	Pyroseq.	Caucasians, m and w	Meth differs between SAT and OVAT and is linked to mRNA expr level in obese subjects. OVAT meth and expr associate to waist girth, WHR and parameters of glucose metabolism in obese subjects. T-Allele of rs2943650 near <i>IRS1</i> is linked to increased OVAT meth at <i>IRS1</i>
fat distribution	TMEM18	DNA binding	Rohde K. et al. <i>J Mol Med. (Berl)</i> 2014 [114]	SAT, OVAT	Pyroseq.	Caucasians, m and w	Lower expr level in SAT than OAVT while meth shows opposite direction (strongest in obese subjects); SAT meth is positively correlated to BMI, visceral fat area and metabolic traits
%BF	PPARG	Lipid metabolism	Drogan D. et al. <i>Nutr Diabetes.</i> 2015 [145]	SAT	Illumina 450 K	Caucasians, m and w; EPIC-cohort	Meth of one CpG site correlates with increased %BF and VAT mass
overall obesity fat distribution BMI	LEP	Eating behavior	Houde AA. et al. <i>BMC Med Genet.</i> 2015 [92] Hjort L. et al. <i>Clin Epigenetics</i> 2017 [93] Obermann-Borst SA. et al. <i>Pediatr Res.</i> 2013 [103]	WB, SAT, VAT SAT biopsies WB	Pyroseq. MassArray Epityper MassArray Epityper	Caucasians, m and w Caucasian m Caucasians, Children	Meth in blood negatively associated to BMI and positively to LDL-C; in SAT positively to LDL-C. Meth increases during fasting in subjects with NBW; positive association with BF% in LBW.

fat distribution CVD risk	IGF2/H19	Growth, Glucose metabolism	Huang R-C. et al. <i>Clin Epigenetics</i> . 2012 [146] Drake AJ. et al. <i>Clinical Endocrinology</i> . 2012 [102]	WB PBS	MassArray Epityper MassArray Epityper Pyroseq.	17 year old m and w; Australian offspring of Motherwell cohort study	Duration of breast feeding associates negatively with <i>LEP</i> meth in offspring; boys had lower meth than girls. Higher BMI and Leptin level correlated with lower meth. Meth of the ICR of <i>IGF2/H19</i> locus correlates with higher abdominal skin fold thickness and subcutaneous obesity. Meth correlates with increased weight, waist, BMI and BP in adult offspring of mothers who had an unbalanced diet during pregnancy
overall obesity CVD risk	HSD2	Steroid hormone biology	Drake AJ. et al. <i>Clinical Endocrinology</i> . 2012 [102]	PBS	Pyroseq.	Offspring of Motherwell cohort study	Meth is associated with adult obesity and increased systolic BP in offspring of mothers with an unbalanced diet during pregnancy
overall obesity CVD risk	GR	Steroid hormone biology	Drake AJ. et al. <i>Clinical Endocrinology</i> . 2012 [102]	PBS	Pyroseq.	Offspring of Motherwell cohort study	Meth correlates with increased waist, BMI and weight while meth in <i>GR</i> exon1 is inversely associated to BP
overall obesity CVD risk	SREBF1	Cholesterol and lipid metabolism	Mendelson MM. et al. <i>PLoS Med</i> 2017 [147] Wahl S. et al. <i>Nature</i> 2017 [24]	WB blood	Illumina 450 K Illumina 450 K	FHS offspring cohort; LBCs of 1921 and 1936 from the Scottish Mtl Surveys KORA (EUR) and LOLIPOP (IA) m	Differential meth and expr of <i>SREBF1</i> in relation to BMI; further relations to other adiposity traits and CAD DNA meth in blood is correlated to BMI
dyslipidemia CVD risk	ABCA1	Cholesterol and lipid metabolism	Guay S-P. et al. <i>Clin Epigenetics</i> . 2014 [109]	leucocytes	Pyroseq.	m	Meth associates with aging and CAD; older men represent higher meth which is correlated with higher total C, LDL-C and TG level
fat distribution dyslipidemia	TNFA	Proinflammatory cytokine; lipid metabolism	Hermsdorff HH. et al. <i>Cytokine</i> . 2013 [101]	WB	MassArray Epityper	Caucasian w	Higher meth at <i>TNFA</i> in women with lower truncal fat; meth further correlates to circulating <i>TNFA</i> level. Meth explained by central fat, HDL-cholesterol, insulin, plasma <i>TNFC</i> , and daily n-6 PUFA intake SNPs in <i>CD36</i> associating with LDL-C level and <i>CD36</i> expr, the latter correlates further to its meth in SAT; hypo-meth associate to lower <i>CD36</i> gene expr in SAT
dyslipidemia	CD36	Eating behavior, lipid metabolism	Love-Gregory L. et al. <i>J Lipid Res</i> . 2016 [148]	WB, SAT	Illumina 450 K	Caucasians, m and w; GOLDN cohort; MuTHER cohort	High meth in blood at one CpG site correlates negatively with blood-TG level; variation of TG level explain variance in meth by 6–13% depending on study cohort
dyslipidemia	PHGDH	Amino acid synthesis	Truong V. et al. <i>Sci Rep</i> . 2017 [110]	WB	Illumina 450 K; bisulfite RT-qPCR	F5L family study, MuTHER cohort	4 meQTLs were identified in VAT of severe obese subjects while carriers are related to either high plasma TG level or low total C level
overall obesity dyslipidemia	TOMM20	mitophagy	de Toro-Martín, J. et al. <i>Diabetol Metab Syndr</i> . 2016 [108]	VAT	Illumina 450 K	m and w (Canadian)	<i>ABCG1</i> top candidate for negative association of meth with HDL-C and TG level and its gene expr in blood. Meth in blood correlates positively with blood TG level. Meth in blood associate with future risk of T2D and is positively correlated with BMI, HbA1c, FI and TG; DNA methylation in blood and AT differs from monozygotic twins discordant for T2D. DNA meth in blood associates with BMI
overall obesity dyslipidemia T2D	ABCG1	Cholesterol and lipid metabolism	Pfeiffer L. et al. <i>Circ Cardiovasc Genet</i> . 2015 [107] Truong V. et al. <i>Sci Rep</i> . 2017 [110] Dayeh T. et al. <i>Epigenetics</i> 2016 [149] Wahl S. et al. <i>Nature</i> 2017 [24]	WB WB blood, AT blood	Illumina 450 K Illumina 450 K Illumina 450 K; Pyroseq. Illumina 450 K	Caucasians, m and w KORA F4 study; KORA F3 and InCHIANTI; MuTHER cohort F5L family study, MuTHER cohort Caucasians, Bosnia prospective study KORA (EUR) and LOLIPOP (IA)	Meth in blood is associated with future risk of T2D and increased HDL level in
overall obesity dyslipidemia	PHOSPHO1	Phospholipid metabolism	Dayeh T. et al. <i>Epigenetics</i> 2016 [149]	blood, AT blood	Illumina 450 K; Pyroseq.	Caucasians, Bosnia prospective study	

(continued on next page)

Table 2 (continued)

Associated clinical variable	Genes	Involved pathways (related to obesity)	Study reference	Tissue type	Analysis technique	Population ancestry (replicated by)	Main findings
T2D			Wahl S. et al. <i>Nature</i> 2017 [24]		Illumina 450 K	KORA (EUR) and LOLIPOP (IA)	blood; differential meth in blood and AT from monozygotic twins discordant for T2D. DNA meth in blood is correlated to BMI
%BF MetS	Clock-genes (BMAL1 , PER2 , CLOCK)	Circadian rhythm	Milagro F.I. et al. <i>Chronobiol Int.</i> 2012 [98]	WB	MassArray Epityper	Caucasians, m and w	Meth of <i>CLOCK</i> and <i>BMAL1</i> differs in normal weight and overweight+obese subjects; meth of all 3 genes correlated positively to one or all factors: %BF, BMI and MetS score; % meth of <i>CLOCK</i> correlated with intake of fatty acids
overall obesity MetS	PER3	Circadian rhythm	Samblas M. et al. <i>Pediatr Obes.</i> 2018 [99] Ramos-Lopez O. et al. <i>Chronobiol Int.</i> 2018 [100]	WB WB	Illumina 450 K; MassArray Epityper Illumina 450 K	children; GENOI study Caucasians, m and w; MA project	Differences between normal weight and obese children; correlation to BMI Z-score. Meth in blood correlates to BMI also in adults and further to IR and BP
fat distribution MetS	HIF3A	Hypoxia	Pfeiffer S. et al. <i>Sci. Rep.</i> 2016 [75] Main AM. et al. <i>Clin Epigenetics</i> 2016 [74] Wang S. et al. <i>PLoS One</i> 2015 [77]	blood, SAT, OVAT blood, SAT PBL	Pyroseq. Pyroseq. MassArray Epityper	Caucasians, m and w Caucasians, m and w EUGENE2 Consortium children; CPOOA study (CHN)	Tissue specific meth; associations with mRNA expr, fat distribution, adiponectin level; obese subjects displayed highest <i>HIF3A</i> meth. Meth in blood correlates with BMI and meth in SAT; meth in SAT is dependent on family relatedness; no correlation to gene expr in SAT, while gene expr is related to HbA1c level. Higher meth of 2CpGs in obese vs. normal weight children; positive correlation to parameters of MetS
%BF diabetes	TXNIP	Oxidative stress, hyperglycemia	Houshmand-Oeregaard A. et al. <i>PLoS One</i> 2017 [150]	SAT biopsies	Pyroseq.	Caucasians, m and w	Higher meth while lower gene exp. in SAT in offspring of mothers with GD; meth in SAT correlates negatively with %BF and 120 min plasma insulin level
T2D	PEG3	DNA binding	van Otterdijk, SD. et al. <i>PLoS One</i> 2017 [151]	PBL	Pyroseq.	Caucasians, m and w	<i>PEG3</i> meth higher in MetS patients compared to subjects with only T2D
fat distribution diabetes inflammation	LY86	Cytokine, immune system	Su S. et al. <i>Twin Res Hum Genet.</i> 2014 [105]	PBS	Illumina 27 K Beadchip Pyroseq.	m and w (AA and EA)	Associations with increased BMI and %BF, parameters of IR and increased CRP level
overall obesity inflammation	ADRB3	Lipolysis, thermogenesis	Lima RPA. et al. <i>Clin Epigenetics.</i> 2017 [106]	WB	Pyroseq.	Caucasians, w	Hazel nut oil in diet reduces DNA meth of <i>ADRB3</i> of obese and overweight women; improved level of HDL-C and total antioxidant capacity

This table summarizes candidate gene approaches for DNA methylation in obesity and related traits in blood and AT including top genes identified in recent epigenome wide studies. Only human observational studies in adult Caucasians have been taken into account. T2D = type 2 diabetes; %BF = % body fat; CVD = cardio vascular diseases; CAD = coronary artery diseases; MetS = metabolic syndrome; AT = adipose tissue; WAT = white AT; SAT = subcutaneous AT; OVAT = omental visceral AT; PBL = peripheral blood leukocytes; PBS = peripheral blood samples; WB = whole blood; Pyro(seq) = Pyro(sequencing); m = men; w = women; meth = CpG DNA methylation (meth* = ALU-element methylation); expr = gene expression; NBW = normal birth weight; LBW = low birth weight; ICR = imprinting control region; BP = blood pressure; IR = insulin resistance; FI = fasting insulin; HbA1c = glycosylated hemoglobin; VMR = variable methylated region; HFD = high fat diet; CRP=C-reactive protein; HDL-c = high density lipoprotein-cholesterol; LDL-c = high density lipoprotein-cholesterol; total c = total cholesterol; TG = triglycerides; meQTL = methylation quantitative trait loci; GD = gestational diabetes, WHR = waist to hip ratio; MSH = melanocortin stimulating hormone; SNP = single nucleotide polymorphism.

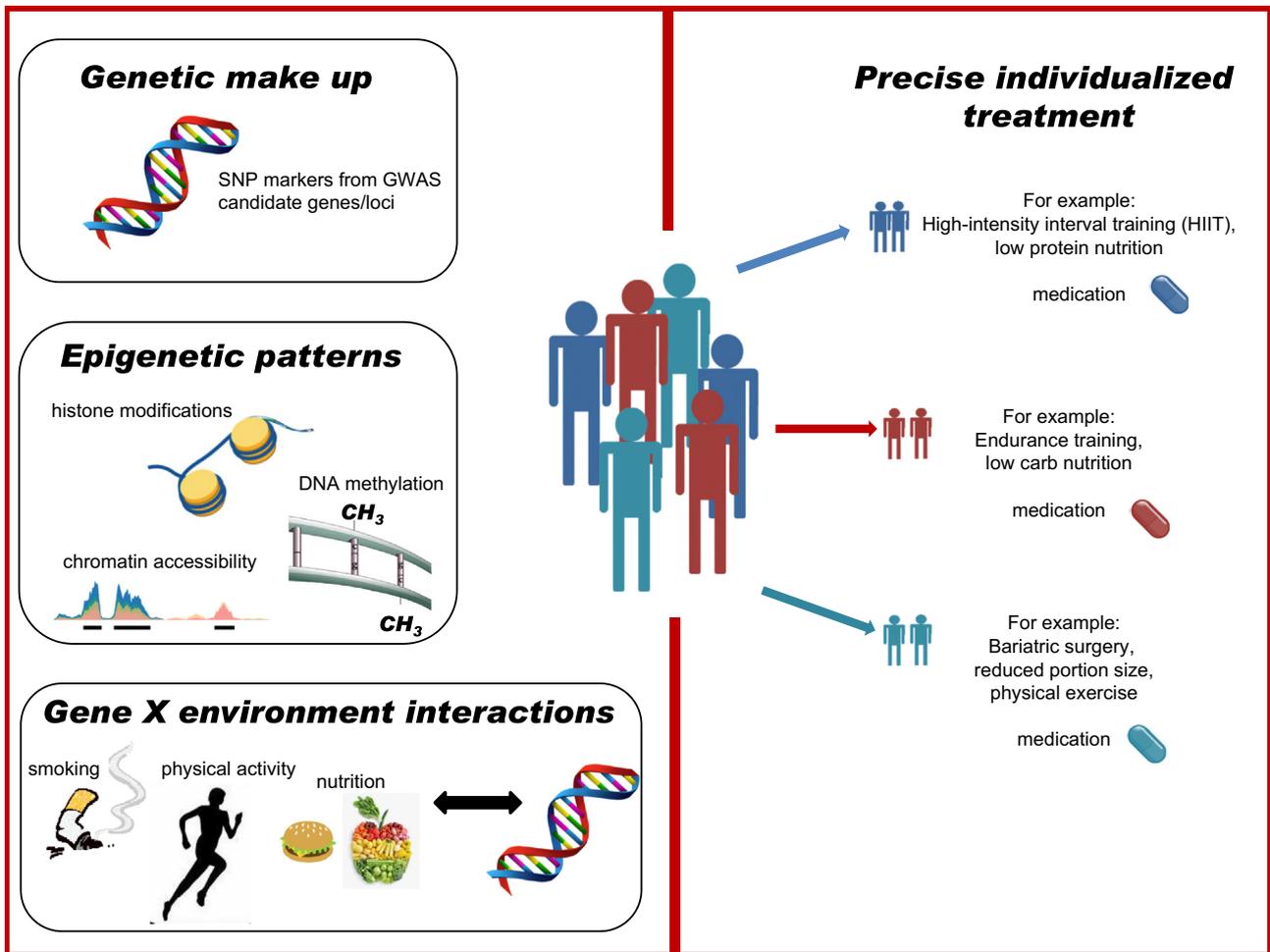


Fig. 1. Precision medicine and individualized treatment in obesity.

meQTLs in whole blood and adipose tissue (depot-specific meQTLs in SAT and OVAT) associated to BMI or metabolic traits [80,83]. For instance, a SNP variant in *ADCY3* was found to be related to proximal CpG site methylation in whole blood [83] but also in SAT [80]. Combined information of genetic variation, gene expression and DNA methylation might help to better understand potentially causative relationships with clinical traits. Genetic variants can modulate methylation status of CpGs sites and to induce co-methylation patterns at nearby sites that may finally translate into alterations of clinical traits, suggesting a genotype-phenotype correlation.

3.3. Candidate Gene Approaches for DNA Methylation in Obesity and Associated Traits

Numerous studies (Table 2) provide insights into DNA methylation contributing to obesity and metabolic syndrome mainly through pathways involved in eating behavior, circadian rhythm but also lipid metabolism. For instance, the adipokines leptin and adiponectin mediate hunger and satiety, and DNA methylation at these genes (*LEP* in blood and *ADIPOQ* in SAT) was associated with BMI and LDL cholesterol levels [92]. Moreover, body fat mass has been shown to be related to both leptin and adiponectin gene DNA methylation [93]. Interestingly, candidate genes involved in monogenic obesity such as *POMC* [94], are also subject of epigenetic changes contributing to common obesity [95,96]. Blood derived DNA methylation levels of *POMC* were linked to BMI with higher levels in obese compared to normal weight adults and children [95,96]. Furthermore, weight regain is associated with increased methylation of *POMC* but with lower blood methylation levels of *NPY* while

the latter was linked to hunger and satiety controlling peptides leptin and ghrelin [97]. Interestingly, in obese individuals methylation of *POMC* was also higher in MSH-positive neurons (melanocyte stimulating hormone) compared to lean counterparts, suggesting a regulatory function of methylation on the downstream pathway of *POMC* [97].

Another important mechanism associated with obesity is circadian rhythm, where clock-genes contribute to a 24 h rhythm underlying physiological processes. Differences in blood CpG methylation of important clock-genes such as *BMAL1*, *PER2* and 3 and *CLOCK* were found between lean and obese adults and children [98–100].

Different nutrients have been shown to correlate with changes in DNA methylation for a variety of obesity associated genes, including *TNFA*, *IGF2/H19*, *LEP*, the circadian genes (*CLOCK*, *BMAL1* and *PER2*), *HSD2*, *MCHR1*, *LY86* [98,101–105]. Methylation of *IGF2/H19* and *HSD2* has been linked to maternal diet (increased protein and reduced carbohydrate intake) during pregnancy [93] and methylation of *LEP* has been linked to the duration of breast feeding [101–103]. Mostly, various lipids have been linked to changes in DNA methylation, such as n-6 PUFAs for *TNFA*, components in hazel nut oil for *ADRB3*, other fatty acids for *CLOCK* and triglycerides for *ABCG1*, *ABCA1*, *PHGDH*, *TOMM20* [98,101,106–110]. The majority of these genes play a role in lipid metabolism suggesting that, a) lipids induce dynamic changes in DNA methylation and b) alterations in DNA methylation can impact on lipid pathway genes being of immense importance for the development of obesity and comorbidities. This is further reinforced by studies highlighting an association of blood lipid levels with genome-wide DNA methylation while affecting transcription of numerous genes involved in lipid metabolism [111,112].

DNA methylation of certain genes significantly differs between adipose tissue depots [22,79,113], which correlate with alterations in metabolic variables and fat distribution. Most studies hint on changes of DNA methylation in subcutaneous adipose tissue (SAT) being critical for an unfavorable metabolic outcome in regard to comorbidities of obesity [113]. For instance, while DNA methylation in the promoter region of *TMEM18*, a previously identified GWAS candidate gene for BMI, is higher in OVAT compared to SAT, methylation levels in SAT were positively associated with BMI, visceral fat mass and also metabolic parameters [114]. Moreover, *ADIPOQ* and *LEP* DNA methylation in SAT was correlated with increased BMI, waist circumference and/or LDL-C level and *MCHR1* methylation in SAT was related to weight gain upon high fat diet [92,104]. However, omental visceral adipose tissue (OVAT) methylation of specific genes is also linked to parameters of fat distribution as well as glucose metabolism in an unfavorable way as shown for *IRS1* [115]. These studies suggest that gene specific DNA methylation differences in SAT and OVAT contribute to the pathophysiology of obesity and underline the importance of tissue specific gene regulation. Therefore, applying blood methylation levels as surrogate markers for methylation status in adipose tissue were proven useful only for a limited number of genes such as *HIF3A* and clearly need further investigations [74].

In conclusion, gene specific DNA methylation in obesity is tissue specific and seems to be highly affected by lipid metabolites and other dietary factors. There is no doubt that changes in DNA methylation at certain genes do correlate not only with BMI and overall obesity, but also with the development of comorbidities such as T2D or dyslipidemia.

3.4. Lessons from Intervention Studies

Numerous intervention studies examining the effects of physical activity or weight loss due to bariatric surgery on DNA methylation clearly corroborate the vast evidence for correlations of clinical variables with epigenetic signatures. An early study [116] reported dynamic alterations in skeletal muscle DNA methylation at *PPARGC1A*, *PDK4* and *PPARD* induced by acute exercise intervention. Accordingly, others [117] have observed significant improvements in lipid metabolism and increased content of mitochondria in human myotubes after 12 weeks of extensive endurance and strength training comparing lean and overweight men. Lund et al. [117] further discovered decreased *IRS1* mRNA expression along with higher DNA methylation levels in response to exercise in cultured human myotubes. Recently, Bajpeyi et al. [118] provided evidence that *PPARGC1A* DNA methylation discriminates high vs. low responders post-exercise. Similar to the observed epigenomic plasticity in skeletal muscle, exercise intervention also induces genome wide changes in DNA methylation in human adipose tissue. Rönn et al. [88] described altered DNA methylation in SAT after a six months exercise intervention. These alterations were confirmed in mouse adipocytes and potentially affect adipocyte metabolism [88]. Further, others have shown that individual training status alters the genomic response on epigenetic and transcriptomic levels to acute exercise [119]. Interestingly, significant epigenomic remodeling in sperm was observed after short-term endurance training [120]. One of the scarce intervention studies in overweight adolescents investigated DNA methylation signals derived from whole blood before and after 6 months of high-intensity interval training (HIIT) [121]. While providing significant evidence for beneficial effects on body composition and cardio-metabolic health, there were no epigenetic changes [121].

Other interventions, most importantly those inducing significant weight loss such as bariatric surgery have shown evidence for dynamic epigenetic tissue-specific changes in association with improved metabolic health. DNA promoter methylation levels in skeletal muscle at *PPARGC1A* and *PDK4* were, after gastric bypass surgery, restored to levels comparable with non-obese individuals [21]. Similarly, altered promoter methylation in blood was shown for *PDK4*, *IL1B*, *IL6*, and

TNFA 12 months after RYGB [122]. Dynamic changes in DNA methylation were observed for *SORBS3* in human skeletal muscle, showing that RYGB intervention restored DNA methylation levels to normal levels [123]. Others reported differential modifications in DNA methylation at several genes (*CEPT*, *FOXP2*, *HDAC4*, *DNMT3B*, *KCNQ1*, *HOX* genes) in adipose tissue following gastric bypass surgery [124]. Accordingly, a similar study revealed specific differentially methylated loci between SAT and OVAT before and after weight loss surgery [125]. Others described changes in DNA methylation levels after RYGB related to improvements in fatty acid metabolism [126] and systolic blood pressure [127]. Interestingly, comparing the methylomes of siblings born either before or after maternal bariatric intervention, revealed evidence for a large number of differentially methylated genes, including genes important for insulin receptor and leptin signaling. These data suggest that maternal weight loss may affect the methylomes of offsprings [128]. Moreover, other data show clear evidence for epigenomic changes in human spermatozoa which are significantly altered after weight loss [129].

In summary, there is evidence for a strong relationship between behavioral changes induced by weight loss surgery or exercise interventions and epigenetic changes that in turn may contribute to beneficial metabolic effects.

4. Precision Medicine in Obesity – A Long Way to Go

In monogenic obesity individualized counseling is possible through genetic testing of candidate genes such as *LEP*, *LEPR*, *MC4R* and *POMC*. Mutations in *LEP* result in severe leptin deficiency, which could be treated by administration of recombinant leptin [35]. Recently, strong evidence was reported for treating severe obesity in individuals with mutations in *LEPR* with a novel *MC4R* agonist setmelanotide [130]. Similarly, as described in two rare cases of *POMC* deficiency, application of α -melanocyte-stimulating hormone analogue induced significant weight loss [131]. It has been reported that children carrying mutations in *MC4R* and *POMC* were able to lose weight through changes in lifestyle [132,133], but were at a high risk of weight regain. Taken together, personalized treatment in monogenic obesity is established for genetic mutation screening, and treatment scenarios for rare cases are available for mutations in *LEP*, *LEPR* or *POMC*.

Individual treatment taking into account personal risk profiles and response to various treatment options is considered to become the most effective therapeutic approach also for complex diseases in the future [134–136]. Therefore, biomarkers suitable for powerful precision medicine approaches to fight common obesity shall have a high potential in predicting risk or response to treatment and/or intervention (Fig. 1). Individualized treatment may include personalized type of exercise intervention, diet and specific medication (Fig. 1). Although tremendous technological advances opened new avenues in deciphering the genetic architecture of common obesity [15,16], precision medicine aiming at individualized therapy, its co-morbidities and related clinical variables are still in its infancy [137]. As SNP markers confer small effect sizes and genetic risks scores have a relatively low predictive value, genetic markers do not fulfill criteria of suitable biomarkers in precision medicine so far. Further limitations lie in the large inter-individual variability in clinical variables [138] which additionally hampers individualized treatment. Nonetheless, significant progress has been made in establishing large genetic databases and bioinformatics tools, which will prove extremely useful in future efforts deciphering individual phenotypic variability [139]. Importantly, GxE interactions that influence personal outcome on weight loss or regain, diet intervention or lifestyle changes [60–64] further increase the inter-individual variability while the risk prediction is not significantly improved when combined with genetic scores [67].

Taking into account the influence of environmental factors on the etiology of obesity, highlights the importance of including epigenetic markers in future precision medicine efforts (Fig. 1). Indeed, numerous

studies have emphasized strong relationships between DNA methylation and important clinical traits. Moreover, growing evidence suggests that such modifications are reversible and can be dynamically altered by environmental factors such as physical activity, nutrition or weight loss. In the context of obesity-related co-morbidities, which is per se strongly related to adipose tissue distribution, there is also evidence for a clear depot-specificity differentially influencing clinical traits. Although epigenetic markers alone are most likely insufficient to serve as biomarkers towards precision medicine, the effect size and direction of a non-causative correlation with clinical traits may still be informative as a prognostic or diagnostic tool in combination with other markers such as genetic variants. Moreover, for precision medicine to become part of clinical practice in the future, analysis of circulating epigenetic biomarkers from whole blood as a surrogate tissue would be a preferred scenario, which is still challenging with regard to the described tissue specificity of epigenetic patterns. So far, clinical applications of precision medicine in common obesity are limited and further progress in identifying and validating suitable biomarkers is warranted.

5. Closing Remarks

Prevention and treatment of obesity are challenging, because the interplay of biologic including genetic obesity risk factors with the obesogenic environment is incompletely understood. Epigenetic modifications may translate the environment and behavior into individual biologic responses, which may contribute to obesity and its comorbidities. However, how eating habits, food preference and physical activity affect gene expression through epigenetic mechanisms are not known to an extent that it could be used for a personalized prevention or treatment of obesity. Therefore, future research should clarify whether: a) rare genetic variants conferring larger effect sizes can partially account for the BMI variability unexplained by genetic variation; b) SNP markers associated with obesity in cross-sectional settings overlap with those contributing to changes in body weight in weight loss interventions, c) epigenetic modifications in circulating blood cells could be used as “biomarkers” for parallel epigenetic changes in tissues relevant in the etiology of obesity.

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Author Contributions

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