Epigenetics of eating disorders: from genetic and molecular pathways to therapeutic possibilities

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Abstract

Eating disorders (EDs) are complex, multifactorial conditions influenced by biological, psychological and environmental factors. Recent discoveries in genetic epidemiology research have confirmed a genetic component in EDs, particularly in anorexia nervosa. However, the biological processes underlying the causal pathways to disease onset remain poorly understood and biomarker research in this area significantly lags behind. Emerging empirical evidence from the past decade suggests that epigenetic mechanisms serve as key mediators of environmental and genetic risk factors that underlie major mental health conditions, including EDs. This article highlights recent findings from genetic studies on EDs and emphasises the emerging role of epigenetic mechanisms. It introduces epigenetic mechanisms, in particularly DNA methylation, and explores how dynamic DNA methylation changes may influence disordered eating behaviours through alterations in gene expression, offering a fresh perspective on the interplay between genetics, environment and epigenetics in EDs. Recent findings in the field of ED epigenetics provide promising insights into the development of these conditions, despite current limitations in epigenomic coverage, sample size and the identification of reliable biomarkers. Future studies employing comprehensive epigenomic scans across a broader spectrum of EDs are crucial for uncovering the mechanistic relevance of epigenetics and advancing biomarker research, ultimately enabling the development of improved, novel and more personalised clinical treatments.

Keywords: epigenetics, eating disorders, anorexia nervosa, binge eating disorders, gene-environment interaction, epigenome-wide association studies (EWAS)

Introduction

Eating disorders (EDs), including anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED) and avoidant/restrictive food intake disorder (ARFID), are severe, and often chronic, psychiatric illnesses that have a devastating impact on those affected, as well as their families and friends. All EDs are marked by some disturbances in eating behaviours (e.g., fasting, vomiting, binge eating) and often come with dissatisfaction with body shape and size. Despite their chronic nature and high comorbidity with other psychiatric disorders, our understanding of the risk factors and treatment for EDs is still lacking (1) and biomarker research is lagging (2). Such research is especially urgent, as the COVID-19 pandemic and lockdown measures have resulted in a spike of new ED diagnoses, as well as hospitalisations and deteriorations in symptoms (3). Empirical evidence from research in the past two decades has highlighted a complex interplay between biological, psychological and environmental factors in the development of EDs (4).

This review introduces the fundamental concepts of epigenetics and explores evidence supporting the role of environmental regulation, through epigenetic mechanisms, in shaping susceptibilities to EDs. Our aim is not to conduct a systematic review of epigenetics in EDs, as such reviews already exist elsewhere (e.g., 5-9), but rather to offer an informed update on recent discoveries, especially those from epigenome-wide association studies (EWAS), and provide key takeaways, ongoing advancements and emerging themes. As published work in this area is relatively scarce, we also draw upon concepts and discoveries from related disciplines, exploring their potential relevance for the epigenetics of EDs field. Our discussion concludes with suggestions for advancing the field and potential translational research that could influence clinical practice.

The aetiology of eating disorders

Family, twin and adoption research has consistently highlighted the heritable nature of EDs. Heritability estimates from twin studies range from 48% to 74% for AN, from 55% to 62% for BN and from 39% to 45% for BED, establishing the genetic underpinnings (10-14). Recent genome-wide association studies (GWAS) enabled the identification of novel common human variants associated with AN. The largest recent GWAS conducted on a European ancestry sample including 16,992 AN cases and 55,525 controls identified eight AN-associated genome-wide significant loci, with 11% to 17% of the heritability being attributed to common genetic variants (14). These AN-associated genetic

loci exhibited a significant positive association with other psychiatric disorders including obsessive-compulsive disorder, major depression, schizophrenia and anxiety, and a significant negative correlation with anthropometric and metabolic traits such as body mass index (BMI), body fat percentage, insulin and leptin (14). These findings suggested reconceptualising AN as a metabo-psychiatric disorder (15). Apart from common genetic variants, genetic studies of rare and structure variants in EDs have revealed enrichment of structural 13q12 deletion (1.5 Mb) and copy number variations disrupting the CNTN6/CNTN4 region in several AN cases (16). Whole-genome sequencing analyses in AN also identified novel variants in seven genes including TTC22, MRPS9, DNAJC30, HEPACAM2, USP20, ESF1 and CDK5RAP1 (17).

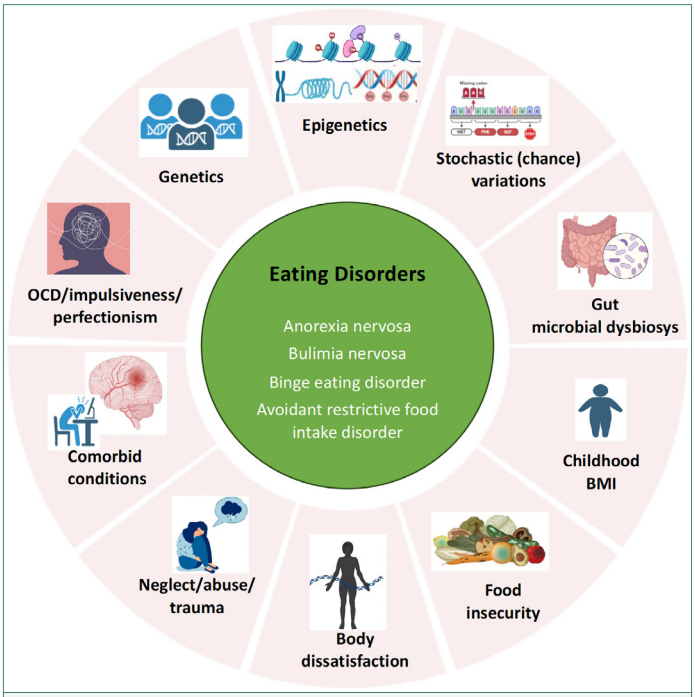

Figure 1. Developmental and risk factors for eating disorders

Given the complex nature of EDs, environmental factors, from socio-cultural influences to personal experiences, as well as stochastic chance variations in cells and biological factors such as gut microbiota in appetite regulation and epigenetics, also contribute to ED development (18). Examples of key risk factors for EDs are illustrated in Figure 1.

An introduction to epigenetics

Epigenetics ("epi" meaning "on top of" in Greek) acts as a crucial bridge between genetics and the environment, offering a nuanced perspective on how external and internal stimuli interact with genetic variations, influencing gene expression and downstream phenotypes. The term "epigenetics" and the concept of an epigenetic landscape were first coined in 1942 by the British biologist, Conrad Waddington, to describe the relationship between genotype (i.e., the sequence of genes) and phenotype (i.e., the way they are expressed in the organism), mainly during early embryonic development. Currently, epigenetics, as proposed by the National Institutes of Health Epigenomics Roadmap Project initiative, is defined as "both heritable changes in gene activity and expression (in the progeny of cells or of individuals) and also stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable" (19). This biological mechanism is essential for normal cellular development and differentiation and has important implications on the long-term regulations of gene expression and chromatin packaging (20).

There are three main epigenetic mechanisms: DNA methylation, histone modification and non-coding RNA. In this article we will focus mainly on DNA methylation (DNAm), one of the best understood and the most stable epigenetic modification that regulates gene expression. Typically, DNAm level in the gene promoter region is often inversely correlated with gene expression level due to transcriptional silencing; that is, hypermethylation of the gene promoter region is associated with reduced gene expression, and vice versa (21). DNAm is the intricate interplay between two families of enzymes, DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) methylcytosine dioxygenases, which control DNAm and demethylation, respectively (22, 23). DNAm occurs when DNMTs transfer a methyl (CH3) group from S-adenosylmethionine (SAM) to the 5 position of cytosine, one of the four bases of DNA, to generate 5-methylcytosine (5mC). DNA demethylation takes place when TET

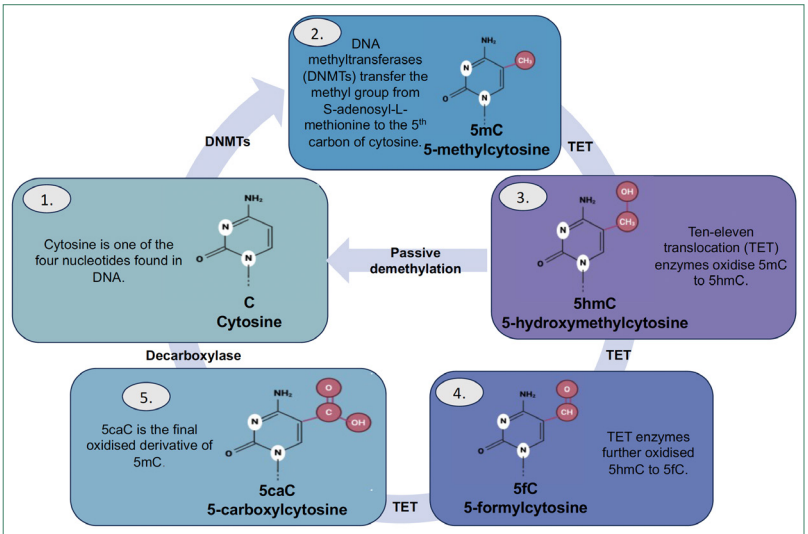

Figure 2. The dynamic cycle of DNA methylation and demethylation

DNA methyltransferases (DNMTs) catalyse the formation of 5-methylcytosine (5mC), while TET enzymes oxidise 5mC to 5hmC and initiate DNA demethylation, which can take place actively or passively. Active DNA demethylation involves an enzymatic process that eliminates or alters the methyl group from 5mC, whereas passive DNA demethylation refers to the loss of 5mC during successive rounds of replication when functional DNA methylation maintenance machinery is absent.

enzymes oxidise the methyl group of 5mC to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) in DNA (Figure 2). DNAm predominantly targets cytosines followed by guanine residues (CpG), a phenomenon commonly referred to as CpG methylation (24). However, non-CpG methylation, such as methylation at cytosines followed by adenine, thymine or another cytosine, has also been observed in specific cell types such as pluripotent stem cells and glial cells (25, 26).

There is now growing evidence that suggests a link between DNA methylation dysregulation and a range of mental health disorders, including depression, anxiety, psychosis, autism spectrum disorders and addiction (27-31). Due to its prevalence in the human brain and its potential role in human brain development, 5hmC has also gained increasing attention in the mechanistic studies of neurodevelopmental and neurodegenerative disorders (32). While conventionally considered independent of the DNA sequence, findings from recent research have revealed widespread effects of genetic variants on variation in DNAm between individuals. The genetic variants that may affect the DNAm patterns of CpG sites are called methylation quantitative trait loci (mQTLs). By incorporating mQTLs with GWAS data, studies have identified a potential role for DNAm in genetic regulatory mechanisms as well as molecular links between genetic variation and complex traits (33, 34).

While the genome and associated genetic alterations persist throughout an organism's lifespan, the epigenome and DNAm are dynamic and reversible, as well as varying across tissue/cell types, development and age. Epigenetic processes can also be affected by exposure to various external environmental factors, either broadly or at specific epigenetic sites. For instance, DNAm has been demonstrated to fluctuate in response to nutritional, chemical (e.g., smoking), physical and psychosocial factors (e.g., exposure to severe stress). DNAm levels have also been shown to correlate highly with chronological age, and such DNAm-based age estimators are commonly known as epigenetic age. Intriguingly, the difference between epigenetic age and chronological age, termed epigenetic age acceleration or deceleration, has been associated with environmental exposures (35), BMI (36, 37), functional and cognitive aging (38), psychiatric disorders (39) and mortality (including cardiovascular mortality and all-cause mortality) (40, 41).

Since epigenetic modifications are inherited mitotically in somatic cells, they offer a potential mechanism through which the impacts of external environmental factors during specific developmental stages can induce enduring changes in behaviour and/or phenotype. The malleability of the epigenome thus offers a mechanism for understanding the gene–environment interactions that are fundamental in psychiatry, including those interactions underlying predisposition to EDs.

Of particular interest are nutrition and diet, which are known to have a direct effect on epigenetic processes (42) and these alterations may contribute to the biological and molecular basis of the development of EDs. One important example of epigenetic processes is the Agouti viable yellow allele (Avy) inbred mouse strain. This strain showcases various coat-colour phenotypes, depending on the epigenetic state of a large transposable element positioned upstream of the Agouti gene. Within this transposon lies a hidden promoter that triggers a phenotype characterised by yellow fur and metabolic issues such as obesity (43). DNA methylation of the transposon suppresses this phenotype, resulting in mice with agouti (brown) fur and healthier metabolic profiles. Intriguingly, the DNA methylation pattern across this region, and consequently the phenotype, can be altered in offspring by modifying the diet of pregnant mothers (44, 45). Prenatal supplementation of the diet of pregnant mice with methyl donors such as folic acid, vitamin B12, choline, betaine and genistein (the primary phytoestrogen in soy) has been shown to increase DNA methylation in offspring postnatally, leading to gene expression associated with brown fur and improved metabolic health. In humans, the impact of maternal nutritional effect on the epigenome of the unborn offspring has also been observed, for example in the Dutch Hunger Winter study. Individuals exposed to prenatal undernutrition during periconception have altered DNA methylation signatures of the insulin-like growth factor II (IGF2) gene (with known importance in growth and metabolism regulation) when compared with their unexposed same-sex siblings 60 years after the exposure (46).

DNA methylation studies in eating disorders

The malleability of the epigenome represents a plausible biological mechanism with the potential to make important contributions to improving our understanding of the development of and susceptibility to EDs. For example, the exposure of a social environment that promotes thinness and unattainable body image could result in disordered eating behaviours which in turn trigger epigenetic changes and downstream upregulation of genes suppressing appetite or weight. Similarly, in individuals susceptible to obesity, environmental factors such as exposure to stressful life events and the availability of high-fat and high-carbohydrate foods might lead to epigenetics and expression changes to genes related to adiposity (47-49). Figure 3 illustrates how such epigenetic changes mediated by the interaction of inherited predispositions, environmental stimuli, stochastic epigenetic variations and disordered eating can trigger the long-lasting alterations in gene expression that influence susceptibility to EDs.

Despite the potential role of epigenetic mechanisms in the development of EDs, research in this field is still in early development. Akin to the beginning of genetic research in EDs, the majority of earlier epigenetic studies undertook a hypothesis-driven, candidate-gene approach with particular focus on genes related to potential ED-associated

pathways, including the dopaminergic pathway, which regulates reward (50, 51), the cannabinoid system, which is involved in appetite regulation (52), and the oxytocin system, which is associated with psychosocial modulation (53). Much of these candidate epigenetic studies focus on AN, with a minority including individuals with BN. In addition to candidate gene studies, ED-associated global DNA methylation differences have also been investigated with some inconsistent findings reported, for example, both global hypomethylation as well as hypermethylation were associated with AN (54-57). Despite some promising findings, these studies offer limited conclusions due to their narrow focus on DNAm, primarily examining promoter regions of selected candidate genes. Additionally, sample sizes have been small, with the largest study including fewer than 150 participants (8).

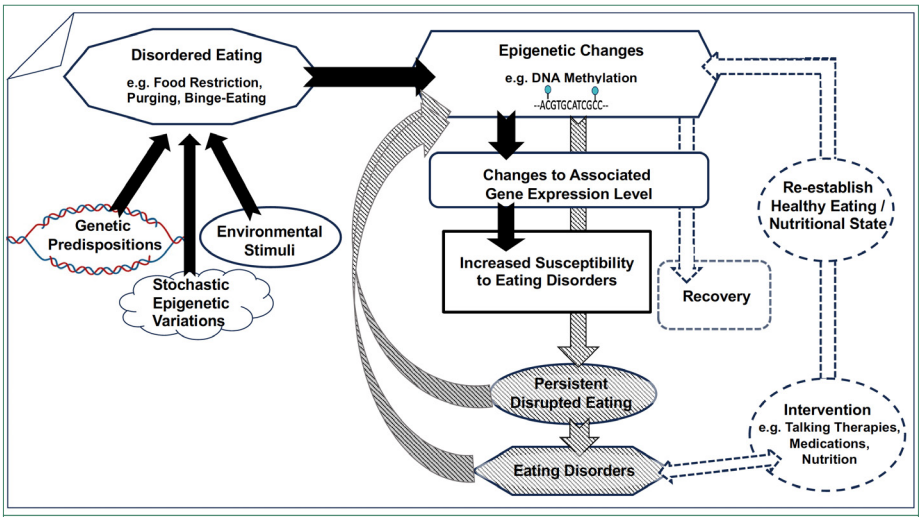

Figure 3. The intricate relationship between environmental factors, genetic predispositions, stochastic (chance) epigenetic variations, disordered eating behaviours, epigenetic changes and vulnerability to eating disorders

Exposure to adverse environmental stimuli and stochastic epigenetic variations may elevate the risk of disordered eating behaviours in individuals who carry susceptibility genes predisposing to eating disorders. Disordered eating may produce enduring alterations to gene expression via epigenetic (e.g., DNA methylation) changes that influence vulnerability to eating disorders. Increased susceptibility to eating disorders will subsequently contribute to ongoing disrupted eating behaviours (as depicted by the arrow filled with lines), leading to additional modifications in the epigenome and gene expression. The malleability of the epigenome offers a potential "reset" with the remission of the illness (as depicted by the dashed arrows) via intervention and re-establishment of healthy eating and nutritional state.

The human epigenetic research field has seen a significant rise of EWAS across health research disciplines in the past two decades due to technical advancement and the decreasing laboratory cost of measuring epigenome-wide DNAm (58). The most widely used technology for EWAS is the Illumina DNAm microarray, with its latest edition enabling a high-throughput quantification of up to 900K DNA methylation CpG sites within a single experiment (59). To our knowledge, there have been five published EWAS that investigated genome-wide DNAm profiles in AN with four presented findings using the Illumina Infinium® HumanMethylation450 BeadChip and one using the Illumina Infinium® HumanMethylation EPIC v1.0 BeadChip, which provide quantitative DNAm data on over 450K and 850K CpG, respectively (60, 61).

The first ED EWAS analysed genome-wide DNAm profiles from lymphocytes of 29 women with AN and 15 normal-weight, sex-matched controls (54). The authors reported a total of 14 differentially methylated AN-associated sites, annotated to 11 genes, including PRDM16, HDAC4, TNXB, FTSJD2, PXDNL, DLGAP2, FAM83A, NR1H3, DDX10, ARHGAP1 and PIWIL1. Interestingly, some of these reported genes have known psychological, metabolic and physical relevance to AN. For example, NR1H3 is involved in lipid metabolism and inflammation (62), and TNXB and DSE have been associated with Ehlers-Danlos syndrome, a connective tissue disorder linked to EDs (63). Kesselmeier et al. (64) examined DNAm levels in whole-blood DNA from 47 women with AN, 47 lean women without AN and 100 population-based women. Given the known potential cell-type composition effect on DNAm signals, careful considerations and adjustments were applied for the data analyses. The authors reported a total of 51 and 81 AN-associated differentially methylated sites when comparing 22 AN-active women with 24 lean women and 30 non-AN women, respectively. Approximately two-thirds of these AN-associated sites also exhibited directionally consistent differential DNAm differences in a comparison of five pairs of twins discordant for AN. The authors also reported a replication of TNXB hypermethylation associated with AN (54). It is worthy of note that the cohort analysed had significant age differences (mean ages for AN and control samples were 16 and 60 years, respectively), which is a potential confounder when interpreting the results, given the known effect of age on DNAm profiles (65). Steiger et al. (66) quantified genome-wide DNAm in leukocyte DNA from 75 AN-active women, 31 AN-remitted and 41 with no ED. The authors reported a total of 58 AN-associated differentially methylated sites, when comparing the AN-active and no ED groups, with an enrichment of genes that are relevant to metabolic and nutritional status (lipid and glucose metabolism), psychiatric status (serotonin receptor activity) and immune function. Interestingly, in a subset analysis focusing on 28 differentially methylated sites that were common to "AN-active versus no ED" and "AN-active versus AN-remitted" comparisons, effects across the analyses were consistently in opposite directions. Specifically, when group DNAm was higher in AN-active versus no ED, it was lower in AN-remitted versus AN-active, and vice versa. The authors proposed that these findings suggest an average shift toward restored DNAm levels in people who are remitted. Similar analyses were conducted by the same research group but with a slightly extended sample size consisting of 145

women with AN, 49 showing stable one-year remission of AN and 64 with no ED (67). A total of 205 and 162 AN-associated differentially methylated sites were reported when compared between "AN-active vs no ED" and "AN-active vs AN-remitted" groups, respectively. Interestingly, amongst these AN-associated differentially methylated sites, very comparable group DNAm levels between AN-remitted and no ED groups were reported. The authors concluded that this observation replicates previous findings (66) and indicates a restoration to normal levels following remission, suggesting the presence of state-dependent changes in DNAm levels that can be positively "reset" with the remission of the illness (Figure 3). In addition, the authors explored the potential relationships between DNAm profile, duration of exposure, malnutrition (as reflected by chronicity of illness) and the severity of malnutrition (as reflected by low BMI). Intriguingly, there was a significant association between 18 and 20 sites with chronicity of illness and BMI, respectively. These findings confirm the effect of dietary nutrition on the epigenome. It is worthy of note that this study, although it contains an expanded sample size compared to other ED epigenetic studies, is still small compared to EWAS in other psychiatric fields.

The study of disease-discordant monozygotic twins represents a powerful strategy in epigenetic epidemiology because they are matched for genotype, age, sex, maternal environment, population cohort effects and exposure to many shared environmental factors (68). Iranzo-Tatay et al. (69) combined this unique study design with the Illumina Infinium® HumanMethylation EPIC v1.0 BeadChip to dissect potential AN-associated differentially methylated sites in a small cohort of seven discordant twin pairs for AN. The authors of this discovery study reported nine AN-associated differentially methylated sites, including two validated in a replication cohort (consisting of seven AN patients and seven controls) and mapped onto genes associated with metabolic traits PPP2R2C and CHST1. There is, to our knowledge, no EWAS study published on other EDs.

Future perspectives and conclusions

Epigenetic research in EDs is still in its infancy, yet preliminary findings are revealing the potential relevance and impact this field of study could hold for enhancing our understanding of the aetiology and development of these disorders. Findings from hypothesis-free EWAS studies conducted thus far have indicated an interesting overlap with recent GWAS meta-analysis studies (14), highlighting the enrichment of AN-associated genetic and epigenetic dysregulation of genes enriched in psychiatric and metabolic pathways. The resemblance in methylation signatures between the AN-remitted and no ED groups, as opposed to the AN-active groups identified by Steiger et al. (67), emphasises the potential adaptability of AN-associated differential methylation signatures and the clinical application of epigenetic biomarkers. These observations add to the growing body of evidence that DNAm dysregulation plays a fundamental role in psychiatric phenotypes and that large-scale epigenetic research in EDs is warranted.

ED epigenetic research conducted thus far has primarily focused on AN and with small sample sizes; it is crucial for future EWAS studies to increase their cohort size as well as to widen the research scope to other subtypes, including BN, BEDs and ARFID. Large sample sizes (N > 1000) are fundamental for detecting small individual (epi)genetic effects; the consolidation of samples within research consortia has been instrumental in the successful execution of GWAS and EWAS across numerous human traits, as well as psychiatric phenotypes (70-72). National and international initiatives, such as the UK Eating Disorders Genetics Initiative (EDGI) (73), the Binge Eating Genetics Initiative (BEGIN) (74) and the ARFID Genes and Environment (ARFID-GEN) study (75), which are collecting both deep phenotypic data and biological samples from different subtypes of ED, have been established in the past few years. These innovative cohorts pave the way for future large-scale (epi)genetic research to be conducted, shedding light on the biological mechanism of EDs.

Expanding from ED subtypes, studying diverse populations is vital for comprehending the aetiology and risk factors of EDs. In line with genetic and epigenetic research across psychiatry, the majority of ED research published is Eurocentric with a lack of racial or ethnic diversity (76-78). Future research effort that enhances diversity in population representation within epigenomics research is essential for interpreting epigenetic biomarkers associated with EDs as well as providing crucial insights into underlying biological mechanisms (76).

Preliminary findings from AN-focused EWAS have provided insightful contributions to the epigenetic basis of EDs, highlighting potential enrichment of the DNAm dysregulations of genes involved in psychiatric and metabolic traits. However, due to technical limitations, only a very small fraction of the DNA methylome (less than 3%) has been captured and studied so far. Recent technological advances in long-read sequencing technology, including Oxford Nanopore sequencing, have greatly expanded the capacity of long-range, single-molecule DNA-modification detection, providing reliable and quantitative data of up to 97% of the DNA methylome (79). Epigenetic studies on EDs employing long-read sequencing are poised to offer valuable insights into the genetic variations contributing to EDs while deepening our understanding of their complex genetic and epigenetic landscapes. This approach could also illuminate disrupted biological pathways associated with EDs and advance the discovery of potential biomarkers. While much of the focus has been on DNA methylation, expanding ED research to include other epigenetic mechanisms, such as histone modifications and non-coding RNAs, could provide valuable insights.

Epigenetic changes associated with EDs hold significant potential as targets for personalised treatment. While psy-

chological therapies remain the cornerstone of ED management, pharmacological interventions are also recognised in clinical guidelines (80), for example, fluoxetine for BN and comorbid anxiety or depression (81), and lisdexamfetamine (82) and topiramate for BED (83, 84). Emerging evidence suggests that epigenetic mechanisms may influence the efficacy of these medications (85, 86). For example, fluoxetine has been shown to regulate brain-derived neurotrophic factor via epigenetic mechanisms (87), potentially alleviating and preventing depressive symptoms. Understanding an individual's epigenomic profile could enable clinicians to make more informed decisions, tailoring pharmacological treatments to optimise personalised management plans for EDs.

In conclusion, epigenetics represents a crucial biological mechanism and a promising innovative biomarker for EDs. Advancing epigenetic research in this field is essential to enhance our understanding of the origins of EDs and to identify intervention targets, paving the way for the development of more effective and personalised treatments.

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