REVIEW

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Applying epigenetic science to the understanding of eating disorders: a promising paradigm for research and practice

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Purpose of review
Studies indicate that environmental factors, acting at various moments throughout the life cycle, can result in epigenetically mediated alterations in gene expression. In this article, we review recent findings on the role of epigenetic factors in eating disorders, address methodological issues that need to be considered when interpreting research findings, and comment on possible clinical applications.

Recent findings
Evidence suggests that eating disorders implicate alterations of methylation in genes involved in the mental status, metabolism, anthropometric features and immunity. Furthermore, some research in individuals with anorexia nervosa suggests the presence of reversible, malnutrition-induced epigenetic alterations that 'reset' as patients recover.

Summary
Epigenetic studies in the eating disorders corroborate the idea that eating disorder cause is multifactorial, and identify markers that could help inform our understanding of illness staging and subtyping that may explain the commonly progressive course of these disorders, and that may provide insights towards the development of novel interventions. Already, there is evidence to suggest that, in people with eating disorders, epigenetically informed interventions help reduce stigma and shame, and increase self-acceptance and hopes of recovery. Although findings are intriguing, further research is required as, to date, studies apply modest sample sizes and disparate methodologies.

Keywords
DNA methylation, eating disorders, epigenetics, gene–environment interactions, neurobiology

INTRODUCTION

Eating disorders are characterized by intense preoccupations with eating, weight and body shape, and such maladaptive eating behaviours as excessive caloric restraint, binge eating, and self-induced vomiting [1▪]. Eating disorders can be highly debilitating, and are associated with significant morbidity, mortality and decreased quality of life [1▪,2].

Theories of eating disorder etiology have come to increasingly emphasize the contribution of heritable genetic factors [3]. Providing substantive empirical support for this view, a large genome-wide association study (GWAS) conducted by the Eating Disorders Work Group of the Psychiatric Genomics Consortium (involving 3495 individuals with anorexia nervosa and 10 982 individuals with no eating disorder) documented the world literature's first genome-wide significant effect for anorexia nervosa – a locus on chromosome 12 at a site linked to type-1 diabetes and autoimmune diseases [4]. An even larger follow-up study by the same consortium involved 16 992 people with anorexia nervosa and 55 525 normal eaters, and associated eight loci with anorexia nervosa at genome-wide significance [5▪▪]. Both GWAS studies

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KEY POINTS

- Genetic and epigenetic research showed that eating disorders have psychiatric, metabolic and autoimmune components.
- Epigenetic mechanisms provide a physiological explanation of how gene and environment interact in (the development of) eating disorders.
- Although study findings need proper replication and validation, epigenetic research may help to identify markers for illness staging and subtyping and targets for future innovations in treatment.
- Epigenetically informed models of eating disorders may increase self-acceptance and hopes of recovery in individuals affected by eating disorders.

(GWASs) reported positive genetic overlap between anorexia nervosa and anxious–depressive phenotypes (e.g. neuroticism, obsessive–compulsive disorder) and metabolic factors affecting high-density lipoprotein cholesterol [4,5▪▪]. Interestingly, both studies found negative genetic overlap between anorexia nervosa and certain disorder-relevant metabolic and anthropometric traits (e.g. body mass index, hip circumference, fasting insulin). In contrast, cross-disorder analyses showed no genetic correlation between anorexia nervosa and neurological phenotypes [6]. Together, findings from these GWASs suggest that anorexia nervosa is a polygenic disorder, implicating genetic transmission of expected psychiatric traits and a predisposition towards particular anthropometric and metabolic characteristics [5▪▪]. That being said, correspondence between genotypes and phenotypes is imperfect, indicating that a viable etiological model must account for the actions of other factors beyond those coded in genes alone.

Contemporary views on the etiology of eating disorders support a diathesis-stress model, involving the activation of genetic predispositions by environmental stressors at various stages throughout the life cycle [7▪]. Although their role remains hypothetical, epigenetic processes have increasingly been proposed as a physiological 'platform' upon which genetic and environmental factors may converge to produce mental-health phenotypes – among them eating disorders [8]. Extending recently published reviews [7▪,9▪], the current article summarizes the most recent epigenetic research related to eating disorders, addresses the ways in which epigenetic research has helped improve the modelling of the multifactorial nature of eating disorders, and discusses the potential of epigenetic science to inform clinical practice.

WHAT IS DNA METHYLATION?

Epigenetic mechanisms influence gene expression (and corresponding phenotypic variations) in the absence of actual DNA-sequence changes. The most widely studied of these mechanisms – DNA methylation – involves the addition of a methyl group to the nucleotide base pair cytosine when found next to a guanine, a region of the gene called a CpG site [10]. Typically, methylation of CpGs in gene regulatory regions suppresses gene expression, either by inhibiting the binding of transcription factors or deactivating affected chromatin [10].

DNA methylation provides interesting potentials for psychiatric research, as it can be assessed noninvasively in readily accessible peripheral tissues, such as blood, buccal cells and saliva. The latter is important, given that epigenetic patterns cannot be assessed directly in the brains of living beings [11]. Although methylation patterns of some genes are tissue-specific [11,12], the idea that peripheral DNA methylation is reflective of brain processes, and thus informative in a mental-health context, has been quite well validated. First, animal and human postmortem studies have shown that methylation of many genes in peripheral tissues parallels that observed in brain tissues [12]. Second, recent studies in living humans that combine peripheral methylation measures with brain-imaging have reported associations between methylation levels of various genes (e.g. *SLC6A4*, *GR*, *FKBP5*) and human brain outcome [11,13▪,14,15]. Additionally, peripheral methylation signals may be especially informative in eating disorders – given that they are illnesses that impact both brain and periphery. Peripheral methylation patterns in individuals with eating disorders might, for instance, reflect a body-wide systemic response to environmental conditions having central and peripheral effects. Perhaps most importantly, dieting and weight loss – key precipitating factors for eating disorders – have been shown to impact DNA methylation patterns across various bodily tissues [16]. Relevant to the preceding, recent evidence has shown that activity-induced anorexia (a syndrome in which rodents can be induced to choose the running wheel over food) is associated with altered brain methylation [17].

Various forms of evidence indicate that methylation levels are malleable and responsive to environmental influences. For example, research in animals, living humans, and postmortem human brains has shown associations between early environment (e.g. trauma) and DNA methylation [18▪,19–24]. Likewise, exposure to gestational distress (e.g. maternal depression, malnutrition) has been associated with peripheral DNA methylation outcome later in life [18▪,20,22–24]. Although the studies in question

are heterogenous with respect to methodology and results [18▪,23], available findings point to the potentials of epigenetic processes to constitute molecular mechanisms that could link environmental impacts, experienced at various moments throughout the life cycle (perinatal, childhood and adult) to mental-health outcomes, including eating disorders [8,18▪,23]. Importantly, methylation of some genes can also be altered by psychotherapeutic, nutritional or pharmacologic interventions [25,26▪▪], which raises the promise that changes in DNA methylation could serve as a marker for disease risk, staging, prognosis or therapeutic response.

CANDIDATE-GENE METHYLATION STUDIES IN EATING DISORDERS

We preface our remarks about methylation studies in candidate genes by stating that this literature has fallen out of favour in recent years, largely as it has been subject to problems of stability of results owing to reliance on small sample sizes, and applications of heterogeneous techniques that yield divergent results – for example, differences in epigenetic assessment methods, chosen CpG sites, peripheral tissue types, and so on [7▪,9▪]. We will, however, summarize main themes from the early literature, and review findings from recent candidate-gene studies that have not been addressed elsewhere.

A general theme of the candidate-gene methylation literature in anorexia nervosa suggested tendencies towards hypermethylation (implying silencing) of genes that are involved in stress accommodation, impulse control, affect and neural plasticity (e.g. genes regulating dopamine, serotonin, oxytocin, brain-derived neurotropic factor). A recent study investigated treatment-induced changes in DNA methylation in genes regulating leptin – a hormone involved in energy regulation [27]. It found that individuals with anorexia nervosa had lower leptin gene (*LEP*) and leptin receptor gene methylation than healthy eaters. Furthermore, it associated better clinical outcomes at a 12-month posttreatment follow-up with lower baseline *LEP* methylation and larger increases in *LEP* methylation during treatment and follow-up [27]. Combining measures of serotonin transporter gene (*SLC6A4*) methylation with brain-imaging resting-state functional connectivity, Boehm *et al.* [13▪] found that individuals with anorexia nervosa had increased brain connectivity in the salience network – a brain circuit important for the regulation of cognitions and emotions. Within the anorexia nervosa group, greater salience network brain connectivity was also associated with eating disorder severity.

Our group conducted some of the earliest studies comparing candidate-gene methylation levels between people with and without bulimia nervosa. We focused on genes involved in the regulation of the HPA-axis (e.g. *GR*), neuroplasticity (*BDNF*) and monoamines (e.g. *DRD2*). The gist of results from these studies indicated that alterations in methylation seen in individuals with bulimia nervosa tended to correspond more closely to variations in comorbid tendencies (like suicidality, personality disorder or substance abuse) or to variations in exposure to childhood abuse, than they did to presence or absence of bulimia nervosa per se [28,29].

EPIGENOME-WIDE METHYLATION STUDIES IN EATING DISORDERS

To date, three studies have conducted epigenome-wide analyses in individuals with eating disorders [26▪▪,30,31], all three involving anorexia nervosa. The most recent of these [26▪▪] compared epigenome-wide DNA methylation patterns in leukocytes of 75 individuals with anorexia nervosa, 31 in remission from anorexia nervosa for at least 1 year, and 41 normal-weight healthy eaters [26▪▪]. It also assessed DNA methylation after 4 months of standardized treatment for anorexia nervosa. Consistent with some of the GWAS findings reviewed above [4,5▪▪], we observed DNA methylation differences between individuals with active anorexia nervosa and normal eaters in loci related to mental health (e.g. receptors for serotonin *2A* and *2B* and glutamate), metabolic status (lipid and glucose metabolism), and immune function. In other words, our findings nicely paralleled those of the large-scale GWAS studies in implicating a trio of systems in anorexia nervosa – one influencing mental status, one metabolism and one immune function. Furthermore, within the actively ill anorexia nervosa group, chronicity of illness was associated with larger methylation alterations in genes regulating glutamate and serotonin activity and insulin function. Finally, body mass index increases after 4 months of treatment correlated with methylation changes in genes linked to lipid and glucose metabolism and immune function. Notably, DNA methylation patterns from individuals remitted for 1 year did not differ from those seen in normal eaters, suggesting the possibility that illness-induced methylation changes might be reversed by nutritional rehabilitation [26▪▪]. As an additional note, we find it intriguing that epigenome-wide analyses conducted by our group [26▪▪,30] and by an independent group [31] corroborate associations between anorexia nervosa, on the one hand, and altered methylation in *NR1H3* (involved in lipid metabolism and inflammation) and *TNXB* (associated with connective-tissue disorders), on the other.

DISCUSSION

Since the publication in 1982 of the landmark book, '*Anorexia Nervosa: A Multidimensional Perspective*' [32], it has been quite widely accepted that eating disorders have multiple, biopsychosocial determinants. However, early modelling allowed for little more precision than to acknowledge that eating syndromes must result from an unspecified interaction among biological, psychological and social factors. The advent of epigenetic science has allowed for a more principled modelling of the ways in which biological, psychological and social factors might interact to produce eating-disorder phenotypes. Indeed, the epigenome presents as a compelling 'platform' on which effects of perinatal stresses, early-life experiences, later environmental impacts and nutritional factors might converge to influence hereditary biological propensities. Recent advances in genetic and epigenetic research allow us to characterize eating disorders as being truly multidimensional – encompassing psychiatric, metabolic and immunological components that are each, in turn, subject to diverse environmental programming effects. In other words, epigenetic modifications such as DNA methylation might help explain how adverse life experiences and socially induced triggers like excessive dieting set off and sustain eating disorders in genetically disposed individuals. Given its dynamic nature, DNA methylation studies may also identify molecular targets for epigenetically based interventions. Indeed, in cancer – arguably a prototypical epigenetic disease – DNA methylation-based screening tests and epigenome-targeted therapies are gradually being implemented in clinical practice [33]. Likewise, more and more clinical trials testing DNA methylation-based screenings and drug treatments are being conducted for neurological, metabolic, immunological and infectious diseases [33]. In this light, our observation that nutritional rehabilitation may reverse DNA methylation alterations in anorexia nervosa hold promise for the development of epigenetic markers for disease staging, nutritional adjuncts in treatment or pharmacological interventions.

Identification of epigenetic markers that are predictive of course of illness and treatment response may also facilitate the development of personalized medicine approaches to eating disorder treatment. For example, we can envision eventual applications of epigenetic markers in the differentiation of cases for whom acute weight-restoration treatments may be fruitful, from those with longer standing or more entrenched disorders, and for whom such intensive treatment approaches may be counter-therapeutic or traumatizing (see [34] for a thorough treatment of this question). Or, arguably, it may become feasible to use epigenetic markers to isolate etiologically distinct eating disorder subtypes. For instance, based on current genetic and epigenetic findings [4,5▪▪,26▪▪,30], it is compelling to speculate that there may exist etiologically distinct anorexic subtypes, some of which have a strong psychiatric component, others of which depend more strongly on metabolic or even autoimmune substrates. If so, epigenetic signatures might eventually guide the principled assignment of individuals to individually tailored treatments in a precision-treatment type of approach. Although the preceding is promising, the relevance of DNA methylation measures for clinical decision-making still needs to be established with longitudinal studies in large patient cohorts.

Although the idea that eating disorders depend upon the environmental regulation of gene expression has many appeals, it is necessary to temper enthusiasm surrounding this notion with the knowledge that the evidence base is 'thin', and has many limitations. Available studies are still based on very small samples, meaning that stability of findings is suspectable. As has been the case in the genetics literature, real progress in epigenetic research will likely require large-scale, multisite collaborations, with careful coordination of efforts to standardized measurement techniques, tissues tested, diagnostic criteria and other variables. Obtaining large samples also offers the promise of opening up new discoveries related to subtyping, chronicity, comorbid features and differential impacts of environmental adversity. If studies include longitudinal components, then they may also inform our understanding of disease staging and recovery, and help in the differentiation of trait effects (reflecting disorder-specific vulnerabilities) from state effects (linked to secondary effects of malnutrition or dietary distress). Of note, to date, all epigenome-wide methylation studies in eating disorders have addressed anorexia nervosa, meaning that studies on bulimia nervosa, binge eating disorder and related eating disorders are needed. From a methodological standpoint, further studies into the reliability and functional relevance of identified DNA methylation marks are warranted [35]. Finally, it is well established that methylation levels of CpGs in certain genes are allele/genotype-dependent [36–38]. Identifying genetic influences on DNA methylation patterns in individuals with eating disorders may provide insight into how genetic variations influence risk for eating disorders.

Although it is early to apply epigenetic concepts in treatment, there is reason to believe that epigenetically informed models may already benefit the work of practicing clinicians. Arguably, epigenetically informed models help 'humanize' the process

of treatment, as they help clinicians and patients alike understand that eating disorders occur, not because of 'character weaknesses' in those affected, or because of dysfunctional families from which affected people arise, but because of the activation of measurable biological susceptibilities by specific environmental impacts [8]. In other words, we propose that epigenetic science encourages an understanding of eating disorder etiology and treatment response that blames sufferers and their relatives less, and that supports and validates more.

CONCLUSION

Although epigenetic research so far is characterized by a limited number of small-scale studies applying diverse methods, some conclusions can be gleaned. First, the epigenome presents as a compelling physical 'locus' at which genes may be impacted by various environmental effects, occurring at various moments in the life cycle (perinatal, childhood and later-in-life). Second, epigenetic research may help in the development of personalized medicine techniques that could improve screening of high-risk individuals and treatment of people in whom full-blown eating disorders develop. Third, an epigenetically informed model of eating disorder development and maintenance may improve the sensitivity of clinicians and other carers to the realities of people affected by eating disorders, and in this sense, helps reduce blameful messages and stigma.

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Conflicts of interest

There are no conflicts of interest.

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