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REVIEW

Genetics and epigenetics of eating disorders

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Abstract: Eating disorders (EDs) are serious psychiatric conditions influenced by biological, psychological, and sociocultural factors. A better understanding of the genetics of these complex traits and the development of more sophisticated molecular biology tools have advanced our understanding of the etiology of EDs. The aim of this review is to critically evaluate the literature on the genetic research conducted on three major EDs: anorexia nervosa, bulimia nervosa, and binge eating disorder. We will first review the diagnostic criteria, clinical features, prevalence, and prognosis of anorexia nervosa, bulimia nervosa, and binge eating disorder, followed by a review of family, twin, and adoption studies. We then review the history of genetic studies of EDs covering linkage analysis, candidate-gene association studies, genome-wide association studies, and the study of rare variants in EDs. Our review also incorporates a translational perspective by covering animal models of ED-related phenotypes. Finally, we review the nascent field of epigenetics of EDs and a look forward to future directions for ED genetic research.

Keywords: anorexia nervosa, binge eating disorder, bulimia nervosa , animal models, genome-wide association studies, high-throughput sequencing

Video abstract

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Overview of eating disorders

Eating disorders (EDs) are serious psychiatric conditions with significant morbidity and mortality. That EDs have a genetic component may come as a surprise to many due to widespread misperception of them being disorders of volition. Research over the past decade has confirmed that genes do indeed play a role, and animal models of core related phenotypes are assisting with defining the underlying biology of these pernicious illnesses. In this review, we focus on three major EDs: anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). Most of the genetic research has focused on AN and BN; less information is available for BED due to its status as a newly recognized ED diagnosis.

Anorexia nervosa

AN (International Classification of Diseases, 10th revision [ICD-10]: F50.00) is a serious ED with substantial morbidity and the highest lifetime mortality among psychiatric disorders.[1–3] Low weight or body mass index (BMI) is the sine qua non of AN and the primary target of initial treatment.[4,5] Symptoms of AN include persistent restriction of food intake, an intense fear of gaining weight or persistent behavior that interferes with weight gain, and a distorted body image.[6] There are two subtypes of AN: restricting subtype (ICD-10: F50.01) and binge/purge subtype (ICD-10: F50.02).[6]

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Although it is not uncommon for postmenarcheal female AN patients to present with amenorrhea or oligomenorrhea, menstrual dysfunction is associated with illness severity[7] and not required for an AN diagnosis.

The lifetime prevalence of AN is 0.3%–0.9%,[8–10] and it is estimated that 90% of afflicted individuals are female. Although onset of the illness typically occurs in adolescence, prepubescent onset is not uncommon,[11] and AN and other EDs are also diagnosed in women in midlife and older adulthood.[12] Crossover between ED diagnoses and subtypes is frequent: for instance, more than half of individuals with AN restricting subtype develop AN binge–purge subtype.[13] Diagnostic migration from AN to BN may be as high as 36%, with higher premorbid and lifetime BMIs being predictors of crossover.[14] Crossover from BN to AN may be less common, with the estimates ranging from 4% to 27%.[14,15] However, studies also report a decline in crossover rates after 5 years,[14,16] with most transitions occurring during the first 3–5 years of illness.[13]

AN, especially in adults, is difficult to treat and is associated with disturbingly high morbidity and mortality.[5,17] Family-based therapy is one of the first-line treatments for adolescent AN patients.[18] Medication trials have yet to identify drugs with clear benefit that target the core pathology of the disorder, rigorously controlled psychotherapy studies are sparse for adults,[4] and the need for ongoing intervention after completion of a treatment program is the norm rather than the exception.[19] In specialist settings, less than 50% of AN patients achieve full recovery, roughly a third of the patients improve, and about 21% develop a chronic course.[20] A 12-year outcome study reported more concerning statistics, with 27.5% of those with AN having a good outcome, 25.3% having an intermediate outcome, 39.6% having a poor outcome, and close to 8% having been deceased at the end of 12 years.[21] However, research in community samples suggests a much better long-term prognosis for AN compared to clinical samples,[22] suggesting that treatment-seeking individuals may present with increased severity and chronicity, thus contributing to poorer outcome in clinical settings.

Bulimia nervosa

Individuals with BN (ICD-10: F50.2) present with recurrent episodes of binge eating – consumption of a large amount of food in a short period of time, accompanied by a sense of loss of control over eating – and compensatory behaviors such as self-induced vomiting, laxative or diuretic abuse, fasting outside of binge episodes, and excessive driven exercise. From a diagnostic perspective, whereas individuals with AN binge/purge subtype meet the low-weight criterion for AN, patients with BN do not and can present in the normal weight, overweight, or obese range. Two subtypes of BN exist: purging subtype and non-purging subtype.[6] The lifetime prevalence of BN is 0.8%–2.9%,[8–10,23,24] and similar to AN, the majority of those who suffer from BN are women.[10,25] Binge eating behavior is relatively common in the general population.[9] Bulimic behaviors often have their onset during adolescence and early adult years, typically somewhat later than AN, and as many as 13% of North American college students display varying degrees of bulimic symptoms.[26,27] However, regular binge eating associated with characteristic psychopathology with purging (as in BN) or without purging (as in BED, discussed below) are less prevalent and require psychiatric attention.

Cognitive behavior therapy and selective serotonin reuptake inhibitors are the first-line treatments for BN.[5,28] Long-term outcome studies have consistently shown that about 55%–70% of BN patients fully or partially recover, whereas 23%–30% of the cases either become chronic or cross over to another ED.[3,24,29,30] Over a decade, while 51% of those with BN will meet criteria for good outcome following psychotherapy,[31] 11% will still meet full diagnostic criteria, and over an additional 18.5% will still suffer from subclinical disordered eating.[30] Although effective treatments for BN are available, their use among primary care clinicians may be limited.[32] Furthermore, due to the secrecy and shame associated with binge eating and purging, many individuals with BN refrain from seeking treatment.[33]

Binge eating disorder

BED (ICD-10: F50.8) is marked by recurrent episodes of binge eating accompanied by a sense of loss of control over eating, but differs from BN, in that recurrent inappropriate compensatory behaviors are absent.[6] Other characteristics of BED include distress about the binge eating, eating alone during a binge episode because of embarrassment about overconsumption, and feelings of guilt or shame after a binge episode.[6] Although overvaluation of the importance of shape and weight is not a diagnostic feature of BED,[6] it is commonly present.[34–36] The prevalence of BED is estimated to be between 2% and 3.5%,[8,9,23] and the majority of individuals with BED are either overweight or obese.[37] Unlike AN and BN, the age of onset for BED tends to be later (ie, early- to mid-20s instead of adolescence),[23] and the prevalence of BED is distributed more evenly across sexes.[9]

Similar to BN, cognitive behavior therapy, selective serotonin reuptake inhibitors, and other medications have

been shown to be effective in the treatment of BED.[5,38] Studies on evidence-based treatments for BED have reported a posttreatment remission rate ranging from 25% to 80%, which suggests significantly better outcome compared to AN or BN.[39] However, many individuals with BED often seek treatment at weight loss clinics instead of receiving psychological or psychiatric interventions.[40] It is also not uncommon for individuals with BED to cross over to BN over time,[8,39] whereas BED-to-AN crossover is rare.[8,41]

In summary, full-syndrome and subsyndromal EDs are relatively common in the general population and are associated with a significant increase in mortality, especially in young women in the case of AN and BN. There are no treatments with strong empirical support for adult patients with AN, and it is not uncommon for patients with BN and BED to relapse in the long run; thus, it is important to focus research efforts on the biological etiology of EDs in order to gain a better understanding of risk factors and develop more effective treatment strategies.

Genetic epidemiology of EDs: family and twin studies

EDs are strongly familial. The relative risk for AN susceptibility is elevated fourfold in family members of AN probands,[42] and female relatives of AN patients are up to eleven times more likely to develop AN than individuals who do not have relatives with AN.[43] Furthermore, individuals who have a relative with AN or BN are at elevated risk for developing either disorder,[43,44] which suggests some genetic correlation between AN and BN. Of note, however, no cases of BN were found in relatives of individuals who had the restrictive subtype of AN in one study,[45] suggesting limited genetic overlap between diagnostically stable restricting AN and BN. Similar to AN and BN, BED is also found to aggregate within families[46] and in a manner independent of obesity.[47]

The heritability estimate for AN obtained from twin studies ranges from 0.48 to 0.74, meaning that up to 74% of phenotypic variation can be explained by additive genetic factors.[48–54] The heritability of strictly defined AN (ie, individuals meeting all diagnostic criteria for the disorder) is usually higher than the reported heritability of broadly defined AN that includes subsyndromal cases.[52,53] Heritability of BN is estimated to be between 0.55 and 0.62,[50,52,55,56] and most of the variance in core BN symptoms (especially vomiting) is due to additive genetic factors.[57] Interestingly, co-twins of individuals who are preoccupied with weight and shape, and/or have AN-spectrum symptoms, are more likely to develop AN, whereas co-twins of individuals with bulimic symptoms are shown to be at a greater risk for developing BN.[58] One twin study identified the genetic correlation between AN and BN to be 0.79,[52] which may explain the high crossover rates between the two presentations. As for BED, twin studies, using varying definitions of illness, have estimated its heritability to be between 0.39 and 0.45.[59,60]

Genetic factors also contribute to disordered eating behaviors and dysfunctional eating attitudes that are associated with EDs. A large population-based twin study has shown that 43% of variance in individual differences in weight- and shape-related concern, and 49% of the variance in individual differences in binge eating, can be explained by additive genetic factors.[61] In addition, shared environmental factors do not have a significant effect on disordered eating in adoptive siblings, and the heritability of disordered eating is high for twins reared apart,[62] further highlighting the importance of genetic factors.

Molecular genetic studies of EDs

Linkage studies

Linkage studies aim to identify genomic regions that have an increased likelihood of containing genes that are associated with a disorder or trait.[63] Linkage analysis is conducted on samples of related individuals (eg, parent-offspring trios, affected sibling pairs, dense pedigrees) and does not require a priori hypotheses based on biological function or prior data.

The first genome-wide linkage analysis in EDs detected a signal at chromosome 1p34.2, with D1S3721 as a possible susceptibility locus for restricting subtype AN.[64] Chromosome 1 was also implicated in AN by a Japanese group as a part of a genome-wide microsatellite study.[65] A later follow-up study on this signal identified serotonin 1D (*HTR1D*) and opioid delta 1 receptor (*OPRD1*) loci to be associated with AN in 191 cases,[66] and similar results were reported in 226 female AN patients in a different study.[67] A subsequent linkage analysis in 196 multiplex families that incorporated covariates detected signals in regions on chromosome 2 for obsessionality, chromosome 13 for drive for thinness, and chromosome 1 for the combined drive for thinness–obsessionality trait in AN.[68] For BN, chromosome 10p was reported as a potential risk locus in 308 samples obtained from multiplex families.[69] Since the publication of these studies, additional loci have been identified for ED-related behaviors and phenotypes in BN, including the involvement of 4q21 for lowest illness-related BMI.[70]

Despite the initial wave of linkage analyses of AN and BN, the findings reported by investigators were not followed

up by rigorous replication studies. One key limitation of linkage analysis is its inability to narrow down regions to an experimentally feasible number of genes. In many instances, potential susceptibility loci could span multiple megabases in size. As a genome-wide approach, linkage analysis is currently reserved for instances in which dense pedigrees are studied, and more sophisticated approaches such as genome-wide association studies (GWAS) have replaced this method.

Candidate-gene association studies

Following the initial wave of linkage studies and technological advancements, candidate-gene studies that focused on single nucleotide polymorphisms (SNPs) with a priori hypotheses based on biological function (as demonstrated in in vitro, in vivo, or animal studies) became a popular method to study the genetics of EDs. However, candidate-gene findings did not replicate due to small sample sizes, lack of rigorous correction for multiple testing, methodological heterogeneity, and potential population stratification. Although it should be noted that the field of psychiatric genetics has moved past candidate-gene methodology, this section will briefly summarize the highlights from candidate-gene studies in EDs in order to provide a historical backdrop for research in the field (Table 1). More comprehensive reviews of the candidate-gene findings in EDs are available elsewhere.[71–73]

Because of the important role serotonin plays in eating behavior and the documented serotonergic abnormalities in EDs,[74,75] serotonergic genes and their involvement in EDs have been studied extensively. As mentioned in the previous section, positive findings involving *HTR1D* SNPs in AN were reported by two preliminary studies.[66,67] The serotonin 2A receptor (*HTR2A*) polymorphisms have yielded mixed findings in AN and BN,[76–82] whereas other serotonin receptors have been studied in small sample sizes and not been followed up.[83,84] Conflicting findings on the involvement of the 43-basepair insertion/deletion polymorphism in the promoter region of serotonin transporter gene (*SLC6A4*; also known as *5-HTTLPR*) in AN have been published.[85–89] In the case of BN, although meta-analyses have failed to replicate the previously reported association between *5-HTTLPR* and BN diagnosis,[89,90] the short variant has otherwise been associated with impulsivity, novelty seeking, and trauma in pilot studies of BN and BN-spectrum disorders.[91–93] Additionally, one study found overrepresentation of the long-allele of *5-HTTLPR* in 77 BED cases compared to 61 normal-weight controls.[94]

Dopamine is an important monoamine neurotransmitter that is involved in a large variety of brain functions, including feeding behavior, motor activity, and reward. Because of these connections, dopaminergic genes have been broadly studied in the context of EDs. In AN, *DRD2* rs1799732 polymorphism has yielded positive findings in 191 cases,[95] but no replication studies have been carried out. *DRD2* and neighboring ankyrin repeat and kinase domain containing 1 (*ANKK1*) SNPs have been implicated in binge eating.[96–98] The seven-repeat variant of the dopamine receptor D4 (*DRD4*) exon III variable number tandem repeats (VNTR) polymorphism has been linked to maximum lifetime BMI[99,100] and a history of childhood attention-deficit/hyperactivity disorder in BN.[101] In the case of AN, no association between *DRD4* and BMI has been reported.[102] In BN, studies have yielded mixed results regarding the overtransmission of catechol-O-methyltransferase (*COMT*) rs4680 variants,[103,104] and a meta-analysis of eight case-control studies failed to find an association between rs4680 and AN susceptibility.[105]

Since the discovery of the role leptin receptor gene (*Lepr*) disruptions play in obesity and hyperphagia in mice, the leptinergic system has been one of the earliest targets for the genetic studies of obesity and weight regulation.[106] Patients with acute AN have low plasma leptin levels,[107,108] and serum leptin levels have also been correlated with BMI in patients with EDs.[109] However, research on the role of the leptin gene (*LEP*) and *LEPR* has yielded variable findings in AN and BN.[110–112] Ghrelin, the natural leptin antagonist often referred to as the hunger hormone, has also been studied in the context of EDs. Similar to *LEP* and *LEPR*, conflicting findings have been reported with regards to the relationship between the ghrelin gene (*GHRL*) polymorphisms and AN or BN;[113–118] however, *GHRL* has yielded preliminary findings in a pilot study with 90 individuals with BED.[119]

Stimulation of the melanocortin system leads to a reduction in food intake and weight, and details of this pathway are discussed in more detail in the "Animal models" sections. Defects in the melanocortin 4 receptor gene (*MC4R*) have been a known cause of autosomal dominant obesity, accounting for 6% of all obesity cases;[120] however, the role of *MC4R* mutations in BED remains controversial.[121–123] *MC4R* haploinsufficiency was associated with maximum lifetime BMI in BN in one case report.[124] Two separate studies failed to find an association between obesity-related *MC4R* common genetic variants[125,126] and AN[112,127] or BN.[112] The research on the agouti related protein gene (*AGRP*), encoding the inverse agonist of melanocortin receptors, has mostly been limited to rs5030980, located in the coding region. Although two stud-

Table 1 Overview of candidate-gene findings in eating disorders

Gene	Description	Polymorphism	Replicated findings in EDs[a]	Sample size for cases[b]	Variants unique to EDs?	References
HTR1D	Serotonin receptor 1D	rs6300 (1080C/T)	AN: ?(+)	186	No	66
		rs674386	AN-R: ?(+)	122	Unknown	67
		rs856510	AN-R: ?(+)	122	Unknown	67
HTR2A	Serotonin receptor 2A	rs6311 (-1438G/A)	AN: +/–	75–316 (family study)	No	76–82
HTR2C	Serotonin receptor 2C	rs6318 (Cys23Ser)	AN: ?(+)	118	No	84
SLC6A4	Serotonin transporter	5-HTTLPR	AN: +/–	55–726 (meta-analysis)	No	85–94
			BN: +/–	88–707 (meta-analysis)		
			BED: ?(+)	77		
			Mixed EDs: +/–	201–1,637 (meta-analysis)		
DRD2	Dopamine receptor D2	rs1799732 (–141C indel)	AN: ?(+)	191	No	95–98
			BED: –	56–79		
		rs6277 (957C/T)	BED: +/–	56–79	No	96–98
		rs2283265	BED: ?(+)	79	No	98
DRD4	Dopamine receptor D4	exon III VNTR	AN: ?(–)	109	No	101, 102
			BN: ?(–)	234		
COMT	Catechol-O-methyltransferase	rs4680 (Val158Met)	AN: +/–	52–2,021 (meta-analysis)	No	103–105
			BN: +/–	28–165		
ANKK1	Ankyrin repeat and kinase domain containing 1	rs1800497 (Taq1A)	BED: +/–	56–79	No	96–98
LEP	Leptin	rs13228377	AN: ?(–)	115	No	110
			BN: ?(–)	71		
		rs7799039	AN: ?(–)	745	No	112
			BN: ?(–)	245		
LEPR	Leptin receptor	rs1137100 (Lys109Arg)	AN: –	176–745	No	111, 112
			BN ?(–)	245		
		rs1137101 (Gln223Arg)	AN: –	176–745	No	111, 112
			BN: ?(–)	245		
		rs8179183 (Lys656Asn)	AN: ?(–)	176	No	111
GHRL	Ghrelin	rs696217 (Leu72Met)	AN: +/–	46–745	No	112–117, 119
			AN-R: ?(–)	131		
			AN-BP: ?(–)	97		
			BN: +/–	30–326		
			BED: +/–	38–90		
			Mixed EDs: ?(–)	114		
		rs4684677 (Gln90Leu)	AN: +/–	46–745	No	112–117
			AN-R: ?(–)	131		
			AN-BP: ?(–)	97		
			BN: +/–	30–326		
			BED: ?(–)	38		
			Mixed EDs: +/–	114		
		rs34911341 (Arg51Gln)	AN: –	46–366	No	114–117, 119
			AN-R: ?(–)	131		
			AN-BP: ?(–)	97		
			BN: ?(–)	30–326		
			BED: ?(–)	38		
			Mixed EDs: ?(–)	114		
		rs2075356	AN-R: ?(–)	131	No	117
			AN-BP: ?(–)	97		
			BN: ?(+)	108		
MC4R	Melanocortin 4 receptor	rs2229616 (Val103Ile)	BED: +/–	43–769 (phenotypic analysis)	No	121–123
		rs52820871 (Ile251Leu)	BED: +/–	43–769 (phenotypic analysis)	No	121–123
		rs17782313	AN: –	267–745	No	112, 127
			BN: ?(–)	245		
		rs489693	AN: ?(–)	745	No	112
			BN: ?(–)	245		

(*Continued*)

Table 1 (*Continued*)

Gene	Description	Polymorphism	Replicated findings in EDs[a]	Sample size for cases[b]	Variants unique to EDs?	References
AGRP	Agouti related protein	rs5030980	AN: +/–	45–745	No	112, 128
			BN: ?(–)	245		
		rs13338499	AN: ?(+)	745	Unknown	112
			BN: ?(–)	245		
POMC	Proopiomelanocortin	rs1042571	AN: ?(–)	745	No	112
			BN: ?(–)	245		
ESR1	Estrogen receptor 1	rs726281	AN: +/–	244–321 (family study)	Unknown	135, 138
			BN: ?(–)	276		
		rs2295193	AN: +/–	244–321 (family study)	Unknown	135, 138
			BN: ?(–)	276		
		rs3798577	AN: +/–	244–321 (family study)	No	135, 138
			BN: ?(–)	276		
			Mixed EDs: ?(+)	126		
		rs2234693	AN: ?(–)	170	No	136
		rs9340799	AN: ?(–)	170	No	136
		5′ promoter TA dinucleotide repeat	AN: ?(–)	170	No	136
ESR2 (*Esβ*)	Estrogen receptor 2	rs1256049 (1082A/G)	AN: +/–	50–170	No	136, 137, 139
			BN: +/–	28–76		
		rs4986938 (1730A/G)	AN: +/–	50–170	No	136, 137, 139
			BN: +/–	28–76		
		rs928554	BN: ?(+)	76	No	139
		Intron 5 CA dinucleotide repeat	AN: ?(–)	170	No	136
BDNF	Brain derived neurotrophic factor	rs6265 (Val66Met)	AN-R: +/–	26–347	No	112, 143, 144, 146–150
			AN: +/–	64–2,767 (meta-analysis)		
			BN: +/–	70–389		
			BED: ?(–)	84		
			Mixed EDs: +/–	143–1,733 (meta-analysis)		
		rs56164415 (–270C/T)	AN-R: +/–	26–347	No	112, 143, 144, 146
			AN: –	64–753		
			BN: +/–	70–389		
			Mixed EDs: ?(–)	143		
CNR1	Cannabinoid receptor 1	AAT trinucleotide STR	AN: –	52–91 (family studies)	No	152, 153
			AN-BP: ?(+)	34 (family study)		
		rs1049353	AN: +/–	115–129	No	153, 154
			BN: ?(+)	149		
OPRD1	Opioid receptor delta 1	rs536706 (8214T/C)	AN: ?(+)	186	Unknown	66
		rs760589 (23340G/A)	AN: ?(+)	186	Unknown	66
		rs204081 (47821A/G)	AN: ?(+)	186	Unknown	66
		rs569356	AN: ?(+)	226	No	67
		rs521809	AN: ?(–)	226	Unknown	67
		rs4654327	AN-R: ?(+)	122	No	67
OPRM	Opioid receptor mu 1	1799971 (118A/G)	BED: ?(+)	66	No	97
FTO	Fat mass and obesity associated	rs9939609[c]	AN: +/–	689–1,085	No	158, 159
			BN: ?(+)	477		

Notes: [a]"+" indicates consistent significant findings; "–" indicates consistent nonsignificant findings; "+/–" indicates conflicting findings; "?" indicates that no replication studies have been conducted despite initial positive or negative reports (as indicated in parenthesis). Unless otherwise specified, the findings pertain to ED case-control analyses, not family or case-only phenotypic analyses. This table comprises some of the most prominent findings and is not meant to be a complete summary of the candidate gene studies of EDs. It should be noted that none of the significant associations in AN have been replicated in GWAS, and genome-wide investigations are yet to be carried out in BN or BED; [b]a range of sample sizes provided if multiple studies have been conducted; [c]a proxy variant in high linkage disequilibrium with the actual variant included in one of the two studies.

Abbreviations: AN, anorexia nervosa; AN-BP, anorexia nervosa, binge/purge subtype; AN-R, anorexia nervosa, restricting subtype; BED, binge eating disorder; BN, bulimia nervosa; EDs, eating disorders; GWAS, genome-wide association studies; VNTR, variable number tandem repeats.

ies reported positive preliminary associations involving this polymorphism in AN,[113,128] another study found a preliminary association with rs13338499 with minimum illness-related BMI in 745 individuals with AN, but no association with BN in 245 cases.[112] In the case of pro-opiomelanocortin (*POMC*), missense mutations have been documented in a patient with AN,[129] but no significant associations with common variants have been reported in AN or BN.[112]

The role of sex hormones in the development of AN and BN has recently garnered significant research attention. An inverse correlation between age of menarche and ED susceptibility has been reported, and since potential overlap between genetic factors linked to an earlier age of menarche and ED risk has been documented,[130] there is some evidence for at least partial involvement for sex hormones in EDs. Although an intrauterine masculinization effect has been proposed for female twins with EDs who have a male co-twin,[131] other twin studies reported no relationship between sex of the twin pair and disordered eating.[132,133] Conversely, males with a female twin are reportedly at a higher risk of developing AN than females with a female twin,[134] which suggests a possible role for intrauterine female hormone exposure and increased ED risk in men. Thus far, the focus on the investigation of genes encoding sex hormones has been on the estrogen receptor 1 (*ESR1*) and estrogen receptor 2 (*ESR2*; also known as *ERβ*) genes in the context of AN, and the studies have yielded variable findings.[135–138] One study reported a positive association between *ERβ* and BN in 76 women.[139] More recently, high-throughput sequencing projects (reviewed below in detail) have also implicated estrogen-related genes.[140,141]

Brain derived neurotrophic factor (BDNF) is a protein that supports the growth, survival, differentiation, and assigned function of neurons. In terms of eating behavior, BDNF is involved in appetite suppression by downstream regulation of melanocortin signaling in the hypothalamus.[142] *BDNF* rs6265 (commonly referred to as Val66Met) has been extensively researched and implicated in AN and BN by various studies,[99,143–148] but the nature of the findings has not been consistent.[112,113,149,150] One study reported an association involving this polymorphism and binge eating frequency in 84 women with BED,[148] which has yet to be replicated. The *BDNF* rs56164415 polymorphism (commonly referred to as –270C/T) and its role in EDs has been more controversial,[99,112,143–146,151] especially due to the challenges associated with studying this low minor allele frequency SNP in small study samples.

Other genes have also been studied in the context of EDs. For instance, mixed findings involving the overtransmission of cannabinoid receptor 1 (*CNR1*) variants in AN have been reported,[152,153] and preliminary case-control findings need replication.[154] As mentioned in the "Linkage studies" section, preliminary results involving the *OPRD1* gene have been reported in AN,[66,67] whereas opioid receptor mu 1 gene (*OPRM1*) has been implicated in hedonic eating in one study with 300 participants.[155] The fat mass and obesity-associated gene (*FTO*), which has been identified as an obesity locus in multiple GWAS publications,[156,157] has yielded mixed findings regarding a possible association with AN or BN,[127,158,159] and studies have yet to be conducted on its possible role in BED. Thus far, the most comprehensive candidate-gene study of AN has investigated the role of 182 genes in 1,085 AN cases and 677 healthy controls, in which none of the markers reached statistical significance following correction.[160]

In summary, various gene systems and polymorphisms – due to their known biological function or previous significant findings in other psychiatric disorders – have been studied in AN, BN, and to a smaller extent in BED; however, conclusive evidence on their role in EDs is uncertain due to small sample size, potential population stratification, and lack of replication. Considering these important limitations, any positive association reported in the literature should be interpreted with extreme caution.

GWAS

In contrast to candidate-gene studies that rely on biology and prior findings to select a small number of genes and devise a priori hypotheses, the GWAS method consists of a scan of the entire genome in a hypothesis-free manner.[161] Recent advances in the field allow for millions of loci to be genotyped on the same genotyping chip, and the assays are designed in a way that utilizes high linkage disequilibrium between markers in order to ensure dense coverage of the genome. However, due to the inclusion of millions of markers in the same analysis, it is important to apply stringent statistical cutoffs to effectively control for potential false-positive findings that may be an artifact of multiple testing.[162]

The first GWAS of AN – carried out in 1,033 AN cases – reported a large and rare copy number variant on 13q12 present in two individuals but did not find any genome-wide significant loci in the case-control analysis.[163] A GWAS collaboration on a twin sample also failed to find genome-wide significant susceptibility loci but provided some evidence for the possible involvement of eight loci with various ED-related phenotypes such as drive for thinness, body dissatisfaction, bulimia, weight fluctuations, as well as childhood obsessive-compulsive personality disorder trait.[164] Similarly, another GWAS on disordered eating in female twins did not report any genome-wide significant findings, but a number of genes were implicated in AN- and BN-spectrum disorder phenotypes.[165]

The largest and most rigorous GWAS in AN – part of the Wellcome Trust Case-Control Consortium 3 – included 2,907 AN cases of European ancestry and 14,860 ancestry-matched female controls in the discovery meta-analysis.[166] Although there were no genome-wide significant findings in the discovery dataset, 72 independent markers with the lowest *P*-values were selected for replication, and approximately 76% of these markers produced results in the same direction

as the discovery sample.[166] This was a promising indication that the prioritized set of genomic variants likely contained true positive signals for increased AN risk; however, the study was unable to detect effects due to lack of statistical power.[166] Further replication studies, larger sample sizes, and experiments on expression and function are required to gain a better understanding of the role of these genes in AN. Thus far, there have not been any GWAS conducted in BN or BED.

Study of rare variants

With the recent advancements in high-throughput sequencing, it is now much easier to detect rare variants (minor allele frequency of less than 1%) and significantly cheaper to sequence a larger number of cases than ever before. While common variants are easier to detect and may confer risk for a larger number of individuals in the population, they also have small effect sizes by themselves. Rare variants, on the other hand, are more likely to have higher penetrance compared to common variants but may only be present in a smaller number of cases. Currently, the most commonly used high-throughput sequencing methods are targeted gene sequencing, exome sequencing, and whole genome sequencing. Targeted gene sequencing allows researchers to focus their efforts on capturing a select number of genes in a manner similar to candidate-gene association studies, whereas exome sequencing consists of sequencing all exons in the genome, and although more costly, whole genome sequencing offers a complete view of an individual's entire DNA sequence. More recently, exome genotype chips that cover an extensive set of novel, rare, or putative functional exonic variants selected based on previous sequencing projects have been developed.

To date, only one high-throughput sequencing study in unrelated ED cases has been published. While the sequencing of 152 candidate genes in a sample of 261 AN cases and 73 controls did not yield any genome-wide significant findings, epoxide hydrolase 2 (*EPHX2*) – one of the top hits in the sequence analysis – was associated with depression and anxiety scores in a small independent AN replication sample and was further linked to BMI and elevated cholesterol measures in healthy controls from a larger longitudinal population study.[141] Another preliminary study combined linkage analysis, exome sequencing, and whole genome sequencing efforts in the examination of two densely affected ED pedigrees. The study reported a missense mutation in estrogen-related receptor alpha (*ESRRA*) in the first pedigree, whereas a potentially deleterious mutation in histone deacetylase 4 (*HDAC4*) was found in the second pedigree.[140] As mentioned in the "Candidate-gene association studies" section of this review, these genes are deemed to be of biological interest because of their possible role in the estrogen system;[140] however, the results of this study need to be replicated, and furthermore, it is important to consider the possibility of any identified rare mutations being private to each pedigree and thus not necessarily explaining common genetic risk for EDs.

Whole genome and exome sequencing projects have yet to be carried out in unrelated AN cases and controls, and considering the rare nature of the sequencing variants, samples sizes in the tens of thousands are required to obtain meaningful data for ED case-control studies. Thus far, there are no published high-throughput sequencing studies in BN or BED.

Gene regulation related to EDs: animal studies

Over the past 20 years, there has been rapid progress in using laboratory animals to model EDs. A significant number of these studies have used behavioral manipulations in wild-type strains of rodents to produce distinct ED-related phenotypes, a topic that has been comprehensively reviewed by others.[167–169] In this section, we restrict our discussion to experiments using model organisms with either spontaneous or induced genetic variations. Globally, these studies have revealed a complex network of genes functioning within anatomically and genetically defined neuronal ensembles to regulate different modalities of feeding. We discuss how these genes function within evolutionarily conserved neural circuits and how maladaptive alterations of neural-circuit activity may explain ED pathology (summarized in Table 2).

Animal models of AN

One of the most long-standing AN mouse models is the *anx*/*anx* mouse. This line contains an allele that arose by spontaneous mutation wherein homozygous carriers display reduced growth and an emaciated appearance. These animals have a significantly reduced body weight that is apparent by 10 days of age, is due to reduced food intake,[170] and leads to death approximately 22 days postnatal. These animals also have other neurological abnormalities like body tremors, uncoordinated gait, hyperactivity, and head weaving. By virtue of their decreased body weight and food consumption, the *anx/anx* mice possess strong face validity as a model of AN. More recent studies, however, suggest that the hypophagia is due to mitochondrial dysfunction and oxidative stress in hypothalamic circuits. This gross abnormality in central nervous system (CNS) function may ultimately derive

Table 2 Eating disorder phenotypes in mouse knockout models

Gene	Description	Feeding	Body weight	Adiposity	References
Pmch	Pro-melanin-concentrating hormone	↓	↓	↓	172
Chrm3	Cholinergic receptor, muscarinic 3	↓	↓	↓	174
Cnr1	Cannabinoid receptor 1	↓	↓	↓	179
Oprd1	Opioid receptor delta 1	↔ Resistant to HFD	↔ Resistant to HFD	↔ Resistant to HFD	181
Lep	Leptin	↑	↑	↑	183
Lepr	Leptin receptor	↑	↑	↑	184, 187
Pomc	Proopiomelanocortin	↑	↑	↑	193
Mc3r	Melanocortin 3 receptor	↔	↔	↑	196
Mc4r	Melanocortin 4 receptor	↑	↑	↑	194, 196
Nmu	Neuromedin U	↑	↑	↑	198
Htr2c	Serotonin receptor 2C	↑	↑	↑	200
Htr1b	Serotonin receptor 1B	↑ Males only	↑	↔	204

Notes: Table reflects phenotypes under ad libitum feeding conditions unless otherwise specified. ↑ indicates increase in phenotype, ↓ indicates decrease in phenotype, whereas ↔ indicates no change in phenotype.
Abbreviation: HFD, high fat diet.

from a mutation of the NADH dehydrogenase (ubiquinone) 1α-subcomplex, assembly factor 1 (*Ndufaf1*) gene which is located in a previously mapped genomic interval of the *anx/anx* allele.[171] As no genomic studies in AN patients to date have implicated CNS mitochondrial protein dysfunction, the construct validity of the *anx/anx* mouse as a model AN is still in question.

Gene knockout studies using homologous recombination in mice have revealed a host of genes involved in feeding and metabolism. Although the clinical validity of these models is not always apparent due to a lack of genome-wide associations in AN patients, these experiments have nonetheless helped reveal the fundamental gene networks and neural circuitry necessary for feeding. Among reverse genetic knockout studies in mice, there are specific genes that produce hypophagic and lean phenotypes when altered. The loss of the neuropeptide melanin-concentrating hormone (MCH), encoded by the pro-melanin-concentrating hormone gene ($Pmch^{-/-}$ mice), results in reduced body weight, body adiposity, and food intake.[172] Conversely, overexpression of MCH through intracerebroventricular injection of this peptide is known to increase food intake.[173] MCH is highly expressed in hypothalamic nuclei like the lateral hypothalamus (LH), but the role of endogenous MCH released from LH neurons in regulating feeding is still unclear.

Hypophagia and reduced body weight and fat are triggered by loss of the M3 muscarinic receptor ($Chrm3^{-/-}$ mice). They also display a reduced capacity for feeding, induced by injection of the orexigenic agent AGRP, but an intact response to MCH,[174] suggesting that M3 acts downstream of AGRP, but either upstream or in a pathway parallel to MCH. The comprehensive mechanism by which the M3 muscarinic receptor promotes feeding and normal adiposity is still unknown, but it may accomplish its orexigenic role through signaling in the nucleus accumbens, where cholinergic signaling is known to modulate feeding.[175–178]

One of the most robust lean-inducing knockouts is the cannabinoid receptor type 1 (CB1) null mouse ($Cnr1^{-/-}$ mice). $Cnr1^{-/-}$ mice display a highly significant reduction in body weight when fed standard chow, are resistant to the obesogenic effects of a high-fat diet, and show a reduction in food intake of either standard or high-fat diet.[179] Recently, it was shown that CB1s are expressed on glutamatergic neurons that project to inhibitory granule cells in the medial olfactory bulb and normally dampen excitatory synaptic transmission at these synapses to drive food intake.[180] The authors elegantly demonstrated that expression of CB1s in the anterior olfactory nucleus is both necessary and sufficient for fasting-induced hyperphagia. Thus the phenotypes apparent in the $Cnr1^{-/-}$ mice are likely due to its function in the anterior olfactory nucleus to medial olfactory bulb circuit.

Lastly, loss of the delta opioid receptors ($Oprd1^{-/-}$ mice) can produce leanness, resistance to high fat diet-induced weight gain, and an increase in thermogenesis.[181] Although the current mechanism by which delta opioid receptors promote feeding is unknown, it is highly expressed in the mouse olfactory bulb and anterior olfactory nucleus.[182] Thus, one hypothesis is that these receptors may act in a pathway that contains CB1s. Furthermore, $Oprd1^{-/-}$ mice may have construct validity as a model of AN as point mutations in the homologous human *OPRD1* locus have

been associated with AN in preliminary studies, as discussed previously.[66]

Animal models of BED and BN

One of the most clinically relevant phenotypes for BED and BN that can be modeled in rodents is binge eating. BED is commonly comorbid with obesity, which is also a prevalent hallmark in mouse models of binge eating.[37] The most well-known models of obesity in mice are the *Lep*$^{ob/ob}$ or *Lepr*$^{db/db}$ mice, which arose due to spontaneous mutations. Similar to alterations in humans, a loss of function mutation in these genes results in hyperphagia and obesity.[183–190] Since the discovery of leptin and its cognate receptor, dozens of studies have revealed how leptin is released in the periphery from adipose tissue and acts on leptin receptors that are expressed in the brain. Their expression is highly enriched on neurons in the arcuate nucleus (ARC) of the hypothalamus,[191,192] which also expresses POMC. POMC is then processed and released as alpha melanocyte-stimulating hormone and binds downstream melanocortin receptors expressed in other hypothalamic nuclei like the paraventricular nucleus of the hypothalamus and LH. These genes are critical for feeding and energy balance, as loss of *Pomc*, *Mc3r*, or *Mc4r* are each sufficient to produce hyperphagia and obesity.[193–196] Selective restoration of MC4R in the paraventricular nucleus and a population of central amygdala neurons expressing the transcription factor *Sim1* incompletely rescues the hyperphagia and obesity of the *Mc4r*$^{-/-}$ mice.[197] These data are consistent with the hypothesis that the anorexigenic properties of melanocortin signaling may derive from its release at the paraventricular nucleus and central amygdala.

In addition to the POMC and AGRP pathways, the ARC expresses additional neuropeptides that may represent critical nodes for feeding. Neuromedin U (NMU) is a highly conserved neuropeptide that is expressed throughout the body including the brain and the gut. Within the brain, the expression of *Nmu* mRNA is enriched in the ARC as well as the dorsomedial and ventromedial hypothalamic nuclei. *Nmu*$^{-/-}$ mice display increased body weight, adiposity, and hyperphagia.[198] These results suggest that NMU normally mediates anorexia, and subsequent research has shown that the NMU 2 receptor is critical in the reduction of feeding mediated by central application of NMU.[199] However, to date, neither *NMU* nor its receptor have been reported in genetic associations with ED patients.

One of the first genetically induced models of binge feeding to be developed was mice lacking the serotonin 2C receptor (5-HT2C; *Htr2c*$^{-/-}$ mice). These mice are overweight relative to their wild-type littermates, display elevated adiposity, are hyperphagic, and display a blunted response to the anorexigenic properties of the serotonin receptor agonist meta-Chlorophenylpiperazine.[200] Recent research suggests that the functional significance of 5-HT2C in regulating food intake and metabolism may derive from its expression in the ARC POMC neurons, as selective restoration of 5-HT2C in POMC neurons in the *Htr2c*$^{-/-}$ mice rescues hyperphagia, obesity, adiposity, and elevated circulating leptin levels.[201] The regulation of ARC POMC neurons by serotonin may be more complex, however, as these neurons also express serotonin 1B receptors (encoded by the *Htr1b* gene), the activation of which can disinhibit POMC neurons to mediate its anorexic effects.[202,203] Interestingly, *Htr1b*$^{-/-}$ mice display increased body weight without causing obesity, but the gene's cell autonomous role in the ARC POMC neurons has not been explored.[204]

One valid critique of each of these models is how closely they resemble the disordered eating phenotypes of ED patients. The presence of hyperphagia, for example, in the aforementioned mouse models of BED only partially captures the construct of binge eating in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Moreover, the majority of the BED mouse models are also obese, and although there is a significant comorbidity between obesity and BED, not all patients with BED are obese.[37,205]

Study of epigenetic changes and gene regulation linked to EDs

Overview of epigenetic mechanisms

Epigenetics refers broadly to the regulation of gene function without a change in the DNA coding sequence. Epigenetic modulation can occur through several discrete mechanisms that include DNA methylation, changes in chromatin structure through modification of histone N-termini with different chemical moieties, and gene expression changes through the actions of small non-protein encoding RNAs.[206,207] The majority of the published studies that examine epigenetic alterations in the context of EDs focus on the role of DNA methylation (as discussed in the next section and summarized in Table 3), so we will limit our discussion to how DNA methylation occurs and how it influences gene expression.

DNA methylation occurs at the 5′ end of cytosine nucleotides that occur almost exclusively in 5′-CpG-3′ islands (CGIs). Methylation of these cytosines is common throughout the genome and is necessary to repress the expression of specific genes throughout development.[208] CpG sequences are not evenly distributed throughout the genome and are preferentially enriched in putative gene promoter regions. Methylation of

Table 3 Genes associated with epigenetic changes in eating disorders

Gene	Description	ED group	Methylation	Expression	Sample size for cases	References
SLC6A3 (*DAT*)	Dopamine transporter	AN	↑	↑	22	213
		BN			24	
DRD2	Dopamine receptor D2	AN	↑/↔	↓	22–45	213–215
		Bulimic spectrum	↔	?	52	
POMC	Proopiomelanocortin	AN (acute and weight-restored)	↔	?	31–61	216, 217
LEP	Leptin	AN	↔	?	45	214
BDNF	Brain derived neurotrophic factor	AN	↔	?	45	214
SLC6A4 (*SERT*)	Serotonin transporter	AN	↔	?	45	214
CNR1	Cannabinoid receptor 1	Mixed EDs	?	↑	43	220, 221
		Mixed EDs with self-injury		↓	9	
NPPA (*ANP*)	Atrial natriuretic peptide	Mixed EDs	↔	↓	46	218
		BN	↑	↔	24	
OXTR	Oxytocin receptor	AN	↑	?	15	219
NR3C1	Glucocorticoid receptor	BN	↔	?	64	222
		BN with borderline personality disorder	↑		32	

Notes: ↑ indicates an increase, ↓ indicates a decrease, ↔ indicates no change, whereas ? indicates that no data are available. Unless otherwise specified, the findings pertain to ED case-control analyses, not within-ED phenotypic analyses.
Abbreviations: AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder.

cytosine nucleotides at CGIs occurs through the actions of DNA methyltransferases, which results in the addition of a methyl group that sits in the DNA major groove. Methylation of CGIs in gene promoter regions normally acts to recruit repressive factors like histone deacetylases and histone methyltransferases, thereby repressing transcription of the methylated gene target through subsequent chromatin modifications.[209] It is estimated that 6%–8% of the CGIs are methylated in human tissues like blood, brain, and spleen, and that most methylated CGIs are associated with known gene promoter regions. Interestingly, certain transcription factors that govern cell fate choice show tissue-specific methylation patterns.[210,211] From an ED perspective, de novo or maintenance DNA methylation provides a mechanism by which to alter gene expression patterns and molecular physiology within defined cell types like CNS neurons, and within peripheral tissues like adipose tissue and the gut, to alter feeding behavior and metabolism.

Epigenetic studies of EDs

In recent years, the study of epigenetics has risen in popularity. It has been proposed that in the case of obesity, environmental factors such as an abundance of high-fat and high-carbohydrate foods may increase the expression of adiposity-related genes in vulnerable individuals;[212] in a similar fashion, it is also possible that an environment that promotes thinness can lead to the overexpression of genes that suppress appetite and/or weight in individuals who are already genetically vulnerable to weight suppression. In accordance with these points, although there may not necessarily be any differences in nucleotide sequence between AN cases and controls, it is possible that gene expression or methylation patterns may significantly vary in individuals with EDs. Thus far, most epigenetic studies have focused on the promoter-specific methylation of the candidate genes that have been studied previously in EDs (discussed in detail below and summarized in Table 3). The majority of the studies comprised AN cases, whereas a small number of studies included BN or BN-spectrum individuals (summarized in Table 3). To date, no epigenetic studies in BED have been published.

Due to their association with reward, dopaminergic genes have been especially of interest to epigenetic researchers. It was first reported that AN patients (n=22) may present with elevated dopamine transporter (*SLC6A3*; also referred to as *DAT*) mRNA expression due to hypermethylation of the gene's promoter region, as well as *DRD2* promoter hypermethylation.[213] The *DAT* hypermethylation was also observed in 24 BN cases.[213] However, another study failed to find significant differences in the promoter-specific DNA methylation for *DRD2*, *LEP*, *BDNF*, and serotonin transporter (*SLC6A4*, also referred to as *SERT*) genes in AN, and similarly, no association between BMI and DNA methylation was observed.[214] In the case of BN and related psychopathology, no difference between women with bulimic spectrum disorder and healthy controls was observed in *DRD2* promoter methylation; however, a subgroup of participants with bulimic spectrum disorders with comorbid psychopathology had increased *DRD2* promoter methylation in this preliminary study.[215]

POMC has also garnered attention due to its important role in appetite regulation. Expression of the functionally relevant long *POMC* mRNA was linked to leptin levels in 31 individuals with acute AN.[216] In a different study by the same group of researchers, no association between BMI or AN status (acute versus weight recovered) and *POMC* promoter methylation was observed, but hypomethylation was associated with cigarette smoking,[217] suggesting a possible role for environmental factors rather than AN diagnosis in *POMC* expression.

Various other candidate genes have been the subjects of epigenetic studies. For instance, decreased atrial natriuretic peptide (*NPPA*, also referred to as *ANP*) mRNA levels have been reported in 46 patients with mixed-diagnosis EDs, whereas hypermethylation of the *ANP* promoter was observed in 24 BN cases.[218] Another pilot study detected a number of CpG sites in the oxytocin receptor gene (*OXTR*) with higher than average methylation levels in 15 AN patients, which was negatively associated with BMI.[219] Significantly higher levels of *CNR1* (also referred to as *CB1*) receptor mRNA in the blood of 43 patients with either AN or BN compared to 26 healthy controls were also reported, but paradoxically, expression was inversely correlated with ED psychopathology,[220] which highlights the need for replication of findings reported by studies with small sample sizes in general. Another small-scale study reported a downregulation of *CB1* receptor mRNA in nine ED patients who engage in self-injury.[221] In the case of BN, increased methylation of the glucocorticoid receptor gene (*NR3C1*) promoter was observed in 32 BN patients with comorbid borderline personality disorder or a history of suicidality, whereas no other case-control differences were significant between women with BN and healthy controls.[222] Taken all together, these results involving various candidate genes need to be replicated in much larger sample sizes in order for researchers to be able to reach more informed conclusions regarding their possible involvement in EDs.

When considering global methylation rather than specific candidate-gene promoter regions, a pattern of significant global DNA hypomethylation was reported in 22 AN patients compared to 30 healthy controls, and a similar trend was observed in 24 BN cases.[223] Similar – albeit modest – reduction in whole-blood global DNA methylation was also reported in 32 adolescents with AN, which was independent of ED-related psychopathology and illness severity.[224] However, another study failed to replicate these findings and reported no alterations in global or gene-specific DNA methylation in AN compared to controls.[225]

In summary, epigenetics is a growing research area that holds the potential to make important contributions to our understanding of the role of elements outside of DNA coding sequence in ED susceptibility. Although a number of preliminary findings have emerged, whether these associations will be replicated is yet to be seen. Furthermore, a number of important limitations akin to those described in the section on "Candidate-gene association studies" (including small sample sizes, almost exclusive focus on candidate genes selected based on a priori hypotheses, and methodological heterogeneity) also merit consideration when reviewing the literature. Additionally, EDs are, at least in part, brain disorders, and considering the tissue specificity of epigenetic modifications, use of blood and buccal cells as proxies to brain tissue is another limitation of the published studies. In the case of candidate-gene promoter methylation studies, no control genes were included to determine whether the methylation changes are specific to the regions of interest or of global nature.

Future directions

In the last few decades, significant advances have emerged in our understanding of the etiology of AN, BN, and BED. Our knowledge of genetics and its contribution to the etiology of psychiatric disorders has greatly increased, and with the development of more sophisticated laboratory and bioinformatic tools, researchers are now able to make more meaningful connections between genomic variants and complex disorders.

Currently, the greatest barrier to identification of genetic variants for EDs is sample size. The largest GWAS in AN conducted to date had over 5,000 samples in the discovery and replication datasets combined,[166] and yet the study was underpowered to produce genome-wide significant results. The only way to reach the statistical power required to find risk variants in AN and other EDs without sacrificing statistical rigor is to focus research efforts on the recruitment of large case-control cohorts. For instance, the schizophrenia analysis conducted by the Psychiatric Genomics Consortium (PGC) initially yielded promising findings but failed to produce any genome-wide significant results before reaching around 10,000 samples.[226,227] Since that threshold has been met, the PGC GWAS projects have yielded many significant associations that were successfully replicated, thus making enormous contributions to our understanding of genetic risk factors for numerous psychiatric disorders.[162,227–234] In a similar fashion, there is no reason to doubt that GWAS in EDs can also achieve this outcome once statistical power is attained. While boosting sample size, future GWAS efforts should also include BN, BED, and analysis of large male cohorts alongside females in order to make meaningful discoveries about the genetic risk factors for EDs in men.

As epigenetic investigations gain popularity in EDs, researchers should consider the complex nature of epigenetic regulation and focus their efforts at a genomic level as opposed to the study of select candidate-gene promoters. In addition, the role of environmental and individual risk factors further complicate epigenetic research, and sample sizes as large as those required for GWAS (if not larger) may be warranted to discover meaningful and replicable epigenetic risk factors. Future research should also explore epigenetic mechanisms other than DNA methylation, including but not limited to histone modification, chromatin remodeling, and microRNA studies. Finally, it will be crucial for research to tie any epigenetic changes to actual protein expression in disease-relevant tissues (such as the brain), so future studies should include relevant biomarkers in research design as well.

It is also important to consider rare variants alongside common variants for conferring ED genetic risk, which may give researchers a better chance to explain the genetic contribution to EDs.[235–237] Indeed, exome sequencing has contributed to improving our understanding of the role of rare and de novo variants in psychiatric disorders such as autism, bipolar disorder, and schizophrenia.[238–243] In the future, exploration of rare exonic variants with rigorous hypothesis-free methodology in large samples could yield important new information on the effects of rare variants in EDs.

As for the study of ED-relevant animal models, the past 5 years have seen tremendous growth in novel strategies to manipulate model system genomes like zinc finger nucleases, clustered regulatory interspaced palindromic repeats (CRISPR)/Cas9, and transcription activator-like effector nucleases (TALENs).[244] These strategies offer improved efficiency for gene targeting and speed at generating new rodent strains in one step[245] and can even be applied to genome-wide screens in human cancer and stem cell models.[246] Moreover, these approaches can be used in a blue light inducible fashion to control the regulation of gene function temporally and spatially.[247] This is an important consideration to avoid lethality or compensatory effects that may derive from loss of a gene constitutively and at an organism-wide level.

Many of the previously described animal models measure body adiposity and feeding, but do not examine the role of particular genes in construct valid models of ED like the activity-based-anorexia model for AN and a limited-access binge eating paradigm for BED.[167] As these genes function in distinct neural circuits, circuit level manipulations like optogenetics and designer receptors exclusively activated by designer drugs (DREADDs) that allow for the selective activation or inhibition of genetically defined cell types will be necessary to make causal statements about the role of that circuit in an ED-relevant behavior. With regards to feeding, there are a growing number of studies that describe the induction of feeding behavior following activation of mostly hypothalamic-centric circuits.[248–256] As discussed in the Animal models sections, these studies suggest that there exist many parallel, redundant circuits that are sufficient to induce voracious feeding. These studies do not, however, show that these circuits are necessary under normal, non-artificial conditions to promote binge eating or satiety. We argue that a more comprehensive mechanistic investigation will involve the use of inhibitory opsins and DREADDs, temporally and spatially induced genetic modifications, and behavioral models that more closely resemble EDs. Lastly, the comorbidity of EDs with conditions like anxiety and substance abuse suggests there may exist shared, overlapping genetic and neural networks that regulate feeding, reward, and anxiety. Experimental limitations notwithstanding, the use of construct valid ED animal models to determine genetic influences on feeding and metabolism in parallel with other ED-related phenotypes promises a more complete view of genes that might represent novel, specific pharmacotherapeutic targets for ED.

Additionally, it is possible that comorbid psychopathology and traits linked to EDs – such as obsessionality in AN and impulsivity in BN – may have important implications for human genetic studies. For instance, the prevalence of obsessive compulsive disorder is significantly elevated among the first-degree relatives of ED probands compared to controls,[44] and a pilot study reported shared genetic etiology between AN and obsessive compulsive disorder.[257] This possible etiological link suggests perfectionistic and obsessive traits as factors in the disordered eating behavior, suppression of body weight, and maintenance of low weight in AN. In the case of BN, impulsivity could be among the reasons for the inability to suppress body weight despite the drive for thinness. Indeed, prevalence of childhood attention-deficit/hyperactivity disorder – in which impulsivity is often a key symptom – is considerably high among BN cases compared to the general population.[104,258,259] Furthermore, there may be important clinical, neurobiological, and genetic overlap between BN and alcohol/substance use disorders, which are conditions also characterized by impulse dysregulation.[260,261] In future ED genetic research, these differences in comorbidities and key psychopathology should be carefully considered in relation to potentially different genetic etiologies for AN, BN, and BED.

Finally, there is merit in stepping beyond the diagnostic criteria of full-syndromal EDs to explore the important phenotypes in a cross-disorder manner. Indeed, recent work by the PGC highlights the importance of shared genetic risk

loci in the etiology of five separate psychiatric disorders,[232] and with the addition of AN to the PGC working groups, future directions include the study of important ED-related phenotypes (eg, highest and lowest illness-related BMIs, anxiety, anhedonia, obsessionality, impulsivity, etc) in a cross-disorder manner in order to maximize sample size and explore the possibility of common genetic etiology for these overlapping phenotypes across psychiatric diagnoses.

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