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An Evolutionary Genetic Perspective of Eating Disorders

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Abstract
Eating disorders (ED) including anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) affect up to 5% of the population in Western countries. Risk factors for developing an ED include personality traits, family environment, gender, age, ethnicity, and culture. Despite being moderately to highly heritable with estimates ranging from 28 to 83%, no genetic risk factors have been conclusively identified. Our objective was to explore evolutionary theories of EDs to provide a new perspective on research into novel biological mechanisms and genetic causes of EDs. We developed a framework that explains the possible interactions between genetic risk and cultural influences in the development of ED. The framework includes three genetic predisposition categories (people with mainly AN restrictive gene variants, people with mainly BED variants, and people with gene variants predisposing to both diseases) and a binary variable of either the presence or absence of pressure to be thin. We propose novel theories to explain the overlapping characteristics of the subtypes of AN (binge/purge and restrictive), BN, and BED. For instance, mutations/structural gene variants in the same gene causing opposite effects or mutations in nearby genes resulting in partial disequilibrium for the genes causing AN (restrictive) and BED may explain the overlap of phenotypes seen in AN (binge/purge).

Introduction

The Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5) describes three eating disorders (EDs): anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). EDs affect around 5% of the population in Western countries, and are more prevalent in females than males [1]. EDs develop from a complex interaction of psychological risk factors, sociocultural influences, and biological and genetic predispositions [2, 3]. Although heritability estimates range from 28 to 78% for AN, 30 to 83% for BN [4], and 41 to 57% for BED [5], there is limited evidence of robust associations between EDs and candidate genes or associations detected through genome-wide association studies (GWAS) or whole-exome/genome sequencing [6]. The high herita-

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bility and ethnic-dependent prevalence of EDs suggests a possible influence of natural selection; however, theories examining EDs from an evolutionary perspective are limited. The purpose of this article is to investigate the epidemiological, genetic, and biological evidence about ED and to use this information to inform new evolutionary genetic theories of ED. These theories can be used to stimulate research into novel biological mechanisms and genetic causes of ED. A qualitative review of the literature related to the epidemiology (diagnostic criteria, prevalence, time trends, risk factors), neurotransmitters, and genetic determinants (heritability, linkage studies, candidate gene studies, GWAS, and next-generation sequencing) of EDs was conducted (November 2016, no restriction on publication date of articles) using PubMed, Google Scholar, and the MEDLINE databases.

Epidemiology of EDs

Diagnostic Criteria of EDs

People with AN are significantly underweight, have an intense fear of gaining weight or becoming fat, a disturbance in body image, a heavy emphasis on body shape for self-evaluation, and/or denial of the seriousness of their current weight loss [7]. There are two subtypes of AN: the restricting type (ANR), involving food restriction without binging or purging, and the binge-eating/purging type (ANBP), involving overeating and/or purging. Similar to AN, people with BN place a strong emphasis on body shape for self-evaluation, but are not underweight. BN also involves recurrent episodes of binge eating during which large quantities of food are consumed during a discrete period of time. During these episodes, people feel a lack of control and are unable to stop eating. After binges, inappropriate compensatory behaviors including self-induced vomiting, laxative misuse, diuretics, enemas, excessive exercise, or abuse of medications are used to prevent weight gain. This behavior must occur a minimum of once a week for 3 months to be diagnosed as BN. Individuals with BED do not engage in compensatory behavior and are at high risk of being obese [7]. Over self-evaluation of shape and weight is not a diagnostic criterion for BED, but can be present in individuals with this disorder [8]. It is noteworthy that some overlapping EDs are described in the DSM-5 under the "Other Specified Feeding or Eating Disorders" but will not be covered in this review [7].

Prevalence of EDs

The lifetime prevalence of AN is 0.3–3.0% for females and 0.24–0.30% for males with a peak incidence between 10 and 19 years of age [1, 9–21]. BN is similarly more prevalent in females, with 0.88–4.6% of females suffering from the disease compared to 0.10–1.5% of males [1, 10, 11, 13, 15, 16, 22, 23]. There is greater variability in the estimates of peak incidence of BN, which in part could be because of the use of different age cut-offs used in studies as well as the relatively recent changes in diagnostic criteria. The peak incidence is estimated to be as low as 10–20 years of age, or as high as 25–29 years [11, 12, 14, 16, 22, 24]. The lifetime prevalence of BED is higher in females (2.5–3.5%) compared to males (1.5–2.0%) [1, 24–27]. Three studies have found that the incidence of BED is relatively equally distributed across the lifespan [24, 28, 29], while another indicated that the average age at onset of BED ranges from 18.3 to 25.4 years [10].

Ethnicity and culture may alter the prevalence of ED. The prevalence of AN in non-Western countries is estimated to be 0.002–0.9% compared to 0.3–3.0% for females and 0.24–0.30% in males in Western countries [30]. A study in Curacao found the incidence of AN is 1.82 cases per 100,000 persons per year without any cases in Black females [31], and in the United States, 0% of Black females were diagnosed with AN in contrast to 1.5% of White females [32]. Also in the United States, the lifetime prevalence of AN in the adult population was 0.15% for African-Americans and 0% for Caribbean Blacks [33]. BN is also less prevalent in non-Western countries compared to Western countries. A meta-analysis found that there are no studies in non-Western countries reporting the presence of BN without exposure to Western ideals [34] and in the United States, 2.3% of White females versus 0.4% of Black females received a diagnosis of BN [32]. In contrast, BED appears to be more prevalent in African-Americans and Caribbean Blacks compared to Whites. Some studies conducted in Latino populations suggest that the prevalence for Latinos is also higher than for Whites [17, 28, 33, 35, 36].

It is unclear if the prevalence of EDs has changed over time. Most studies indicate that the prevalence of AN, BN, and BED has increased [12, 34, 37]; however, there are studies that have observed declines in prevalence [12, 38]. Changes in the prevalence may not reflect true changes in the number of people with EDs but may instead represent changes in diagnostic criteria, shifting attitudes about mental health disorders, the challenge of identifying patients who often try to keep their disease hidden, differing methodologies [34], and small sample sizes from groups that are not generalizable.

Risk Factors of EDs

Personality Traits

Personality characteristics are associated with EDs, including perfectionism, obsessive compulsive personality, neuroticism, negative emotionality, harm avoidance, low self-directedness, low cooperativeness, and features of avoidant personality disorder [39, 40]. Low novelty seeking, low emotional responsiveness, decreased pleasure, decreased seeking of pleasure, and reduced social spontaneity are common characteristics in individuals with the restrictive type of AN, while those with BN tend to be impulsive, seek out new experiences, and have characteristics of borderline personality disorder [39, 40]. BED is associated with perfectionism and sensation seeking, and both AN and BN are associated with obsessive compulsive personality disorder [39]. Though causality has not been established, psychiatric comorbidities are frequent in all EDs with an estimated prevalence between 31.0 and 88.9% [1, 19, 21, 41]. Depression and anxiety disorders are most prevalent [16, 21, 41–43]; however, bipolar affective disorder, obsessive compulsive disorder, and substance use are also common [21].

Environmental Exposures

Individuals diagnosed with EDs are more likely to have experienced abuse or trauma than the general population. Specifically, sexual abuse has been reported in 20–50% of individuals with AN and BN. Women with EDs who have suffered from sexual abuse also demonstrate higher rates of comorbid psychiatric conditions [7]. Inadequate coping mechanisms are common in those with disordered eating and may explain an individual's adoption of maladaptive eating patterns in response to trauma [44]. Studies have also noted a higher prevalence of EDs among athletes, models, dancers, and performers, activities which emphasize dietary restraint and idealize a thin physique [2]. Family dynamics that involve overprotective, intrusive, controlling, or emotionally unresponsive parents, as well as enmeshment of parents and children and poor conflict resolution have been associated with EDs, though evidence is limited [45–48]. Having a preoccupation with weight in the form of family dieting or receiving criticism about weight, eating, or body shape, is also associated with the risk of EDs [49].

Neurobiological Regulation

Several neural systems have been implicated in the etiology of EDs, including those associated with cognitive self-regulatory control, motivation and reward processing, as well as hunger regulation [40, 50, 51]. Disturbances of brain serotonin activity have been described in acutely ill as well as long-term recovered patients with both AN and BN [40]. It is hypothesized that a disturbance of serotonin activity may create vulnerability for the development of EDs. Alterations in central nervous system serotonin function may contribute to other psychological symptoms associated with EDs, such as the high prevalence of depressive disorders, the impulsive-aggressive behavior observed in patients with BN, and the obsessive-compulsive symptomatology observed in AN. Serotonin activity may also contribute to symptoms such as anxiety, perfectionism, obsessions with symmetry and exactness, and harm avoidance, which, when coupled with psychosocial influences, make people vulnerable to developing AN [52]. Dysfunction of the neural network involved in reward, punishment, and motivational processes is also described in ED patients [40, 53]. Several studies have shown that dopamine system disturbance contributes to the development and maintenance of AN and other EDs [54, 55].

Genetic Determinants of EDs

Different strategies have been used to determine the genetic and epigenetic architecture of EDs including heritability studies, linkage studies, candidate gene approaches, GWAS, next-generation sequencing, candidate gene and whole-genome methylation studies. Linkage studies use related individuals to identify genomic regions containing genes that predispose individuals to a disease [56]. Candidate gene studies investigate genes that have been selected based on their physiological, biochemical, and functional aspects [57]. GWAS are hypothesis-free study attempts to identify common genetic variants that contribute to disease risk using markers covering the entire genome [58]. Next-generation sequencing approaches target rare genetic variants and short deletion/duplication that contribute to ED etiology. Methylation arrays enable the quantitative interrogation of methylation sites across the genome at single-nucleotide resolution [59].

Heritability of EDs

EDs are moderately to highly heritable. Heritability estimates from twin studies range from 28 to 74% for AN, 54 to 83% for BN, and 41 to 57% for BED [5]. Most of the individual studies contributing to these estimates have wide confidence intervals because of the low statistical

power caused by relatively small sample sizes due to the low prevalence of EDs [5]. The range of estimates also reflects that heritability estimates can include just additive genetic effects or all genetic effects including gene × gene interactions and dominant effects [60, 61]. One of the limitations of the heritability estimates is that the studies are predominantly conducted in Europeans. However, a study conducted in both European American and African-American female twins suggests that the contribution of additive genes to BN and BED are similar [62, 63].

Linkage Studies

Few linkage studies have been performed for ED traits, and none of them used a logarithm of odds (LOD) score of 3.6 as the threshold for significant linkage [64]. In a genome-wide linkage analysis of 192 families with at least one affected relative pair with AN and related EDs, only a modest evidence of linkage with AN was reported on chromosome 4 (LOD of 1.80). However, the analysis of the subset of patients with the restrictive subtype of AN led to the identification of a linkage peak close to significance on chromosome 1p36-34 (LOD of 3.03 and of 3.45 after genotyping additional microsatellite markers) [65]. Devlin et al. [66] developed an original methodology based on the linkage study of AN incorporating behavioral covariates. Applying this method to 196 multiplex families, they identified a linkage close to significance (LOD of 3.46) for AN, obsessionality and drive-for-thinness. The analysis of 308 families with BN led to the identification of a suggestive peak of linkage on chromosome 10p13-12 (LOD of 2.92). When the analysis was restricted to 133 families with BN and self-induced vomiting, the linkage value increased at the same location (LOD of 3.39) [67]. Interestingly, significant linkage for obesity has been identified in the same chromosomal region [68–70]. Though noteworthy, these findings are not statistically significant and are from insufficiently powered studies, increasing the risk of false positive results [71]. Furthermore, these linkage experiments have not been confirmed by positional cloning, and no strong predisposing genes have emerged to date [4].

Candidate Gene Studies

Hundreds of candidate gene studies of common variants have been published, but have provided few definitive conclusions [72]. Regardless of the type of ED, most candidate gene studies have focused on genes related to homeostatic control and reward systems due to the hypothesized shared roles of these pathways to all ED. The main pathways explored in candidate gene studies of ED include: (a) homeostatic pathways (leptin melanocortin pathway genes, i.e. *LEP, LEPR, POMC, AGRP, MC4R, BDNF* genes, as well as *GHRL, FTO* genes) and (b) reward-related pathways including central neurotransmission of serotonin (i.e., *HTR1D, HTR2A, HTR2C, SLC6A4* genes), dopamine (i.e., *DRD2, DRD4, ANKK1* genes), noradrenaline (*COMT* gene), opioid (*OPRD1, OPRM* genes) and the cannabinoid endogenous system (*CNR1* gene). These pathways are relevant to candidate gene studies because healthy eating behavior is achieved through the balance of homeostatic controls and reward processes. Dysregulation of these systems is observed in EDs, but it is currently unknown if alterations to these pathways are a cause or an effect [73]. Overall, these studies do not show a conclusive association between a common single nucleotide polymorphism (SNP) and EDs [74]. The contribution of common variants associated with body mass index (BMI) variation to EDs has been recently tested in 3 studies, but the results are conflicting [75–77]. However, a recent atlas of genetic correlations across human diseases supports a shared molecular basis for AN and obesity [78].

Genome-Wide Association Studies

Unsurprisingly, several modestly powered GWAS studies for ED-related traits reported negative findings after correcting for multiple testing [79, 80]. A recent negative two-stage GWAS meta-analysis for AN in 5,551 cases and 21,080 controls concluded that the accrual of large genotyped AN case-control samples should be an immediate priority for the field to identify AN-predisposing genes [81]. Although there were no genome-wide significant hits reported, 72 independent markers with the lowest p values were selected for replication in an independent sample, and 76% of these loci produced results directionally consistent with the discovery sample [82]. Two AN loci have successfully been identified by GWAS. A study including 692 female AN cases and 2,570 controls found a significant association approaching genome wide significant ($p = 2.04 \times 10^{-7}$) between a variant in the Early B-Cell Factor 1 (*EBF1*) gene (rs929626). The inactivation of EBF1 in mice leads to a decrease in circulating leptin levels, in line with the observations of very low leptin levels made in human AN patients. In addition, another SNP (rs4704963) in *EBF1* showed genome-wide significant interaction with psychosocial stress on obesity traits [83]. In a sample of 3,495 AN cases and 10,982 controls, rs4622308 near the v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3 (*ERBB3*) gene was significantly associated with AN [84]. Further replication studies, larger sam-

ple 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, though a large GWAS in 2,564 female twins investigating ED-related phenotypes did not find any significant associations ($p < 10^{-8}$) with BN spectrum, purging via substances, disordered eating behaviors, or AN spectrum [85].

Next-Generation Sequencing

A recent whole-exome/-genome sequencing study in 2 large multigenerational pedigrees affected by multiple EDs identified the estrogen-related receptor-α (*ESRRA*) and the histone deacetylase 4 (*HDAC4*) genes as promising candidates to further investigate in additional studies [86]. HDAC4 is expressed in the brain, including the cortical region implicated in EDs [87] and has a known role in synaptic plasticity [88]. These findings support that a decrease in ESRRA activity may impact the neuronal dysfunction in ED patients. Additionally, ESRRA has a well-established role in mitochondrial regulation of neuronal plasticity [89]. Finally, ESRRA induces the expression of both monoamine oxidase A and B, suggesting a potential role in the metabolism of monoamine neurotransmitters such as serotonin and dopamine [90]. Moreover, given the female predominance of EDs, it is possible that estrogen signaling may mediate the risk of EDs by altering ESRRA-HDAC4 activity [91].

Copy Number Variants

Copy number variants (CNV) consist of small deletions or duplications in the genome. The only genome-wide CNV study of EDs reported a 1.4-Mb deletion on 13q12 in 2 AN cases [80]. A genome-wide search for copy-number variants associated with BMI, found a 600-Kb deletion on chromosome 16p11.2 associated with a highly penetrant form of obesity accompanied by hyperphagia and increased ad libitum food intake [92, 93]. *SH2B1*, one of the genes deleted, encodes a protein involved in leptin signaling and is the best candidate to account for the hyperphagic obesity phenotype observed in deletion carriers [94]. Deletion carriers also exhibited subjective alteration of reward, eating in the absence of hunger and sensitivity to external cues [95], but do not present with BN or BED [96]. Conversely, a duplication at the same chromosome 16p11.2 locus has been associated with failure to thrive in children and underweight in adults, with a high frequency of selective and restrictive eating behaviors [97]. Unfortunately, all these findings have not yet been replicated.

Epigenetics

Epigenetic mechanisms provide a substrate for gene-environment interactions. Starvation is a key clinical feature of patients with AN, and a strong environmental exposure can be expected to trigger epigenetic alterations [98]. A main epigenetic mechanism is DNA methylation. Hypermethylation of the alpha-synuclein (*SNCA*) gene (linked to sensitivity to dietary folate) [99], the atrial natriuretic peptide (*NPPA*) gene, implicated in anxiety, depression, and stress responses [100], and the oxytocin receptor (*OXT*) gene [101] have been associated with AN. Weight loss can also alter methylation and expression of the pro-opiomelanocortin (*POMC*) gene, implicated in hunger, satiety, and energy homeostasis [102]. AN and BN subjects showed increased methylation of dopamine system genes [103]. Taken together, these findings suggest that alterations in DNA methylation can lead to EDs by influencing a wide variety of systems implicated in behavioral/affective regulation, sensitivity to nutritional insufficiencies, and body-weight maintenance [99, 104, 105]. Genome-wide methylation profiles in women with AN-restrictive type, and women with AN-binge/purge type compared with normal-weight/normal-eater control women, showed higher and less variable global methylation patterns in AN than controls [59]. Hypermethylation concerned 11 genes (*PRDM16, HDAC4, TNXB, FTSJD2, PXDNL, DLGAP2, FAM83A, NR1H3, DDX10, ARHGAP1, PIWIL1*) involved in histone acetylation, RNA modification, cholesterol storage and lipid transport, and dopamine and glutamate signaling [59]. Further confirmation of these initial findings is needed at this stage. For instance, the hypermethylation of *TNXB* has been recently confirmed by high-throughput DNA methylation analysis in AN [106]. Developmental experiences and early adversity can also impact methylation levels of neuropsychiatric genes and, in turn, create variations in phenotypes related to stress reactivity and mood regulation [107]. DNA hypermethylation of the glucocorticoid receptor gene (*NR3C1*) has been observed on individuals with a history of childhood abuse, compared to individuals who did not report experiences of maltreatment [107].

Gender Influences on Genetic and Environmental Risk Factors of ED

Genetic and environmental influences on EDs appear to be moderated by sex and developmental stage. The female to male ratio for EDs is between 4:1 and 10:1 [7], and there is a significant increase in EDs in females during puberty. When investigating heritability in males and females separately, heritability appears higher in females

(51–61%) than in males (0–40%) for intentional weight loss, body dissatisfaction, drive for thinness [108–110], and weight concerns [111]. A moderate overlap is also suggested in the genetic factors influencing ED symptoms including body dissatisfaction, drive for thinness [112], and behaviors such as binge eating [42, 113] between genders. This moderate overlap may be explained by sexual dimorphism and different levels of sex hormones. In Mendelian disorders, an exceptionally high female to male ratio suggests a higher rate of mutation of disease-causing genes located on the X chromosome in sperm cells or a high rate of X inactivation of one gene copy or a dominant inheritance mode [114]. It is also possible that some Y chromosome genes are protective against EDs. Together, these may account for the increased genetic risk of EDs in females versus males. The genetic and biological differences between males and females may also interact with environmental factors to alter the risk for developing EDs. Adolescence is also a key developmental period for EDs. Longitudinal twin studies have found that the genetic influences on EDs increase from early to late adolescence [115–117]. One possible explanation is that hormonal changes occur at puberty including an increase in estradiol. Estradiol regulates gene transcription within the central nervous system [118] and during puberty may activate genetic factors for EDs. This theory is supported by recent ED-related genetic variants found to be involved in estrogen metabolism [86]. Estrogens are also involved in the regulation of appetite during the ovarian cycle and between puberty and reproductive senescence in women [119]. Other sex hormones can influence orosensory capacity, hedonics, and homeostasis of food intake via a modulation of gastric mechanoreception, and hormones (i.e., ghrelin, CCK, glucagon-like peptide-1, insulin, amylin, and leptin) as well as central neurochemical signaling (i.e., serotonin, dopamine, and leptin melanocortin pathway) [119].

Limitations of Genetic and Epigenetic Approaches

Across all methodologies, a common limitation to identification of genetic variants for EDs is sample size. Only 2 studies to date have identified SNPs significantly associated with AN [83, 84]. To gain the statistical power necessary for further genome-wide significant results, research efforts should focus on the recruitment of large case-control cohorts. While boosting sample size, future GWAS efforts should also include BN, BED, as well as analysis of large male cohorts alongside females in order to make meaningful discoveries about the genetic risk factors for EDs in men. Differentiating between ANBP and ANR subtypes may also help detect associations if the SNPs contributing to these AN subtypes are unique. The more promising results that emerged from recent epigenetic studies deserve further confirmation in additional samples.

Evolutionary Theories of EDs

A complex and dynamic interplay between personality, life experiences, shared and unique environmental factors, epigenetic marks, and genetic predisposition (Fig. 1) is involved in the development of EDs. Examining the evolutionary theories of EDs can help future gene identification efforts by focusing on novel candidate genes as well as guiding the development of biological evidence to support the findings of GWAS. With the increasing use of GWAS approaches, evolutionary theories of EDs can also help determine new phenotypes to investigate. The limited success of genetic studies so far may also result from a focus on symptoms of the disorders, rather than the causes of them. For AN and BN, abnormal neurotransmitter and hormone levels have been widely observed, but genetic association studies have been inconsistent. If the altered neurotransmitter and hormone levels are a consequence of a physiological adaptation to low food consumption rather than one of the causes of the low food consumption as we propose, then we would not expect genes involved with the production and reception of those neurotransmitters and hormones to be altered in EDs. There is also the possibility that hormones relevant to EDs are yet to be discovered. Investigating metabolites, transcription factors, and protein profiles in people with EDs and comparing these to levels after recovery of the disease or between episodes as well as with controls may help to identify novel biomarkers and pathways in the etiology of EDs. Using personal characteristics and environmental factors which have been identified as risk factors for EDs, we investigate previously identified evolutionary theories of EDs as well as discuss novel hypotheses.

Previously Identified Theories of EDs

Previous evolutionary theories of EDs include the suppression of reproduction theory [120], the sexual competition theory [121], the adapted to flee famine hypothesis [122], the thrifty gene hypothesis [123], and dual intervention point model [124]. Briefly, the suppression of reproduction theory states that AN was a method through which females could suppress reproduction when offspring survival was threatened. Females who were able to

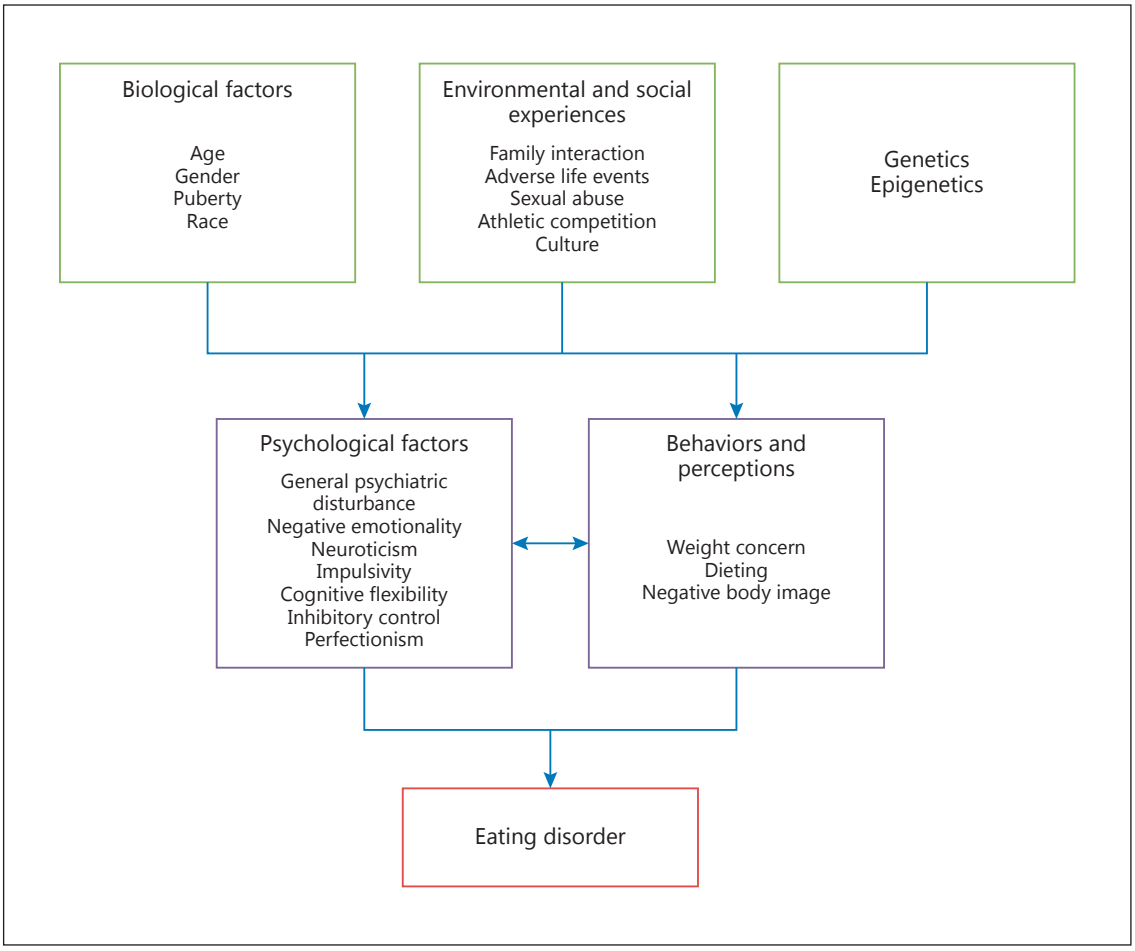

Fig. 1. The relationship between biological factors, environmental and social experience, genetic influences, psychological factors, and behaviors and perceptions in the development of eating disorders.

suppress reproduction until more favorable times are hypothesized to have higher overall reproductive success, therefore passing on the genes for AN characteristics [120]. The sexual competition theory suggests that AN was a method through which females could attract potential high-quality partners by maintaining a nubile shape and consequently increase their reproductive success [121]. The adapted to flee famine hypothesis explains a possible adaptive advantage to what are now known as symptoms of AN. It proposes that food restricting behavior, hyperactivity, and denial of seriousness of weight loss previously enabled migration during periods of local food insecurity allowing individuals to reach more food-secure areas. Individuals who survived the journey would be able to later reproduce explaining why the genes may have been passed on [122]. The previous theories provide potential explanations for AN but not for BN or BED symptoms. The leading theory for these EDs is the thrifty genotype hypothesis stating that extra fat stores were protective because they played a role in helping to avoid malnutrition, regulate reproduction, and allow for survival during variations in the energy supply [123]. An elaboration on the set point theory called the dual intervention point model may also explain excessive food consumption. This theory states that the body has upper and lower limits for weight, which when exceeded triggers physiological adaptations. The lower limit is set at the minimal weight necessary to avoid starvation while the upper weight previously was set to limit predation. As humans have evolved and predatory pressures have been reduced, it is theorized that the genes coding for a higher upper limit have become more common, and fewer people experience the physiological adaptations such as reducing caloric intake, that prevent weight gain [124]. These exist-

ing theories are not widely accepted and though they provide interesting perspectives on the potential historical development of EDs, their applicability is limited especially considering that most people with BN are not overweight [125].

Novel Theories of EDs

The evolutionary theories of EDs clearly distinguish between AN and the other two EDs, BN and BED. However, the disorders have a significant amount of overlap. The diagnostic criteria for ANR includes weighing less than one should and consuming a limited amount of calories per day, while ANBP replaces the limited calories criteria with cycles of binging and purging [7]. ANBP is very similar to BN, except that individuals with BN are not underweight. There is a significant amount of cross-over between those with ANR, ANBP, and BN. In 7 years of follow-up, 49% of women initially diagnosed with AN crossed over between AN subtypes, 34% crossed over from AN to BN, and 18% of women initially diagnosed with BN crossed over to AN [20]. Below, we propose theories as to why the traits seen in BN, ANR, and ANBP overlap from a genetic perspective.

Binge Eating as Protection against ED

The denial of nutrients to the body seen in ANR could switch on a pathway encouraging the consumption of calories, explaining the binging behavior seen in people with the binge/purge subtype of AN. This fits with the adapted to flee famine hypothesis as people should resume eating when food is available again. The cross-over of patients from the subcategories of AN supports this theory when considering that more people cross over from the restrictive subtype to the binge/purge subtype than the contrary [20]. Approximately 25–30% of people receiving treatment for BN were previously diagnosed with AN, while only 5% of people initially diagnosed with BN were later diagnosed with either subtype of AN [126]. The restrictive behavior seen in ANR may be difficult to maintain and consequently cross over to ANBP when the drive to eat becomes overwhelming. The cross-over of individuals from ANBP to BN shows that the binging behavior may slowly lead to weight gain, as the only diagnostic difference between ANBP and BN is that people with AN weigh significantly less than ideal [7]. However, this theory ignores that binge eating is seen outside of the context of AN in both BN and BED and that some people with ANR do not cross over to ANBP during the duration of their disease.

Accumulation of Independent Genes Leading to Binge Eating and ED

Accounting for the limitations of the previous theory explaining the coexistence of binge/purging behavior with AN, we hypothesize that independent genes may lead to the binge/purging behavior seen in BN and the extreme weight loss seen in AN. Through random segregation within populations, some people may cumulate both the genes predisposing to AN and the genes predisposing to BN. This theory is unlikely because both AN and BN are relatively rare diseases. Using our estimated prevalence of 0.3–3.0% for AN and 0.88–4.6% for BN in females, the ANBP subtype should be between 0.0026 and 0.138%, while the actual prevalence of ANBP is somewhere between 0.15 and 1.5% of women based on half of the people with AN having the binge/purge subtype [20]. Therefore, we can conclude that because the actual prevalence of ANBP is higher than would be expected from accumulation of independent genes leading to BN and AN, the genes associated with the individual diseases are either in linkage disequilibrium (i.e., nonrandom combination of alleles at different loci which could result from evolutionary selection, population ancestry history, and genetic linkage), or the same genes are causing the two different diseases.

Mutations/Structural Gene Variations with Opposite Effects in the Same Gene Lead to ED or ED

Mutations or structural variants such as deletion/duplication, gain of function/loss of function, gain of expression/loss of expression in the same genes may lead to AN and binging behavior. Genetic correlation analyses, conducted from GWAS for BMI and AN, provided evidence for a shared polygenic etiology between these two traits, such as overall genetic determinants for higher BMI decreases risk of AN [78]. However, this study does not exclude that some of BMI-increasing variants can also be associated with higher risk of AN, especially when stressed by environmental changes. This ties in with the evolutionary theories as both the genes allowing for the consumption of large amounts of food when available and the ability to be highly functioning with minimal caloric intake may have been historically positively selected for under different environmental conditions and people with both types of mutations may have been favored [122, 123, 127–130]. In the past, people possessing both genetic characteristics may not have suffered from any negative side effects allowing for the transmission of the genes on to future generations. It is reasonable to think that the mixed phenotypes (i.e., ANBP) are now only problematic in the obesogenic environment. Weight concerns are

Table 1. Framework for genetic and environmental predisposition to eating disorders

	Genes predisposing to anorexia nervosa (restrictive subtype)	Genes predisposing to anorexia nervosa (restrictive subtype) and genes predisposing to binge eating	Genes predisposing to binge eating
Presence of pressure to be thin	Anorexia nervosa (restrictive subtype)	Anorexia nervosa (binge/purge subtype)	Bulimia nervosa
Absence of pressure to be thin	No disease – unless anorexia nervosa is triggered by factors other than weight loss	Binge eating disorder	Binge eating disorder

a relatively modern concept and dieting to lose weight could trigger the metabolic changes allowing for survival despite low caloric consumption. However, if the same genes are also causing binging behavior, individuals may purge in order to balance the conflicting biological drives to survive with minimal caloric consumption and to take advantage of the food available to them. The possibility of a single gene having both loss of function and gain of function mutations is supported by recent findings on *MC4R* and the 16p locus where loss of function mutations/deletions lead to hyperphagic obesity while gain of function mutations/duplications lead to leanness and selective/restrictive eating behaviors [93, 97, 131–133]. However, several studies have reported contradictory results on the association between binge eating behavior and loss of function variants in *MC4R* [134–136]; and gain of function variants in *MC4R* are not more frequent in AN patients than in the general population [137]. Analyzing whole-genome SNP array and whole-exome sequencing data and searching for complex patterns of mirror CNVs or enrichment in loss of function and gain of function mutations in ANBP cases may identify promising candidate genes that may be further validated in ANR, BN, or BED cases.

Mutations in Nearby Genes Result in Partial Linkage Disequilibrium of ED and Binge Eating Traits

Similar to the theory that the same genes may contain loss of function/gain of function mutations causing the cross-over of traits seen in EDs is the theory that the genes coding for the different characteristics of EDs are in genes located near each other and in partial linkage disequilibrium. The co-occurrence of two distinct phenotypes because of the linkage disequilibrium of mutations located in different genes has been suggested in few studies on EDs. Epistatic interactions have been found between the serotonin transporter and the norepinephrine transporter genes [138] as well as the monoamine oxidase A genes in AN [139], and between the dopaminergic genes (DRD2/DRD4 and CMOT/DAT1), influencing both eating- and personality-related psychopathology [140].

A Framework for EDs Integrating Genetic Evolutionary Theories and Epidemiological Evidence

We combined the evolutionary perspective of EDs with the possibility of the genetic overlap causing mixed phenotypes, and the epidemiological evidence of differences in prevalence of EDs in different ethnicities and cultures to create a framework suggesting under which conditions each ED will occur (Table 1).

Genetic Component

The genes predisposing individuals to ANR and to binge eating are likely to overlap because they are in partial linkage disequilibrium, either because mutations/structural variants within the same gene have opposite functional effects or because the genes are located close to each other. Therefore, a greater number of people would have characteristics of both diseases than would be expected if the gene variants were independent. Thus, 3 genetic predisposition categories were created, people with mainly ANR gene variants, people with mainly binge eating gene variants, and people with gene variants predisposing to both diseases. There are other genetic factors that contribute to the risk of developing EDs not captured in the model such as epigenetics, gene by gene interactions, gene by environment interactions in addition to the pressure of being thin, and any potential genetic factors which contribute to the predisposition of being more sensitive to the pressure of being thin.

Pressure to Be Thin Component

Body dissatisfaction is one of the most consistent and robust risk and maintenance factors for EDs [141]. The sociocultural model of EDs [2] asserts that exposure to the Western concept of the ideal body type, often via magazines, television, and the internet, promotes internalization of a thin body ideal. Body dissatisfaction ensues when individuals evaluate their own body size negatively because it is thought to vary from the ideal. Subsequently, elevated BMI and increased awareness of body size have been linked to the onset of dieting and body dissatisfaction, both of which being prominent risk factors for EDs [2, 141, 142].

Ethnicity and Culture

Based on the epidemiological evidence, it appears that the racial/ethnic and cultural origins of an individual may be an important driver of the desire to be thin. However, because the terms ethnicity, race, and culture are often used interchangeably and because of the strong association between biological backgrounds versus cultural backgrounds in many people, it is impossible to untangle the genetic versus social contributions of race/ethnicity/culture. Despite these challenges, it is well established that White women are more concerned about weight and have lower weight ideals in comparison to Black women [143–145]. These concerns about weight may explain the higher prevalence of AN in Western countries as well as White individuals compared to African-Americans and Caribbean Blacks [31–33]. Interestingly, when preoccupation with weight is removed as a diagnostic criteria for AN, there was an increase in prevalence of AN of 0.21% in the African-American population, though there was no increase in the Caribbean Black population [33]. Similarly, the prevalence of AN is very similar in Western and non-Western countries when weight concerns were removed as a diagnostic criteria [34, 145].

BN is also less prevalent in non-Western countries compared to Western countries, and there are not any studies in non-Western countries reporting the presence of BN without exposure to Western ideals [34]. This suggests that the culturally derived concept of being thin may be an important driver of the disease. Supporting this theory, a study of the Latino-American population found that recent immigrants have the lowest rates of BN while those who have resided in the United States for 70% or more of their lives have the highest rates [28]. Similarly, a study of Fijian adolescent and adult females found that acculturation to Western ideals was associated with increased body shape concerns [146] and watching Westernized television shows was associated with disordered eating habits such as self-induced vomiting [147]. The fact that White women are more concerned about weight and have lower weight ideals in comparison to Black women [143–145] may explain why White women in the United States have a higher prevalence of BN than Black women [32]. These studies suggest that the culture may play an important role in the development of BN by causing an idealization of a thin body type which drives people to use inappropriate compensatory methods after binging episodes.

Though there is a modest quantity of evidence, studies in the United States have consistently shown that the prevalence of BED is higher in African-American and Caribbean Blacks compared to Whites [17, 28, 33, 35, 36]. The higher prevalence of BED in Blacks compared to Whites may be explained by the lack of weight preoccupation. Even within the BED population, White females are significantly more concerned about eating, dietary restraint, body shape, and weight compared to Black females, despite on average being less overweight [143]. Because a smaller proportion of African-Americans have weight concerns, the population may be less likely to engage in purging behavior compared to their White American counterparts. Therefore, they receive a diagnosis of BED rather than BN. In line with these data, a study found that when weight preoccupation was removed as a criterion, the prevalence of BN in African-Americans and Caribbean Blacks increased [33].

Biological Factors

Biological factors such as age, gender, and puberty status may also contribute to the risk of feeling pressure to be thin. Across all 3 EDs, the prevalence is higher in females than in males. In females, puberty is a risk period for the development of AN and BN which is at least partially mediated by the effects of estrogen. Girls that reach puberty earlier than their peers or are more advanced developmentally are at the highest risk. The relationship between puberty status in males and EDs is less clear [148]. The peak incidence of AN is between 10 and 19 years, which coincidences with puberty. The peak incidence of BN is less clear, but has been estimated to be between 10 and 20 years by some studies and up to 25–29 years in others. There are too few studies to adequately assess the relationship between puberty status or age with BED.

Personality, Environmental, and Neurobiological Factors

Environmental factors such as family interaction, adverse life events, sexual abuse, and athletic competition

are all associated with EDs and have been shown to be associated with an increase in the desire to be thin. The relationship between personality characteristics and the desire to be thin have not been established. However, it is conceivable that traits such as perfectionism and obsessive personality characteristics may be important drivers of idealizing a thin body type. Neurobiological differences relating to cognitive self-regulatory control, motivation, reward processing, and hunger regulation between people may also drive the desire to be thin. For example, serotonin is thought to contribute to the development of anxiety and perfectionism. Certain personality phenotypes such as depression and anxiety are common to all ED [16, 21, 41–43], while other characteristics are more frequently found in specific EDs. For example, low novelty seeking and decreased pleasure are common in the restrictive subtype of AN, impulsivity and novelty seeking are common to BN, and BED is associated with perfectionism [39, 40]. These underlying phenotypes have genetic contributions. Different combinations of these phenotypes and underlying genetic predispositions may also contribute to overlapping characteristics between the ED types.

Perspectives

Even if great progress in genetics and epigenetics have unveiled the pathophysiological architecture of many complex human diseases, most of the genes predisposing to EDs still remain to be discovered. The genetic heterogeneity in different ethnic groups invites collaborations in order to initiate multiethnic international recruitment and come up with novel methodologies to exhaustively study genetic associations. Methodological developments such as hypothesis-driven GWAS and methylation studies relaxing Bonferroni, case-control case design studies, Bayesian approaches [149], and deep phenotype-based cohorts [72, 150] may boost the identification of novel ED-predisposing genes. Moreover, the real effect of genes and their interplay with environmental risk factors is not completely understood yet. Taking advantage of G × E interactions can lead to original experimental designs, such as genome-wide environmental interaction studies [151], variance prioritization [152], and studying EDs in specific comorbid psychopathology contexts (such as obsessionality in AN and impulsivity in BN) [72, 150].

Perfectionism and obsessionality are factors in the disordered eating behavior and maintenance of low weight in AN, and impulsivity could be among the reasons for the inability to regulate body weight despite the drive for thinness in BN. Finally, stepping beyond the diagnostic criteria of full-phenotype EDs, the important ED-related phenotypes (e.g., highest and lowest illness-related BMIs, anxiety, anhedonia, obsessionality, impulsivity, etc.) could be explored 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 [72, 150].

Conclusions

In this review, we have provided a summary of the literature on the epidemiological and genetic origins of EDs. Using this evidence, we have developed a novel theoretical framework which provides a potential explanation for the overlap of different types of EDs. This framework provides a simplified view of the interaction of the potential genetics of EDs and the environment, specifically the pressure to be thin. We hope that this framework will stimulate research looking at the evolutionary roots of EDs and ED-predisposing genes. With recent technological advances (high-throughput genotyping and sequencing) the ability to detect genetic associations is improving. Understanding the genes underlying EDs may shed light on new and more effective methods of treating these disorders.

Disclosure Statement

None of the authors report having a conflict of interest. This research was conducted in the absence of any commercial or financial relationships that could be viewed as possible conflicts.

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Author Contributions

A.J.M. and D.M. were both responsible for developing the key concepts to be assessed by the review, drafting and revising the manuscript, providing approval for journal submission and ensuring the accuracy and integrity of the work. M.P. and J.C. provided a critical review of the manuscript. All authors agreed with the final content of the review.

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