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Genetic Epidemiology of Eating Disorders

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Abstract

Purpose of review—We capture recent findings in the field of genetic epidemiology of eating disorders. As analytic techniques evolve for twin, population, and molecular genetics, new findings emerge at an accelerated pace. We present the current status of knowledge regarding the role of genetic and environmental factors that influence risk for eating disorders.

Recent findings—We focus on novel findings from twin studies, population studies using genetically informative designs, and molecular genetic studies. Over the past two years, research in this area has yielded novel insights into: comorbidity with other psychiatric and medical disorders and with metabolic traits; developmental factors associated with the emergence of eating disorders; and the molecular genetics of anorexia nervosa.

Summary—Insights from genetic epidemiology provide an important explanatory model for patients with eating disorders, family members, and clinicians. Understanding core biological determinants that explain the severity and persistence of the illnesses, their frequent co-occurrence with other conditions, and their familial patterns raises awareness and increases compassion for individuals living with these disorders. Large scale genomic studies are currently underway. Ultimately, this domain of research may pave the way to greater understanding of the underlying neurobiology and inform the development of novel and effective interventions.

Keywords

eating disorders; genetic; GWAS; LD Score Regression; comorbidity

Introduction

Genetic epidemiology has been transformative in our understanding of how genes and environmental factors contribute to the emergence of eating disorders such as anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED). Forming the

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foundation of this knowledge base are large twin studies establishing that all three disorders are heritable. Replicated heritability estimates for AN range between 0.48 and 0.74; for BN, between 0.55 and 0.62, and for BED, between 0.39 and 0.45.[1] Although all of these studies have been conducted on European-ancestry populations, results have converged to support the role of genetic factors in the etiology of these conditions.

In this review, we focus on novel findings from twin studies, population studies using informative genetic designs, and molecular genetic studies with a full-genome approach that bring us to the current state of understanding of eating disorders. For the purpose of this review, we focus on studies of diagnostic categories and component behaviors rather than broader related phenotypes such as body dissatisfaction, disordered eating, and weight and shape concerns.

Recent Insights from Twin and Population Studies

Genetic and environmental contributions to DSM-5 eating disorder phenotypes

Previous heritability estimates for eating disorders were determined based on DSM III-R or IV criteria. Studies are emerging that explore these parameters in DSM-5-defined eating disorders. In a longitudinal study of Finnish female twins, the lifetime prevalence of AN increased from 2.2% to 3.6% with the introduction of DSM-5 criteria (vs. DSM-IV diagnoses in the same group). DSM-5 cases were, on average, less severe, with significantly later age of onset, higher minimum BMI, shorter duration of illness, and higher five-year probability of recovery.[2]

DSM-5 also introduced Unspecified Feeding and Eating Disorders (UFED), where individuals have clinically significant distress or impairment. Adolescent females in the Australian Twin Registry who were labeled as having the “restricting and/or exercise disorders” variant of UFED, reported eating disorder severity [measured via Eating Disorder Examination (EDE) global score] and clinical impairment/distress that were on par with individuals meeting criteria for AN or atypical AN—and significantly greater than the non-eating disorder group.[3] This observation underscores the importance of making treatment available for individuals with this presentation.

Influence of genes and environment on other eating disorder phenotypes

In the first study to examine familial liability to purging disorder (PD), familial effects (both additive genetic effects and shared environmental effects) accounted for 44% of the variance in PD among European-American twins in the Missouri Adolescent Female Twin Study, while 56% was ascribed to non-shared environmental factors. Due to sample size and prevalence, researchers were unable to distinguish between genetic and environmental familial effects.[4]

Further exploring genetic and environmental contributions to purging, self-induced vomiting (SIV) is a highly-heritable behavior common to several eating disorder diagnoses, but how genetic and environmental factors influenced SIV initiation (ever engaging in SIV) vs. SIV progression (regularly engaging in SIV) was previously unknown. Using the Swedish Twin study of Adults: Genes and Environment, researchers found that the majority of genetic and

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environmental factors (83%) were shared between SIV initiation and progression, and that 100% of the genetic liability to SIV progression was shared with SIV initiation. However, a small proportion of variance in SIV progression is unique and can be attributed to both shared and unshared environmental factors.[5]

In a large register-based study of a youth cohort in Stockholm, Sweden, when one or both parents had a lifetime history of psychiatric illness (in particular, bipolar affective disorder, personality disorder, anxiety, or depression), offspring were at increased risk of developing an eating disorder.[6] No evidence for increased risk was found for parental substance use disorder, schizophrenia, or somatoform illnesses.

Psychiatric comorbidity and suicide

In a study using the National Patient Register in Sweden, which included (i) 19,814 individuals with obsessive-compulsive disorder (OCD) and 8,462 individuals with AN; (ii) their first-, second- and third-degree relatives; and (iii) population-matched comparison individuals and their relatives, the risk of having AN in those with OCD was 16-fold greater in females and 37-fold greater in males. Individuals first diagnosed with OCD were at significantly elevated risk for a later diagnosis of AN (risk ratio, RR=53.6), and the reverse also held true (RR=59.6). First- and second-degree relatives of individuals with OCD were at increased risk for AN, and the magnitude of risk increased in proportion to the degree of genetic relatedness. An analysis of female twins (N=8,550) revealed a moderate but significant genetic correlation between self-reported OCD and AN diagnoses (r_a=50.52, 95% CI: 0.26-0.81). This observation supports that the frequently observed comorbid pattern of AN and OCD is at least in part due to shared genetic factors, although disorder-specific genetic factors are also operative.[7]

In the Missouri Adolescent Female Twin Study, common genetic mechanisms were also found for underlying liability to alcohol use disorder (AUD) and bulimic behaviors in both European- and African-American twins.[8] However, familial liability (whether genetic or environmental) was not the only operative factor. In a subsequent analysis of 53 pairs of monozygotic (MZ) twins who were discordant for early alcohol experimentation (use prior to age 15), those who experimented early had greater odds of reporting bulimic behaviors than co-twins without early experimentation (OR=3.12; 95% CI 1.54-6.67). Given that MZ twins share, on average, 100% of their segregating alleles, this pattern of results suggests a role for individual-specific environmental risk factors for bulimic behaviors.[9]

Individuals with eating disorders are known to be at increased risk for suicide, but the nature of the relationship between the two phenotypes has been, until now, unknown.[10] Two twin studies explored the relation among eating disorders, depression, and suicidality. Using the Australian Twin Registry, researchers reported that an eating disorder diagnosis (AN, BN, BED, or PD) was associated with a two-fold increase in suicidality and that common genetic factors underly a combined eating disorders phenotype (AN, BN, BED, and PD) and suicidality (r_a= 0.60; 95% CI: 0.25-1.00), as well as major depressive disorder (MDD) and suicidality (r_a=0.65; 95% CI: 0.43-0.87)—but not eating disorders and MDD.[11] A similar study in Sweden revealed shared genetic risk for AN and suicide attempts (SA) (r_a=0.52; 95% CI: −0.14-1.00), AN and MDD (r_a=0.49; 95% CI: 0.18-1.00), and MDD and SA (0.77;

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95% CI: 0.45-1.00).[12] Finally, a Swedish population study (N=2,268,786) reported significantly increased risk of suicide attempts among individuals with eating disorders and among individuals without eating disorders who had a relative with an eating disorder, even after accounting for the effects of psychiatric comorbidity.[13] This pattern of familial co-aggregation suggests familial liability for the association between eating disorders and suicide. Together, these three studies not only underscore the concerning elevated risk for suicide in individuals with eating disorders, but also confirm that the pattern may be due to familial factors that may be genetic in origin.

Other observations from genetic epidemiology

When examining genetic risk for MDD and overeating-binge eating behavior (OE-BE; i.e., binge eating plus loss of control) in female European- and African-American twins in the Missouri Adolescent Female Twin Study, additive genetic influences accounted for 44% (95% CI: 34-53%) of the MDD variance and 40% (95% CI: 25-54%) for OE-BE, with the remaining variances due to non-shared environmental influences. Genetic overlap was substantial (r_g=0.61; 95% CI: 0.39-0.85), and non-shared environmental influences were more weakly correlated (r_e=0.26, 95% CI: 0.09-0.42), suggesting that some of the genetic and non-shared environmental factors that influence liability to MDD also influence vulnerability to OE-BE.[14] Estimates were similar in European- and African-American twins.

Observations from a Swedish national cohort (N=1,800,643), revealed that the previously reported association between high school achievement and eating disorders could be explained by unmeasured familial confounders, whether genetic or environmental, with associations disappearing as the proportion of shared genes/environment increased (from first cousins to half siblings to full siblings to MZ twins).[15]

Recent Insights from Molecular Genetic Studies

To date, numerous small-scale candidate gene studies have been carried out to explore the molecular genetic etiology of eating disorders, yielding variable findings that failed to replicate.[1] Recent advances in technology and the decreased cost of genomic experiments now allow for millions of loci to be examined simultaneously in large numbers of individuals through methods such as genome-wide association studies (GWAS) and high-throughput exome and whole-genome sequencing. Here we summarize recent eating disorders genetic research with a genome-wide focus.

Genome-wide association studies

The first AN GWAS was notably underpowered to detect genome-wide significant loci.[16] A somewhat larger, yet still underpowered, AN GWAS was conducted under the umbrella of the Genetic Consortium for Anorexia Nervosa (GCAN), funded by the Wellcome Trust Case Control Consortium 3. The analysis included 2,907 cases and 14,860 ancestry-matched controls. While there were no genome-wide significant hits reported, 72 independent markers with the lowest p-values were selected for replication, and 76% of these loci produced results in the same direction as the discovery sample in an independent replication sample. These results provided a strong indication that the prioritized set of genomic

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variants likely contained true positive signals for AN risk and that increased sample sizes would be likely to yield significant associations.[17]

Eating disorders are notably prevalent in individuals with bipolar disorder.[18] A GWAS of 184 bipolar cases with comorbid eating disorders (AN or BN), 2,006 bipolar cases without an eating disorder, and 1,370 controls did not yield any genome-wide significant findings, but the top hits associated with comorbid eating disorders were located in the SOX2 overlapping transcript (*SOX2-OT*) gene on chromosome 3.[19] This finding is of interest because the AN GWAS by Boraska *et al.* also reported a suggestive (but not genome-wide significant) association between *SOX2-OT* and AN (peak $p=3.0\times10^{-7}$).[17]

Although not an eating disorder *per se*, "food addiction" as measured by the Yale Food Addiction Scale[20] has been associated with binge-eating episodes, hedonic eating, emotional eating, impulsivity, and food and snack craving, as well as patterns of neural response implicated in other addictive disorders, and has been previously studied in the context of BED.[21, 22] In a subset of 9,314 women enrolled in the Nurses' Health Study and and Nurses' Health Study II, two genome-wide significant loci were associated with food addiction traits. Specifically, an intronic variant in the protein kinase C, alpha (*PRKCA*) gene and an intronic variant in the neurotrimin (*NTM*) gene reached genome-wide significance for measures of food addiction. While *PRKCA* has been previously associated with BMI through linkage,[23] *NTM* is shown to be closely linked to opioid system genes. [24] Furthermore, the authors reported enrichment in the mitogen-activated protein kinase (*MAPK*) signaling pathway genes—previously identified as a candidate drug addiction pathway[25]—for food addiction accompanied with clinically significant impairment and distress. Of note, there was no association between food addiction and previously identified top 32 BMI loci.[26] Although these findings do not provide convincing support for shared genetic determinants of food addiction and drug addiction, results must be interpreted in the context of incomplete knowledge of the genetic architecture of drug addiction and the absence of replication of the food addiction GWAS.[27]

Genetic correlation between AN and other psychiatric disorders

Cross-disorder analyses of psychiatric disorders have provided strong evidence for shared etiology among schizophrenia, bipolar disorder, MDD, autism spectrum disorder, and attention deficit/hyperactivity disorder.[28, 29] The recent development of an analytic method called LD Score Regression (LDSC)—which accounts for linkage disequilibrium for each marker while estimating heritability—allows for speedy calculation of genetic correlation between different phenotypes and traits using GWAS summary statistics and is not biased by sample overlap.[30]

Through the application of LDSC to AN GWAS data and various publicly available consortia data, a strong positive genetic correlation between AN and schizophrenia was reported ($r_g=0.19$, se=0.04, $p=2\times10^{-5}$), which means that the common variants cumulatively associated with schizophrenia risk also increase risk for AN. Additionally, positive genetic correlations of smaller magnitude were observed between AN and bipolar disorder, as well as AN and MDD.[31] Taken together, these results further highlight the shared genetic architecture and the important role of common variation in the etiology of AN and other

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psychiatric disorders, and these findings are in line with the high observed comorbidity among psychiatric disorders.

Genetic correlation between AN and nonpsychiatric phenotypes

In their paper, Bulik-Sullivan *et al.* examined the genetic correlation between AN and various medical phenotypes and anthropometric traits. The most significant genetic correlation for AN was observed with BMI, which was in the negative direction (r_g=−0.18, se=0.04, p=3×10^{-7}). An inverse genetic correlation of similar magnitude was also reported for AN and adult obesity, providing evidence for the possible involvement of metabolic pathways in the etiology of AN. Other notable—albeit nonsignificant—genetic correlations with AN included childhood obesity (negative), smoking (negative), years of education (positive), infant head circumference (negative), HDL cholesterol (positive), and rheumatoid arthritis (negative).[31]

Copy number variation

Copy number variation (CNV) is characterized by a change in the number of copies of a genomic region, either in the form of deletions or duplications. The only genome-wide CNV study of eating disorders utilized the same dataset as the first AN GWAS, and researchers reported a 1.4 Mb deletion on 13q12 in two AN cases.[16] More recently, in the largest AN case-only CNV study to date, one individual also presented with a deletion which had 80% reciprocal overlap with the 13q12 deletion. Of note, multiple reports of this CNV exists in public CNV databases for phenotypes unrelated to AN or psychiatric disorders; thus, there is currently no strong evidence for 13q12 deletion being an AN-specific risk CNV (Yilmaz *et al.*, personal communication).

High-throughput sequencing

To date, only two high-throughput sequencing studies have been published in eating disorders. In the first study, Scott-Van Zeeland and colleagues[32] reported associations involving estrogen receptor 2 (*ESR2*) and epoxide hydrolase 2 (*EPHX2*) in AN through targeted gene sequencing. Case-control allele frequency differences for variants in these two genes were also observed in an AN GWAS dataset.[16] *EPHX2* was shown to be associated with depression and anxiety in a subgroup of AN cases, as well as BMI and elevated cholesterol in a large longitudinal population cohort.[32]

The second high-throughput sequencing study identified and analyzed genetic mutations that segregated with eating disorders in two families with multiple members affected with AN or BN. Linkage analysis followed by whole-genome sequencing revealed a missense mutation in the estrogen-related receptor alpha (*ESSRA*) gene in the first pedigree. In the second pedigree, a potentially deleterious rare mutation in the histone deacetylase 4 (*HDAC4*) gene was identified through exome sequencing. Immunoprecipitation experiments in HeLa cells and mouse cortices demonstrated functional interaction between *ESRRA* and *HDAC4*, and using transcriptional activity assays, researchers reported that *HDAC4* may act as an inhibitor of *ESRRA* activity.[33]

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Epigenetics

In 29 acutely ill patients with AN and 15 women without disordered eating, increased global methylation was observed in AN cases compared with controls, while no differences in global methylation between AN restricting and binge-eating/purging subtypes were detected.[34] After combining AN subtypes, methylation differences between cases and controls were especially pronounced for genes associated with histone acetylation and RNA modification, cholesterol storage and lipid transport, dopamine and glutamate signaling, and metabolism and weight loss. Some of the probes that correlated significantly with AN age of onset were associated with methylation of genes involved in brain and spinal cord development, hair growth, and development/maintenance of skin and teeth. Similarly, AN age of onset was associated with gene pathways involved in brain development. Researchers also observed a significant correlation between AN duration of illness and methylation levels at probes for genes related to the immune system, liver function, and metabolism, as well as gene pathways associated with anxiety, social functioning, bowel dysfunction, immune function, and liver damage—symptoms commonly reported in patients with AN. Although preliminary and based on a small sample, the results of this pilot study suggest that AN—especially if enduring or with early onset—could significantly alter the expression of genes associated with various metabolic, physical, and psychological functions, disruptions in which are some of the key medical and psychiatric complications of AN.

Conclusions

Studies of the genetic epidemiology of eating disorders are advancing at pace with evolving technology and methodology. The next decade promises to yield significant results that will further reveal the nature, magnitude, and specificity of genetic and epigenetic contributions to the etiology of these pernicious illnesses. Funding for genetic studies of AN has surpassed that for BN, BED, and other eating disorders, meaning that our understanding of those disorders lags woefully behind. Future work adhering to the highest standards of science, and that includes adequate sample sizes and replication, is essential to advancing the science of eating disorders.

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Key points

- Anorexia nervosa, bulimia nervosa, and binge-eating disorder are all heritable conditions that are influenced by both genetic and environmental factors.
- The co-occurrence of eating disorders and other psychiatric conditions, as well as suicide, is—in part—due to shared genetic factors.
- Genome-wide association studies of anorexia nervosa have been underpowered to detect significant loci; however, results suggest that increased sample sizes will yield significant results, and large-scale studies are currently underway.
- LD score regression results reveal significant positive genetic correlations with schizophrenia and significant negative genetic correlations with BMI.
- Genomic investigations of bulimia nervosa and binge-eating disorder lag behind progress in anorexia nervosa.