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Genetics and Epigenetics of Eating Disorders

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Two key features characterize a modern view of eating disorder etiology. First, almost all risk and protective factors, both genetic and environmental, are probabilistic, rather than deterministic. Second, the old debate pitting nature against nurture is overly simplistic. Nature and nurture represent opposite sides of the same etiological coin rather than opposing influences. Eating disorder psychopathology is a function of nature and nurture rather nature or nurture.[1]

Therefore, the foremost goal of current genetic research on eating disorders is to identify all loci and pathways that confer risk or protection. The key advantage of genetic studies is that causation can be inferred because exposure to the genetic risk factor begins at conception and before disease onset.[2] The second goal is to discover the pathophysiology underlying eating disorder development. The third is to use identified loci to inform prevention and treatment approaches.

Behavioral Genetics

Since the 1980s, family, twin, and adoption studies have made significant and replicated contributions to our knowledge of genetic influences on liability to eating disorders.[3, 4] Consensus exists that the observed familiality of eating disorders is primarily due to genetic factors. However these findings are often misreported and misunderstood due to a lack of knowledge about the assumptions and limitations of behavioral genetic methodology. The following sections will summarize how heritability, shared environment, and unique environmental influences are defined in the context of behavioral genetic methodology and provide an overview of recent findings on latent factors which predispose individuals to eating disorders.

Family Studies

Family studies compare a) the lifetime risk that relatives of an individual with an eating disorder will also develop an eating disorder to b) the lifetime risk of that disorder in the population and/or to the lifetime risk of the disorder in relatives of control individuals without an eating disorder.[3, 5] If the so-called relative risk is significantly elevated, then it

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can be concluded that eating disorders aggregate in families. It is well established that eating disorders are familial. First-degree relatives of individuals with anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) are significantly more likely to report lifetime AN, BN and BED than relatives of control individuals without an eating disorder. No family studies of purging disorder (PD) have been published. In addition, eating disorders subtypes coaggregate. The lifetime risk of both AN and BN are elevated in relatives of AN and of BN probands—affected individuals—compared with the relatives of controls, suggesting that that there is a broad spectrum of eating-related psychopathology and common familial causal factors across eating disorder subtypes.[3, 5, 6]

This is consistent with findings that demonstrate considerable diagnostic migration from one eating disorder presentation to another throughout the course of illness.[7, 8] However, family studies are unable to address whether these family-related factors are genetic and/or environmental.[3] For example, increased risk in relatives may be due to shared genetic risks, or due to learned behavior shared within the families (eg, an extreme focus on diet and exercise). Not all cases of eating disorders are familial. Sporadic cases also occur which could be novel presentations in a previously unaffected family, or simply the first detected case—which may not be uncommon given the shame and secrecy often associated with eating disorders.

Twin Studies

The fundamental twin study compares identical twins, who share 100% of their genes, with fraternal twins, who share roughly 50% of their genes, on indices of eating psychopathology. In large populations of both kinds of twins, if identical twins are more likely concordant for eating disorders than fraternal twins, then genetic factors can be assumed. Thus, through comparing the concordance of identical and fraternal twins on eating disorders, researchers can gain an understanding of the relative contribution of genes and environment to liability for these disorders.[9]

From these comparisons, researchers derive estimates of heritability, shared environment, and unique environment. Heritability estimates describe the proportion of the variation between people that is due to genetic variation for a specific population at a specific point in time. Shared environment estimates describe environmental factors experienced by both twins that lead twins to be more similar. Unique environment estimates describe environmental factors that lead twins to be more dissimilar (eg, events experienced by only one twin, or differential reactions to the same experienced event). The unique environment estimate also includes measurement error. Violations of certain assumptions, such as the equal environments assumption (ie, that identical twins are treated no more similarly than fraternal twins on traits relevant to eating disorders), can inflate the heritability estimates, but does not render them invalid.[9]

Several large population-based twin studies, primarily in European ancestry populations, have reported heritability estimates ranging from 33% to 84% for AN, 28% to 83% for BN, and 41% to 57% for BED, with the remaining variance typically attributable to unique environment factors.[10-12] In most twin models, shared environment did not contribute

significantly to liability for these disorders. No twin reports on the heritability of PD have been published, although the behavior of self-induced vomiting is highly heritable (72%).[13]

Progress and Promise in Behavioral Genetics

Advances in behavioral genetics have forwarded the field in three ways: 1) by clarifying eating disorder endophenotypes and elucidating the relationships among them; 2) by estimating heritability of disordered eating across development; and 3) by applying adoption study methodology to disordered eating symptoms.

Eating Disorder Endophenotypes and Disordered Eating Symptoms—

Endophenotypes are heritable, measureable markers that are associated with the disease in the general population and are thought to be more proximal to the genotype than the phenotype (ie, the eating disorder).[14, 15] They are observable in the affected proband even when s/he is not in the ill state. Endophenotypes may also be observed in unaffected family members. The goal of endophenotype identification is to clarify which of these components or underlying traits of eating disorders are most highly heritable, and in turn inform hypotheses about which genes may contribute to disease liability.

To address endophenotypic-like traits, researchers have applied an item-factor approach to twin studies[16] that estimates the relative contributions of genetic and environmental factors to the latent trait (the eating disorder diagnosis) and each diagnostic symptom.[17-19] By deriving heritability estimates for these factors and symptoms, researchers can identify promising eating disorder endophenotypes and traits worthy of further investigation. For example, somewhat surprisingly item-factor analyses for AN have demonstrated that the heritability of amenorrhea is quite low with the majority of variance in liability attributable to unique environmental factors.[18] These results suggest that amenorrhea may not be the optimal trait to consider in choosing traits or endophenotypes to study in AN. In item-factor analyses of BN and BED, the feeling of a loss of control over eating and the frequency of binge eating had the highest heritability estimates, suggesting that these may represent core heritable features of the disorders.[17-19]

Bivariate twin models explore the extent to which genetic and environmental factors contribute to the observed comorbidity between eating disorders and other traits or disorders. For example, a bivariate model of AN and BN can shed light on the commonly observed diagnostic crossover. Such a bivariate model revealed moderate genetic (.46) correlations between AN and BN which indicates a considerable, but not complete, overlap in latent genetic liability to both disorders.[20] In addition in bivariate analyses, a modest correlation was found between binge eating and obesity (0.34), moderate correlations between intentional weight loss and overeating (.61) and binge eating and night eating (.66) and a high correlation between objective binge eating and self-induced vomiting (0.74).[13,21,22] Moderate and high correlations suggest greater sharing of genetic factors. Continued research progress in item-factor, bi- and multivariate, and more sophisticated twin analyses may assist in refining eating disorder nosology further.

Heritability Estimates of Disordered Eating Across Development—

Although they can occur throughout the lifespan, eating disorders most commonly onset in

adolescence or late adulthood. This pattern encourages exploration of differences in contributions of genetic and environmental factors to eating disorders liability across time. Cross-sectional and longitudinal studies comparing early-adolescent to middle- and late-adolescent twins reveal negligible heritability of disordered eating behaviors and weight and shape concerns in the younger twins, but higher heritability with the onset of puberty.[23, 24]

Puberty appears to moderate the genetic influence on eating disorder traits. Genetic factors are likely related to both age and pubertal status. However, the underlying biological mechanisms that influence this shift toward higher heritability in puberty remain unknown. Twin studies suggest a potential role for estradiol, although in animal models, ovarian hormones were not found to moderate binge eating behavior.[25,26]

Adoption Study—Adoption studies are rare and difficult to conduct but have greater power than twin studies to detect shared environmental influences. An adoption design has been applied once in eating disorders by Klump and colleagues.[27] Because AN and BN have a low prevalence, disordered eating symptoms rather than eating disorder diagnoses were examined in these analyses.

Klump and colleagues compared the similarity between biological relatives to adoptive relatives to derive estimates of heritability, shared environment, and unique environment.[27] Participants were biological and adopted female sibling pairs. If biological relatives were more similar than adoptive relatives on disordered eating outcomes, this similarity would be expected to be a result of genetic factors. Likewise, if adoptive relatives were more similar than biological relatives on disordered eating outcomes, this similarity would be expected to a result of shared environmental factors. As in twin studies, heritability estimates for disordered eating symptoms from this adoption study ranged from 59% to 82%, depending on the symptom and shared environment did not contribute significantly to liability for disordered eating. Results of this adoption study converge with twin study findings to suggest that disordered eating liability is primarily a function of genetic and unique environment factors.[27]

Molecular Genetics

Molecular genetic investigations of eating disorders using candidate gene and linkage approaches have searched for loci and pathways that bestow risk or protection.

Genetic Association Studies—In association studies, investigators genotype individuals with eating disorders (cases) and individuals with no eating disorder psychopathology (controls, either family or unrelated), then compare gene variants that are hypothesized to be involved in the pathophysiology of eating disorders. Risk variants for eating disorders have been hypothesized to be in genes involved in biological mechanisms that affect appetite and weight regulation, mood lability, reward, and neural growth.

Studies have focused on: a) single nucleotide polymorphisms (SNPs) in genes, which are involved in the transmission and regulation of neurotransmitters such as serotonin, dopamine, and norepinephrine b) SNPs in genes involved in the endocannabinoid system; neuronal function and growth such as brain-derived neurotropic factor (BDNF); and c) SNPs

genes involved in the regulation of hormones such as leptin and adrenocortiocotrophin (ACTH). Overall, the evidence for the candidate genes that have been observed to play a role in eating disorder liability has been equivocal and no clear etiological role for these candidate genes has emerged.

The genes involved in the regulation and transmission of serotonin have received the most attention; however, there is no evidence that any of these variants confer specific risk of eating disorders. Serotonergic genes represented attractive candidates because variation in serotonin transmission and reuptake are involved in eating behavior,[28] as well as liability to obsessive-compulsive disorder (OCD) and depressive disorders known to be comorbid with eating disorder psychopathology.[29-31] In addition, hyperserotonergic activity persists even after recovery from eating disorders. Weight-recovered patients with AN or BN have elevated cerebrospinal fluid levels of 5-hydroxyindolacetic acid (5-HIAA), a metabolite of serotonin compared to controls.[32, 33] Thus, the genes involved in serotonin transmission such as *5-HTTLPR*, *5-HT$_{1B/1D\beta}$*, *5- HT$_{2A}$*, *5-HTR HT$_{3B}$*, have been examined. However, although approximately half of the studies conducted have found an association between these genes and eating disorders, the other half found no such association. This same pattern can be found in studies examining the role of other genes in eating disorders.[34] Although the lack of replication may represent true failures to replicate, it could also reflect inadequate sample sizes and statistical power to detect replication that exists.

Linkage Analyses—The goal of a linkage analyses is to identify the genomic regions that might harbor risk or protective loci. However, unlike genetic association approaches, linkage does not require *a priori* assumptions about the genes involved in the etiology of eating disorders. Linkage analysis is a method for narrowing high probability locations of risk loci by identifying genetic markers that are co-inherited with the eating disorders phenotype.

By researching a large sample of families with multiple affected individuals, linkage approaches restrict the genomic search space from the entire genome (3 billion base pairs) to one or several chromosomal regions (perhaps 10–30 million base pairs). Genes in these linkage-identified chromosomal regions are more likely to include loci relevant to the phenotype under study.[35]

The largest linkage studies on eating disorders to date included approximately 200 AN patients and 240 of their eating disorder affected relatives with diagnoses of AN, BN, or BED.[35-38] DNA was collected from biological parents when it was possible.[38] Using this sample, linkage analyses based on eating disorders diagnoses were conducted; augmented linkage analyses were conducted by including relevant heritable eating disorder phenotypes such as concern over mistakes, body mass index, and food-related obsessions.

For AN, significant ($P < .05$) peak regions were found on chromosome 1—from 1p36.13–1p34.2 and from 1q25.q– 1q41.[35] For BN, a significant peak was reported on chromosome 10p13.[36] For AN, these large genomic regions contain 546 genes and about half of those genes are expressed in the brain. For BN, relevant genes in this linkage area have not been described. Follow-up studies genotyping SNPs in these regions have suggested two

plausible candidate gene variants at the *OPRD1* (delta opioid receptor), and *HTR1D*(serotonin 1D receptor).[39] This association with AN was confirmed by an independent study.[40]

Genome-Wide Association Studies—Unlike hypothesis-driven genetic association studies which examine one or two candidate genes at a time, a Genome-Wide Association Study (GWAS) is data-driven, agnostic, and compares more than 500,000 loci distributed throughout the genome.[41] Each case and control in the sample is assayed for these loci—SNPs. Although these assays do not cover all of the approximately 3 billion base pairs in the human genome, they are designed so that each SNP assayed could act as a marker for another genetic marker that it is highly correlated to (ie, for other markers that it is in high linkage disequilibrium [LD] with) and thereby ensures good coverage of the genome. By genotyping such a large number of SNPs, there is an increased likelihood that some SNPs will be in LD with a genetic variant that is relevant for the disorder. Because so many SNPs are analyzed, significant findings are corrected for multiple comparisons and must exceed an extremely conservative significance threshold ($P < 5 \times 10^{-8}$).[42]

Thus far, one GWAS of AN has been published. It included 1,033 cases with AN and 3,773 controls.[43] Although a number of suggestive SNPs were reported, none met the genome-wide significance threshold. The single most important factor for "successful" GWAS is sample size. In schizophrenia, only studies with greater than 5,000 cases were able to detect SNPs that met genome-wide significance thresholds;[2] AN has similar heritability estimates to schizophrenia and GWAS of AN may follow a similar path. A GWAS funded by the Wellcome Trust Case Control Consortium 3 (WTCCC3) including ~3,000 cases with AN from 15 countries is underway.[44] Hopefully, the addition of GWAS methods will elucidate the genetic architecture of eating disorders and improve eating disorder taxonomy. GWAS will continue to be a powerful tool for understanding the genetic liability for eating disorders in the near future and a springboard for articulating the genetic component of gene-environment interplay in eating disorder risk.

Progress and Promise in Epigenetics—Epigenetics refers to the study of mechanisms that regulate gene expression independently of DNA sequence.[45] Researchers have begun to investigate whether women with eating disorders demonstrate systematic differences in their DNA methylation. Only a series of three published articles have examined DNA methylation in eating disorders using the peripheral blood samples of 46 inpatients with AN and BN.[46, 47] Women with AN had global DNA hypomethylation and hypermethylation of the *DRD2* promoter,[48] and women with BN had hypermethylation of the atrial natriuretic peptide (ANP) gene promoter region and down regulation of ANP mRNA.[47]*DRD2* is associated with dopamine regulation and ANP inhibits corticotropin releasing hormone, corticotropin and cortisol and thus, has an anxiolytic effect.[49, 50]

These findings match clinical observations that eating disorders are associated with increased anxiety and reward dysfunction, although the biological mechanisms for these observations are not well understood. Furthermore, it is likely that environmentally induced epigenetic changes are tissue-specific and whether these DNA methylation changes are present in all types of tissues and cells requires investigation. Therefore, these methylation

changes may not be found in all tissue samples that are related to the pathophysiology of eating disorders such as tissue samples from brain.

Conclusion

The journey to describe the genetic architecture of eating disorders is replete with challenges —not the least of which is achieving adequate sample sizes given the fairly low prevalence of the disorders. In European ancestry populations, eating disorder traits and disorders are heritable as replicated in twin studies and confirmed in an adoption study. Promising new genetic and epigenetic technologies (GWAS and DNA methylation measures) could help further our knowledge of the complex interplay between genes and environment for eating disorder risk and pathophysiology across development. Although much is to be accomplished, new genetic technologies, the increase in computing power, and its rapidly diminishing cost hold the capacity to allow research to embrace the full complexity of eating disorder biology.

Indirectly, research on the genetics of eating disorders has already made a considerable contribution to eating disorder treatment. The reexamination of the role of the family in eating disorder liability has ushered in a new era of eating disorder clinical practice. Whereas families had been excluded systematically from treatment and often pinpointed as etiological factors in eating disorders, our enhanced understanding of biology and heritability has shifted the floodlight of blame away from families and toward empirically identified biological and environmental risk factors. While taking care not to place too much hope in the fruits of genetic research, ongoing biological work will enhance our ability to unlock the myriad ways in which an individual's genotype and environment can interact to create, maintain, and recover from eating disorders.

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