The Genetics of Eating Disorders

by Wade Berrettini, MD, PhD

The eating disorders anorexia nervosa and bulimia nervosa traditionally have been viewed as sociocultural in origin. However, recent behavioral genetic findings suggest substantial genetic influence on these disorders. Molecular genetic research of these disorders is in its infancy, but initial results are promising. This article reviews findings from family, twin, and molecular genetic studies that support substantial genetic influences on disordered eating and highlights additional areas for future research.

INTRODUCTION

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by abnormal patterns of eating behavior and disturbances in attitudes and perceptions toward weight and shape. In AN, there is an extreme fear of weight gain despite increasing emaciation. BN usually emerges after a period of dieting[1,2] and is characterized by alternating patterns of binge eating and compensatory behavior. Binge eating, which is the consumption of a large amount of food in an uncontrollable manner, is typically followed by either self-induced vomiting, excessive exercise, fasting, and/or the misuse of laxatives, diuretics, or enemas. Although abnormally low body weight excludes a BN diagnosis, 25 to 30 percent of patients with BN have a prior history of AN.[3–6] Common to individuals with AN and BN are pathological concern with weight and shape, depression, and anxiety.[7–10]

The etiology of these disorders is presumed to be influenced by developmental, social, and biological processes.[11,12] However, the exact nature of these interactive processes remains incompletely understood. Cultural attitudes toward thinness have relevance to the psychopathology of eating disorders, but they are unlikely to be sufficient to account for the pathogenesis of these disorders. Notably, dieting behavior is quite common in industrialized countries throughout the world, yet AN and BN affect only an estimated 0.3 to 0.7 percent, and 1.7 to 2.5 percent, respectively, of females in the general population.[13] Moreover, numerous descriptions of AN date from the middle of the 19th century suggesting that factors other than modern culture play an etiologic role. In addition, both syndromes have a relatively homogeneous clinical presentation, sex distribution, and age-of-onset, supporting the possibility of some biological susceptibility. This is not to discount the role of culture, as the introduction of Western ideals of thinness may serve to release a biological propensity toward eating disorders[14] possibly by increasing behaviors, such as dieting, that may trigger the spiral of disordered eating.

Recent findings from behavior genetic studies suggest that this biological vulnerability might be genetic in nature. In this article, I will highlight these emerging findings and suggest areas for future research.

HERITABILITY

Family studies. Family studies provide initial data regarding genetic influence on a disorder by establishing whether it clusters amongst biologically related individuals. Controlled family studies have generally found increased rates of eating disorders in relatives of women with AN and BN compared to relatives of controls.[15–18] Findings from the largest and most systematic studies[16,17] suggest a 7 to 12-fold increase in the prevalence of AN and BN in relatives of eating disordered probands. This clustering of eating disorders in families of AN and BN individuals provides strong support for familial transmission of both disorders. However, given that first-degree relatives share both genes and environments, these studies cannot differentiate genetic versus environmental causes for the observed familiality. Systematic studies of twins are the means by which to disentangle the relative etiological influence of genes and environment.

Twin studies. Twin studies differentiate genetic from environmental effects by comparing similarity for a trait/disorder between identical (monozygotic [MZ]) and fraternal twins (dizygotic [DZ]). This comparison is based on the fact that MZ twins share all of their genes identical by descent, whereas DZ twins share, on average, half of their genes identical by descent. Consequently, MZ twin correlations that are approximately two times greater than DZ twin correlations suggest genetic effects. In general, greater MZ relative to DZ twin similarity for AN and BN has generally been found.[19–22] Estimates indicate that roughly 58 to 76 percent of the variance in the liability to AN,[23,24] and 54 to 83 percent of the variance in the liability to BN[25,26] can be accounted for by genetic factors. Although the confidence intervals on these estimates are wide, consistent findings across studies support moderate heritability of these traits.[27] For both AN and BN, the remaining variance in liability appears to be due to unique environmental factors (i.e., factors that are unique to siblings in the same family) rather than shared or common environmental factors (i.e., factors that are shared by siblings in the same family).

Eating disorder symptoms themselves also appear to be moderately heritable. Twin studies of binge eating, self-induced vomiting, and dietary restraint suggest that these behaviors are roughly 46 to 72 percent heritable.[28,29] Likewise, pathological attitudes such as body dissatisfaction, eating and weight concerns, and weight preoccupation, show heritabilities of roughly 32 to 72 percent.[28,30–32] Taken together, findings suggest a significant genetic component to AN and BN as well as the attitudes and behaviors that contribute to and correlate with clinical eating pathology.

Developmental differences. A caveat to the above conclusions is that there appears to be developmental differences in genetic effects across adolescence. Two recent twin studies[33,34] from the Minnesota Twin Family Study

(MTFS) have examined this issue by comparing genetic influences on eating attitudes and behaviors in population-based samples of 680 11-year-old twins and 602 17-year-old twins. In the first of these studies, essentially no genetic influence was found for weight preoccupation scores and overall eating pathology in 11-year-old twins, whereas 52 to 57 percent of the variance in these attitudes and behaviors could be accounted for by genetic factors in the older cohort.[28] Increased genetic influence across age was also found for body dissatisfaction scores, although effects were much less dramatic. The authors speculated that these findings may reflect an activation of etiologic genes during puberty.

In a follow-up study,[35] the 11-year-old cohort was divided into a pre- and post-pubertal group in order to directly examine the effect of puberty on the heritability of these traits and behaviors. Findings revealed a pattern of results similar to those reported in the initial study.[28] Genetic factors accounted for zero percent of the variance in weight preoccupation and overall eating pathology scores in pre-pubertal twins, but accounted for 26 to 35 percent of the variance in post-pubertal twins. Although sample sizes were small in the post-pubertal group (n=39 pairs), the similar pattern of twin correlations in the two studies suggested that puberty may account for the dramatic age differences observed earlier. Increased heritability in post-pubertal relative to pre-pubertal twins who were the same age provided strong evidence of potential pubertal activation of the heritability of eating pathology that may be mediated by ovarian hormones. These findings are important for highlighting not only developmental differences in genetic effects, but also the potential role of ovarian steroids in the heritability of these disorders.

COMORBIDITY

Individuals with AN and BN commonly present with comorbid psychopathology, most notably affective and anxiety disorders.[7] Family and twin studies have been effective in illuminating the causes of comorbidity[36] and addressing to what extent comorbidity among these disorders might arise as a function of a shared genetic effect.

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Psychopathology. *Substance use disorders.* Family studies investigating substance use disorders suggest relatively low prevalence among relatives of restricting AN probands.[16,37] In contrast, rates are elevated in relatives of probands with BN. However, results from three studies[38–40] indicate that there is no evidence of a cross-transmission of BN and substance use disorder in families, and twin data[41] have shown that the genes influencing susceptibility to alcoholism were independent of those underlying risks to BN.

Major depression. Several family and twin studies have examined the covariation between eating disorders and major depression. Studies of AN probands have yielded relative risk estimates for depression in the range of 2.1 to 3.4.[16,18] Likewise, studies of BN probands indicate that their first-degree relatives are significantly more likely to develop major depression than relatives of controls.[16] However, most studies considering the effects of proband comorbidity on familial risk have shown that affective illness is more likely to be transmitted by probands with this same diagnostic comorbidity.[16,18] These later studies suggest that although eating disorders and depression may share some etiologic factors, there are also unique factors specific to each. Two recent twin studies support this conclusion, as both found evidence for shared as well as unique genetic influences on major depression and both AN and BN.[24,42]

Anxiety disorders. Several different anxiety disorders have been examined for their genetic relationships with eating pathology. In general, evidence supports shared genetic transmission between these disorders and both AN and BN. For example, although obsessive-compulsive disorder (OCD) appears to segregate independently from AN and BN in families,[16] shared familial transmission has been found between obsessive-personality disorder (OCPD) and AN and BN.[16] In addition, shared familial transmission has been found between broadly-defined AN and BN and separation anxiety and overanxious disorder, and between BN and both simple phobia and panic disorder. Taken together, these findings suggest the existence of a broad, genetically influenced obsessive pheno-

type with core features of rigid perfectionism, anxiety, and a propensity towards behavioral constraint.

Personality and physical characteristics. *Personality traits.* Individuals with AN and BN exhibit characteristic personality traits including high levels of stress reactivity, negative emotionality, and harm avoidance.[27,28,43–49] These characteristics persist after recovery from the disorder[45,48,49] and are independent of body weight,[28] suggesting that they may be trait disturbances contributing to the disorders' development. The moderately heritable nature of these traits[50] suggests that relationships may be genetic in nature.

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Four studies have examined familial relationships between personality traits and eating disorders, with many suggesting familial co-transmission. Klump, et al.,[48] found increased levels of negative emotionality and stress reactivity and decreased levels of well-being in family members of restricting AN probands compared to control relatives. Likewise, Lilenfeld, et al.,[51] found increased perfectionism and stress reactivity scores in non-eating disordered relatives of bulimic probands compared to control relatives. Carney, et al.,[52] failed to find shared transmission between DSM-III-R personality disorder characteristics and BN, although their use of lower prevalence personality disorder symptoms rather than more normative personality characteristics may have prohibited detection of significant effects.

Recent twin study results suggest that familial relationships between personality and eating pathology may be genetic in nature,[35] as genetic rather than environmental influences have been found to underlie phenotypic and familial relationships between these characteristics. However, genetic influences that are independent of those operating in personality also appear to contribute to eating pathology.[35]

Body mass index (BMI). Vulnerability to obesity has been found to be a risk factor for bulimia nervosa.[53] Body weight is highly heritable[54] leading to questions of shared genetic transmission between body weight and eating pathology. One study directly examined this question by investigating shared genetic transmission of BMI and disordered eating, including body dissatisfaction, weight preoccupation, overall eating pathology, and the use of compensatory behaviors, such as self-induced vomiting and laxative abuse.[28] Findings suggested some shared genetic transmission, although again, the majority of genetic influence on these disordered eating variables was independent of the genes influencing BMI.

Shared transmission between AN and BN. Cumulating evidence suggests that AN and BN likely share some etiologic features. Clinically, approximately 50 percent of women with AN develop BN during the course of their illness and approximately 30 percent of women with BN report a history of AN.[3–6]

Family and twin studies indicate an increased risk of both AN and BN in relatives of AN and BN probands,[16,17,54,55] suggesting a shared familial component between the two disorders. In addition, subthreshold forms of eating disorders appear to lie on a continuum of liability with full eating disorders.[26] These findings suggest the existence of a broad eating disorder phenotype with possible shared genetic predispositions.

Research reviewed above suggests that AN and BN may share genetic transmission with each other and with body weight, personality, anxiety, and possibly major depression. However, findings also suggest that there are genetic influences on eating pathology that are independent of those influencing the traits/disorders mentioned above. This complexity is the norm rather than the exception in psychiatric genetics and highlights the need for additional research to further characterize the genetic variance of these disorders.

MOLECULAR GENETIC STUDIES

A detailed comparison of the molecular genetic designs that can be brought to bear upon complex traits is beyond the scope of this article.[56–58] Briefly, there are two general strategies in humans: linkage and association studies.[59]

Linkage studies can be used in gene discovery: with a sufficiently large number of multiplex pedigrees or extreme sibling pairs,[60] anonymous genetic markers scattered across the genome can be used to identify the chromosomal regions that may contain genes that contribute to a disorder such as AN or BN. This appealing

strength is tempered by the low power[61] and resolution[62] likely for linkage studies of complex traits.

Association studies are conceptually equivalent to the familiar case-control design. This design is particularly useful and powerful when prior knowledge of the pathophysiology of a trait suggests a number of candidate genes. However, the use of this design is controversial because of the risk of false positive findings when studying a sample that contains individuals of evolutionary diverse ancestry.[63] Obtaining genotypes on other family members can reduce this risk but at the cost of reduced statistical power.

Association studies. Evidence linking AN and BN to monoamine functioning[64] have led researchers to target serotonin and dopamine-related genes in association studies. Several groups have reported an increase in the -1438/A allele of the 5-HT2A receptor gene in AN women compared to controls.[65–68] However, additional studies of this and other serotonin-related genes (5-HT1Dß, 5-HTT, 5-HT7, tryptophan hydroxylase receptor [TPH]) have failed to find significant associations in AN individuals.[67,69–75] Studies have also failed to find increased allele frequencies of the dopamine D3 and D4[76] receptor genes in AN relative to controls. These genes have not yet been examined in individuals with BN.

The primary role of weight control, feeding, and energy expenditure in the pathology of AN and BN has lead researchers to examine genes related to these processes. Results thus far have been mixed, as tests for association between AN and neuropeptide Y5 and Y1,[77] the ß3 adrenergic receptor gene,[78] the melanocortin-4 receptor gene,[79] and the leptin gene[80] were all negative. However, studies have found an increase in the D11S911 allele located near the UCP-2/UCP-3 gene in AN subjects relative to controls,[81] as well as an increase in the estrogen receptor ß 1082/G allele in AN relative to obese and overweight subjects.[82] Once again, associations between most of these genes and BN have not been investigated.

Findings suggest possible associations between the 5-HT2A receptor gene, the UCP-2/UCP-3 gene, and the estrogen receptor ß gene with AN. However, additional research is necessary to clarify conflicting findings and replicate initial results. Moreover, association studies of BN are needed, as this disorder has been much less studied than AN and findings thus far have been generally negative.

Linkage studies. A number of collaborators[83] and I recently have completed the first study to date[84] using genome-wide linkage analyses in AN or BN. This multicenter study is funded by the Price Foundation of Switzerland and uses allele-sharing linkage analyses to identify genes contributing to eating disorders in 196 families with two or more family members with AN, BN, or eating disorders not otherwise specified (EDNOS). Initial analyses of this dataset show only modest evidence for linkage, with peaks observed on chromosomes 4, 11, 13, and 15 with NPL scores >1. The highest peak was a NPL score on chromosome 4.[84] These modest results are likely due to decreased power to detect linkage as a result of large number of loci influencing the phenotype as well as considerable sample heterogeneity (i.e., inclusion of AN, BN, and EDNOS). These possibilities suggest that additional studies using more homogeneous phenotypes and larger numbers of subjects would increase power to identify genetic effects.

We have recently completed a larger, genome-wide linkage study of approximately 400 families with two or more family members with AN, BN, or EDNOS. This larger study will provide the necessary power to detect linkage and may prove to be the first to identify susceptibility loci for these disorders. In addition, we are currently in the process of collecting genetic data on approximately 700 AN individuals and their parents. This homogeneous sample will be used to conduct association analyses such as those described above and will provide additional power to detect genes of modest to large effect.

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CONCLUSIONS

Data described above are clear in establishing a role for genes in the development of eating pathology. Estimates from the most rigorous studies suggest that greater than 50 percent of the variance in liability to eating disorders and disordered eating behaviors can be accounted for by additive genetic effects. The remaining variance appears to be due to unique rather than common environmental effects. These high estimates indicate a need for studies identifying the specific genes contributing to this large proportion of variance. Twin and family studies suggest that a number of heritable characteristics that are frequently comorbid with AN and BN may share genetic transmission with these disorders, including anxiety disorders/traits, body weight, and possibly major depression. Developmental twin research is beginning to shed light on why eating disorders tend to develop within a relatively narrow developmental window. Additional work is required to enhance our understanding of how puberty (and which aspects of puberty) influences the apparent activation of genetic effects on disordered eating.

Molecular genetic research of these disorders is in its infancy. However, promising areas for future research have already been identified (e.g., 5-HT2A receptor gene, UCP-2/UCP-3 gene, estrogen receptor ß gene), and several large-scale linkage and association studies are currently underway. These studies are likely to provide invaluable information regarding both the appropriate phenotypes to be included in genetic studies as well as the genes with the most influence on the development of these disorders.

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Dr. Berrettini is the Karl E. Rickels Professor of Psychiatry, University of Pennsylvania School of Medicine, and the Director, Center for Neurobiology and Behavior, Philadelphia, Pennsylvania.