The Genetics of Eating Disorders

Sara E. Trace,[1] Jessica H. Baker,[1] Eva Peñas-Lledó,[2] and Cynthia M. Bulik[1,3,*]

[1]Department of Psychiatry, [3]Department of Nutrition, University of North Carolina, Chapel Hill, North Carolina 27599; email: strace@med.unc.edu, jhbaker@med.unc.edu, cbulik@med.unc.edu

[2]University of Extremadura Medical School, Badajoz E-06071, Spain; email: elledo@unex.es

Annu. Rev. Clin. Psychol. 2013. 9:589–620

The *Annual Review of Clinical Psychology* is online at http://clinpsy.annualreviews.org

This article's doi: 10.1146/annurev-clinpsy-050212-185546

*Corresponding author

Keywords

anorexia nervosa, bulimia nervosa, binge eating disorder

Abstract

Over the past decade, considerable advances have been made in understanding genetic influences on eating pathology. Eating disorders aggregate in families, and twin studies reveal that additive genetic factors account for approximately 40% to 60% of liability to anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). Molecular genetics studies have been undertaken to identify alterations in deoxyribonucleic acid sequence and/or gene expression that may be involved in the pathogenesis of disordered eating behaviors, symptoms, and related disorders and to uncover potential genetic variants that may contribute to variability of treatment response. This article provides an in-depth review of the scientific literature on the genetics of AN, BN, and BED including extant studies, emerging hypotheses, future directions, and clinical implications.

Contents

AN: anorexia nervosa

BN: bulimia nervosa

EDNOS: eating disorder not otherwise specified

INTRODUCTION

Eating disorders, as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV (Am. Psychiatr. Assoc. 2000) include anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS). Although currently housed within EDNOS, binge eating disorder (BED) is slated to become an independent diagnosis in DSM-5. The core eating disorders—AN, BN, and BED—vary somewhat in lifetime prevalence, with AN being the least

common (0.5%–3%), BED being the most common (2%–4%), and BN falling in between (1%–3%; Hoek 2006, Hudson et al. 2007, Smink et al. 2012). AN is characterized by low weight (less than 85% ideal body weight), intense fear of gaining weight, body image disturbance, and amenorrhea in postmenarcheal women. In DSM-5 amenorrhea will no longer be required due to a lack of evidence supporting the utility of this criterion. BN is defined by binge eating episodes, inappropriate compensatory behaviors (i.e., self-induced vomiting) to prevent weight gain, and self-evaluation that is unduly influenced by weight and shape. BED is marked by regular binge eating episodes in the absence of regular inappropriate compensatory behaviors.

BED: binge eating disorder

G × G: gene-by-gene interaction

G × E: gene-by-environment interaction

5-HT: serotonin

The conceptualization of eating disorders, specifically AN and BN, has undergone considerable transformation historically (Vemuri & Steiner 2007). Dominant theories have ranged from psychodynamic to sociocultural, and current theories have reached a tentative consensus that eating disorders rest squarely on the border between psyche and soma, fitting a truly biopsychosocial model. This convergence can in part be attributed to a systematic series of investigations of family, twin, and molecular genetic studies of eating disorders that have painted a rich picture of the familiality and genetic contributions to these disorders.

Generally, when we consider traits to be heritable, we think of Mendelian patterns of inheritance, which is the transmission of traits from parents to children at a single locus (i.e., one gene is responsible for one trait). However, heritable traits also have a polygenic or additive genetic pattern of inheritance in which several genes are responsible for the development of a trait. It is the combined or additive effect of these genes that converge on the observed trait (or phenotype). Most complex traits, including eating disorders, follow this pattern, which makes identifying specific genes difficult since each gene may contribute only a small proportion of variance to the observed phenotype. Moreover, our ability to identify gene-by-gene (G × G) interactions—especially in the presence of many contributing genes—is underdeveloped. Further, although genes clearly contribute to eating disorder liability, they do not act alone but rather in concert with environmental factors. Therefore, G × G plus gene-by-environment (G × E) interactions will no doubt be critical in accounting for the observed phenotypes.

In this review, we discuss the contributions of genes and environment to eating disorders. For each disorder, we familiarize the reader with the state of the science of family, twin, and molecular genetic studies, as the maturity of the genetic research differs across the three primary eating disorders. We also discuss burgeoning approaches and directions focusing on endophenotypes, gene-environment interactions and correlations, epigenetics, gene expression, cross-disorder analyses, and pharmacogenetics. Finally, we highlight the clinical implications of this research.

ANOREXIA NERVOSA

The familial nature of AN is well established. First-degree relatives of individuals with AN are 11 times more likely to have lifetime AN than are relatives of unaffected controls (Strober et al. 2000). Population-based twin studies corroborate the familiality of AN and indicate that genetic factors are operative. Heritability estimates for varyingly broad definitions of AN range from 28% to 74%, with the remaining variance largely attributed to unique environmental factors (Klump et al. 2001, Kortegaard et al. 2001).

Both linkage and association studies have been conducted on AN. Linkage studies have suggested chromosomes 1, 2, 4, and 13 as possible regions of interest (Devlin et al. 2002, Grice et al. 2002), with chromosome 1 receiving the most support. Chromosome 1 houses the delta opioid receptor (*ORPD1*) and serotonin (5-HT) receptor 1D (*5-HTR1D*) genes, which have been followed up in an association study (Bergen et al. 2003). Overall, linkage has not been a fruitful approach to identify vulnerability genes.

DA: dopamine

Given the volume of work in the area for AN (i.e., 175 candidate gene studies of AN covering 43 genes; Rask-Andersen et al. 2010), we do not review all studies exhaustively. Rather, we focus on genes that have been included in more than one report and have shown at least one significant association with AN. We categorize our discussion of the results on the basis of the primary system the gene is involved in [e.g., 5-HT, dopamine (DA), appetite, and weight regulation].

Serotonergic Genes

Secondary to its global involvement in mood, appetite, and body weight regulation, the 5-HT system is a frequent target of study in AN. Further, it is well established that 5-HT activity is altered in the acute illness state of AN and in those who are long-term weight restored. Despite the convincing face validity of studying the 5-HT system, results are inconclusive. Much attention has been paid to the *5-HT2A* receptor gene and the 5HT-transporter-linked polymorphic region (*5-HTTLPR*). Although not all studies have shown a significant association with this region, a 2003 meta-analysis suggested that, according to transmission disequilibrium studies, the −1438G/A polymorphism of *5-HT2A* is significantly associated with risk for AN (Gorwood et al. 2003). Specifically, across nine studies, the A allele was found in 46.8% of patients and in 43.6% of controls, a significant excess. A second meta-analysis on the −1438G/A polymorphism of *5-HT2A*, conducted in 2009 and including the nine studies analyzed by Gorwood and colleagues as well as an additional analysis in an independent sample, confirmed the significant association with AN (Martásková et al. 2009). Further, in a reanalysis of negative findings including 43 additional participants with AN and 98 additional healthy controls, Kipman et al. (2002) found a significant association between the −1438G/A polymorphism and age of AN onset. A significant correlation was observed between age of onset and the A allele, such that patients with the A allele had a significantly older age of AN onset. The authors concluded that the −1438G/A polymorphism of *5-HT2A* may modify the timing of AN expression rather than being a specific risk factor for its development.

Similar to *5-HT2A*, findings have been mixed in regard to the role of *5-HTTLPR* in AN risk. Two meta-analyses of *5-HTTLPR* association studies, including reports published through October 2009 (eight studies; Calati et al. 2011) and through July 2008 (seven studies; Lee & Lin 2010), respectively, suggest that carriers of the short allele, versus the long allele, are at increased risk for AN. The short allele consists of 14 repeats of a sequence and makes half as much transporter protein as the long allele, whereas the long allele consists of 16 repeats. Further, exploring the impact of *5-HTTLPR* on diagnostic crossover from AN to BN over the course of a six-year follow-up period revealed that women with AN who are carriers of the short allele were approximately four times more likely to cross over from AN to BN (Castellini et al. 2012). However, there was no significant association between the short allele and AN diagnosis.

The *5-HT1D* receptor gene has also been significantly associated with AN (Bergen et al. 2003, Brown et al. 2007, Kiezebrink et al. 2010), specifically with the restricting type (Brown et al. 2007, Kiezebrink et al. 2010). Further, these three studies met the calculated sample size required to obtain 80% power, assuming a dominant model (Bulik et al. 2007b). Therefore, this gene may be a promising candidate for AN vulnerability. Additional 5-HT transporter genes, including *5-HT2C*, *5-HT1B*, *5-HT1D*, and *5-HT3B*, have shown significant associations with AN; however, replications are needed to confirm their importance.

Tryptophan hydroxylase (*TPH*) is the rate-determining enzyme in the synthesis of 5-HT. Exploring whether regions of the *TPH* gene are involved in the etiology of AN has yielded mixed results. One study reported a significant effect of *TPH2* for AN (Slof-Op't Landt et al. 2011). However, other studies showed no significant association (Han et al. 1999, Kim et al. 2009).

Despite the inconsistency of results, 5-HT does play an important role in systems that are awry in AN, namely mood, anxiety, appetite, and weight. As such, it is likely to have some involvement in the disorder. However, this involvement is unlikely to be unique, as 5-HT has been implicated in the pathophysiology of a range of psychiatric disorders, suggesting it may not be a specific vulnerability factor for AN.

NE: norepinephrine

Dopaminergic Genes

The dopaminergic system modulates feeding, thinking processes, motor activity, and reward-motivated, drug-seeking behaviors and is therefore a worthwhile candidate for eating disorders. Increased DA has been hypothesized to be associated with several AN symptoms, including weight loss, hyperactivity, amenorrhea, body image distortion, and obsessive-compulsive behavior (Kaye et al. 2004). To date, candidate gene studies have focused primarily on the *DRD2* and *DRD4* receptor genes. Specifically, a follow-up analysis to a linkage study (Bergen et al. 2005) found that *DRD2* polymorphisms (i.e., 141C indel; C939T) displayed a significant association with AN in haplotype analyses and two that were significantly associated with AN binge eating/purging type (i.e., Taq1A; 725 bp 3′ C/T). Transmission disequilibrium has also been observed for two *DRD4* polymorphisms in AN (i.e., C521T) or AN binge eating/purging type (i.e., 120 bp tandem repeat; Bachner-Melman et al. 2007). However, other *DRD2* and *DRD4* polymorphisms have not shown significant associations with AN (Hinney et al. 1999b, Nisoli et al. 2007).

The catechol-*O*-methyltransferase gene (*COMT*) is involved in the metabolism of DA and norepinephrine (NE) and has been shown to play a possible role in AN. Significant associations have emerged between the Val158Met polymorphism of the *COMT* gene and AN (Frisch et al. 2001, Mikolajczyk et al. 2006). Individuals with AN are more likely to have the Val158 form of the polymorphism, and individuals homozygous for this allele have a twofold increased risk of AN (Frisch et al. 2001). Replications of this finding have not been consistent, and when the initial study was expanded, the association was found only for restricting AN type (Michaelovsky et al. 2005). A recent meta-analysis of the Val158Met polymorphism, including eight published studies, did not show a significant effect of this polymorphism on AN risk (Brandys et al. 2012). However, AN diagnosis was not broken down by type, which could have attenuated findings.

Although speculative at this point, it is possible that there are differential genes involved in risk for AN restricting type and AN binge eating/purging type. Two *DRD2* and two *DRD4* polymorphisms have been implicated in AN binge eating/purging type, whereas the Val158Met polymorphism of the *COMT* gene has been associated with the AN restricting type. Further, the *COMT* gene has been implicated in risk for several other psychiatric disorders, and the enzyme produced by this gene can also indirectly affect brain levels of 5-HT due to reciprocal interactions between DA and 5-HT. This suggests that DA dysregulation, specifically related to the *COMT* gene, is not a specific vulnerability factor for AN and may play a synergistic role in risk with 5-HT.

Opioidergic Genes

Opioid receptors are involved in food intake, reward sensitivity, and pain and are thought to play a role in vulnerability to addictive disorders. One study identified significant linkage in a region on chromosome 1, which houses *OPRD1*, in AN (Grice et al. 2002). Follow-up analyses indicated that three *OPRD1* gene polymorphisms were significantly associated with AN. An additional report, examining different *OPRD1* polymorphisms than those of the aforementioned study, also found associations between *OPRD1* and AN (Brown et al. 2007).

It has been theorized that individuals with AN have a dysregulation of the opioid system, creating a predisposition toward "addiction" and that restriction and exercise become a means to compensate for diminished response to reward. This hypothesis aligns with findings that suggest *OPRD1* polymorphisms are significantly associated with AN restricting type but not AN binge eating/purging type. Although fewer studies have addressed the role of opioid receptors in the pathophysiology of AN compared to other genes (e.g., 5-HT), results are quite consistent in finding a significant association.

Appetite Regulation Genes

Ghrelin is an appetite-stimulating hormone that is inversely associated with body mass index (BMI) in the general population. Further, ghrelin levels are increased in women with AN compared to healthy controls (Himmerich et al. 2010), and the repeated administration of ghrelin increases food intake in women with AN (Hotta et al. 2009). Association studies exploring the role of the gene encoding ghrelin have been mixed, with a majority finding no significant associations with AN (Ando et al. 2006, Cellini et al. 2006, Kindler et al. 2011, Monteleone et al. 2006b). However, one report revealed that the 72Met variant of the Leu72Met gene was more frequently observed in individuals with the AN binge-purge type than in controls or individuals with the restricting AN restricting type (Dardennes et al. 2007). Further, a ghrelin gene variant significantly predicted weight recovery in AN, such that those individuals homozygous for the TT genotype of the T3056C variant were more likely to achieve weight restoration (including remission or cross-over to another eating disorder diagnosis, e.g., EDNOS, BN; Ando et al. 2010). Finally, genetic variants within the ghrelin-activating gene, ghrelin O-acyl-transferase (*GOAT*), have been implicated in the etiology of AN, such that individuals homozygous for the risk allele are approximately 1.5 times more likely to have AN (Müller et al. 2011).

Agouti-related protein (AgRP) has a similar function as ghrelin such that it inhibits appetite-inhibiting signaling and is increased upon hunger, promoting feeding and leading to increased body weight. Plasma AgRP concentrations are higher in AN than in healthy controls and return to normal levels upon weight recovery (Merle et al. 2011). Associations between the Ala67Thr polymorphism of the gene encoding AgRP and AN were reported in a case-control association study and a transmission disequilibrium test (Dardennes et al. 2007, Vink et al. 2001), with one study reporting that carrying the risk allele conferred a 2.5 times increased risk for developing AN (Vink et al. 2001). Cholecystokinin is a hormone that stimulates the digestion of lipids and proteins in the small intestine and serves as a satiety signal. Preliminary findings are mixed in regard to the association between genes encoding cholecystokinin and AN.

Although genes involved in appetite regulation are valid candidates for a role in the pathophysiology of AN, results are inconclusive. Given that the hormones associated with these genes, which are involved in appetite stimulation or satiety, change with decreasing or increasing weight, it is unclear whether the changes observed in AN are a cause or consequence of the disorder, and whether they are related to the disease process or are simply an effect of starvation.

Genes Influencing Food Intake

Estrogens play a critical role in normal food intake. Animals that are ovariectomized display an increase in food intake and body weight that is reversed upon exogenous administration of estradiol (Brown & Clegg 2010). Moreover, AN is more common in females and typically onsets around puberty (Am. Psychiatr. Assoc. 2000). However, molecular genetic studies exploring the

association between estrogen receptor genes and AN yield mixed findings. One report found a significant association between the *ESR2* gene and AN (Eastwood et al. 2002). Exploration of transmission disequilibrium of polymorphisms on the *ESR1* gene indicated that this gene is significantly associated with AN and shows a stronger association with the restricting type than the binge eating/purging type (Versini et al. 2010). Associations between these polymorphisms and AN were driven by paternal overtransmission, and women with the risk allele were approximately two times more likely to have AN (Versini et al. 2010). However, an additional report showed no association between AN and *ESR1* (Eastwood et al. 2002).

GWAS: genomewide association study

NE is involved in increased and decreased food intake, affects activity of the reward system, and is involved in arousal. Transmission disequilibrium has been observed for *SL6A2* and AN (Urwin et al. 2002). However, this association was not confirmed in a subsequent report (Hu et al. 2007). Cannabinoid receptors mediate the psychotropic effects of tetrahydrocannabinol and stimulate appetite. Transmission equilibrium tests of *CNR1* showed that a 13-repeat allele was more frequent in AN restricting type, whereas the 14-repeat allele was more frequent in AN the binge eating/purging type (Siegfried et al. 2004). An additional *CNR1* polymorphism and cannabinoid receptor (*GPR55*) have shown significant associations with AN (Ishiguro et al. 2011, Monteleone et al. 2009). However, several polymorphisms have shown no association with AN (Müller et al. 2008).

Decreased food intake is a core feature of AN. Genes involved in food intake may influence AN vulnerability independently or work in conjunction with other systems (e.g., appetite regulating genes, 5-HT). Although findings are mixed, estrogen receptors are an intriguing candidate for AN risk. Estradiol is involved in the transcription of 5-HT genes and the regulation and production of appetite hormones; therefore, these systems may interact to increase risk for AN. Future research should focus on interactions with other systems and genetic factors and attempt to elucidate any differences between AN types.

Genes Influencing Weight Regulation

Because low body weight is one of the core features of AN, genes involved in weight regulation are promising candidates for their role in AN. Uncoupling proteins 2 (*UCP2*) and 3 (*UCP3*) mediate ion transfer across the mitochondrial membrane and regulate thermogenesis. It has been theorized that dysfunction of mitochondrial energy metabolism increases metabolism, facilitating weight loss in individuals with AN (Rask-Andersen et al. 2010). Studies have explored the association between AN and genes encoding *UCP2* and *UCP3*, and only one *UCP2* marker has shown a significant association (Campbell et al. 1999).

Studies have also examined whether genes known to be involved with obesity are associated with AN risk. Mutations in the melanocortin 4 receptor (*MC4R*) gene are known to cause severe, morbid obesity. However, significant associations have not been observed between *MC4R* variants and AN diagnosis (Brandys et al. 2010, Hinney et al. 1999a). Through a genomewide association study (GWAS), the fat mass and obesity-associated gene (*FTO*) was discovered to play a significant role in obesity, which is now a widely replicated finding. Currently, results are mixed about the role of *FTO* in AN (Jonassaint et al. 2011, Müller et al. 2012).

Given that extreme weight dysregulation is the core feature of AN, it is striking that the majority of known genes involved in weight regulation have not yet been explored in association studies with AN (Rask-Andersen et al. 2010). It will be important to explore these genes if, in fact, some of these genetic variants may influence weight dysregulation in both directions, namely overweight and underweight. If, however, the directionality of dysregulation reflects different underlying processes, we may find little overlap in genes that influence obesity and AN.

Other Genes

DNA: deoxyribonucleic acid

Brain-derived neurotrophic factor (*BDNF*) plays an essential role in brain development and learning and memory, and also appears to play a role in mood, eating, and weight. Serum BDNF concentrations are lower in individuals with AN compared with normal-weight controls (Nakazato et al. 2003), and animal models have shown that *BDNF* induces appetite suppression and body weight reduction. The Val66Met polymorphism is the most frequently examined polymorphism of the *BDNF* gene, and it has been implicated in several psychological disorders, including AN. Association studies and transmission disequilibrium studies have implicated the Met66 variant in AN (Dmitrzak-Weglarz et al. 2007, Ribasés et al. 2004), whereas additional studies only found an association between Met66 and restricting-type AN (Ribasés et al. 2003, 2005). However, a recent analysis of the Val66Met polymorphism and AN, including a meta-analysis of nine published studies, indicates that this variant is not associated with AN (Brandys et al. 2011). Although results of the initial meta-analysis suggested increased odds of the Met66 variant in AN, a reanalysis of the data—excluding a report that was identified to be overly influential—rendered findings nonsignificant. A 2012 association study, not included in the meta-analysis, also suggests no association between Val66Met and AN in a Japanese sample (Ando et al. 2012). However, additional candidate genes associated with *BDNF* have been associated with AN and AN restricting type.

SK3, a calcium-activated potassium channel, controls pacemaker frequency and has also been implicated in learning and memory. The gene encoding SK3 contains an area of CAG repeats that has been associated with psychological disorders, including AN. Specifically, the longer CAG repeat region is significantly associated with AN and shows preferential transmission to individuals with AN in transmission disequilibrium tests (Koronyo-Hamaoui et al. 2002, 2004, 2007).

Tumor necrosis factor-α is an inflammatory cytokine that is involved in anorexia during cancer, and plasma TNF levels are increased in patients with AN (Nakai et al. 1999). However, findings have been mixed in regard to association between TNF-α polymorphisms and AN, with only one study showing a significant association (Kanbur et al. 2008).

Although findings have been mixed, *BDNF*, specifically the Val66Met variant, has shown many significant associations with AN. There is also evidence to suggest that this association may be limited to AN restricting type, which could account for the variability of findings across reports and for the null findings of the meta-analysis, which did not tease diagnosis apart by type. A complete model for how dysregulated *BDNF* or SK3 function increases risk for AN has not yet been developed. However, an interplay between the estrogen and 5-HT systems and *BDNF* has been hypothesized (Klump & Culbert 2007). As noted above, estradiol is involved in the expression of 5-HT genes as well as *BDNF* genes. Therefore, estradiol may be the mediating factor between 5-HT and *BDNF* for AN risk.

Summary and Future Directions

Molecular genetic studies of AN have been inconsistent and are plagued by nonreplications and small sample sizes. The majority of studies in this area have been underpowered, challenging our ability to determine whether null results are truly negative or simply a result of inadequate statistical power. Even the studies that have used genomewide approaches have been inconclusive, with limitations including reliance on deoxyribonucleic acid (DNA) pooling and approximately 23,000 microsatellite markers (Nakabayashi et al. 2009) and use of a small sample size (Wang et al. 2011)—a plausible explanation for no results reaching genomewide significance. The sample and diagnostic definition of AN also vary across studies. Indeed, due to the low prevalence of AN, most studies combine the restricting and binge eating/purging types, which may confound results.

Because of these limitations, it is difficult to make definitive conclusions about the specific genes that influence risk for AN, and GWAS with much larger sample sizes and homogenous definitions must be conducted in order to fully elucidate the genetic architecture of AN (Sullivan et al. 2012).

BULIMIA NERVOSA

A number of controlled family investigations reveal that relatives of probands with either AN or BN have significantly elevated proportions of AN and BN compared to relatives of unaffected controls (Lilenfeld et al. 1998, Strober et al. 2000). Investigations examining the prevalence of only BN in family members of probands with the disorder are lacking. Twin studies have yielded heritability estimates for BN ranging from 28% to 83% (Bulik et al. 2000). Only one linkage study has been conducted for BN examining 308 multiplex families with eating disorders that were identified through a BN proband. Significant linkage was observed on chromosome 10, and another region on chromosome 14 met the criterion for genomewide-suggestive linkage (Bulik et al. 2003a). The majority of molecular genetic investigations in BN are candidate gene association studies. As with AN, we categorize our results based on the specific system the gene is involved in.

Serotonergic Genes

Abnormalities in peripheral 5-HT uptake have been observed in individuals with BN who are both acutely ill and recovered (Stamatakis & Hetherington 2003, Steiger et al. 2011), suggesting that these alterations may be trait features of the diagnosis rather than the result of abnormal eating patterns. As with AN, the majority of research investigating the genetics of the 5-HT system in BN have focused on the *5-HTTLPR* transporter gene and the *5-HT2A* receptor gene.

Several meta-analyses (Calati et al. 2011, Lee & Lin 2010) have examined the association between *5-HTTLPR* polymorphisms and BN, with the most recent published in 2012 (Polsinelli et al. 2012). In contrast to the findings on AN, meta-analyses uniformly suggest no significant association between *5-HTTLPR* polymorphisms and BN. Findings regarding an association between BN and other 5-HT genes, such as the promoter polymorphism −1438G/A of the *5-HT2A* receptor gene, have been mixed and largely inconclusive. Two investigations have reported a significant association between polymorphisms of −1438G/A and BN; however, findings have been inconsistent. One study found a significant association between the A allele and BN (Ricca et al. 2002), whereas another reported that the G allele was significantly more frequent in individuals with BN than controls (Nishiguchi et al. 2001). Further, several additional investigations have failed to find an association (Scherag et al. 2010).

Although limited by small sample sizes, these investigations preliminarily suggest a lack of support for involvement of the promoter polymorphism −1438G/A of the *5-HT2A* receptor gene in liability to BN. The Thr25Asn 102 T/C and His452Tyr polymorphisms of the *5-HT2A* receptor gene, as well as the Tyr129Ser polymorphism of the *5-HTR3B* receptor gene, have also been explored in one study for the relation to BN, and findings have been nonsignificant (Scherag et al. 2010). Although the 5-HT system is the most thoroughly investigated for genetic liability to BN, research in this area has largely been characterized by a parade of nonreplicated studies. The occasional significant findings that have been documented for the *5-HTTLPR* tend to wash out in meta-analyses.

Dopaminergic Genes

The dopaminergic system has also been of interest in the pathophysiology of BN; however, few investigations have examined the association between genetic polymorphisms of the DA system and

BN. Nisoli et al. (2007) examined the prevalence of the TaqA1 polymorphism of the *DRD2* gene in individuals affected by a variety of eating disorders, including BN, and in control individuals. Results revealed no significant association between the A1+ allele in BN for either the A1/A1 or A1/A2 genotypes. Although abnormalities observed within the DA system have been observed through neuroimaging investigations (Tauscher et al. 2001), it is unknown whether these changes are a biomarker of disease or a consequence of the illness. Currently, molecular genetics research suggesting that genetic polymorphisms in the DA system contribute to a diagnosis of BN is lacking.

SNP: single-nucleotide polymorphism

Appetite Regulation Genes

A small number of investigations have explored the role of genetic variations in ghrelin and ghrelin receptor genes in BN, with mixed findings. In one investigation including women with BN and normal weight controls, Monteleone et al. (2006b) failed to find a significant association between either the Arg51Gln or the Leu72Met polymorphism of the ghrelin gene and BN.

A second large case-control study (Cellini et al. 2006) examined three common variants in ghrelin genes (Gln90Leu, Leu72Met, and Arg61Gln) in women with eating disorders and control individuals and also failed to find any significant associations. A third study, by Miyasaka et al. (2006), explored the 171C polymorphism of the ghrelin receptor [growth hormone secretagogue receptor (*GHSR*)] gene in Japanese individuals with eating disorders and age- and gender-matched controls. Results revealed a significant association of the *GHSR* gene 171T/C polymorphism and BN. Specifically, the CC type of the *GHSR* gene was significantly more frequent in individuals with BN than control participants. The authors conclude that the CC type of the *GHSR* gene polymorphism may be a risk factor for BN, although additional well-powered studies are needed to replicate this finding.

Although genes involved in appetite regulation are intuitive genetic candidates to explore in BN liability, studies thus far have been limited, and the majority of findings null. Many appetite-regulating genes that are plausible candidates for the pathogenesis of BN have not yet been explored. For example, studies investigating polymorphisms of leptin genes have been very limited, and findings have been nonsignificant (Hinney et al. 1998). Given the dearth of research on the association between genes within the appetite system and BN, little can be concluded.

Genes Influencing Food Intake

Few studies have examined the association between genetic polymorphisms within the estrogen system and BN. One of the earliest studies examined the association between the estrogen receptor beta gene (*ERβ*) and individuals with BN (Rosenkranz et al. 1998). *ERβ* is located on chromosome 14q, which is within the region suggestive of genomewide linkage (Bulik et al. 2003a). However, Rosenkranz et al. found no significant associations between sequence variants in the *ERβ* and BN. A study by Nilsson et al. (2004) also explored the association between three polymorphisms of *ERβ* and BN. An association was found between BN and the 1730 G→A and *ERβ* cx +56 G→A *ERβ* gene variants, leading the authors to conclude that their findings suggest a possible role of *ERβ* and neighboring genes in the pathogenesis of BN.

The cannabinoid system has also been hypothesized to contribute to the liability to BN. Type 1 cannabinoid receptor (CB1R) dysregulation has been found in BN in the insular cortex (Gerard et al. 2011). Monteleone et al. (2009) examined the association between polymorphisms of the gene encoding *CNR1* and the gene coding the fatty acid amide hydrolase (FAAH), the major degrading enzyme of endocannabinoids. Results revealed that the *CNR1* 1359 G/A single-nucleotide polymorphism (SNP) and the *FAAH* cDNA 385C to A SNP were significantly associated with

BN. Specifically, compared to controls, individuals with BN showed significantly higher frequencies of the AG genotype and the A allele of the *CNR1* 1259 G/A SNP. Individuals with BN were significantly more likely to have the AC genotype and the A allele of the *FAAH* cDNA 385C to A SNP relative to controls. The authors conclude that this preliminary evidence, which suggests the involvement of genes within the endocannabinoid system, necessitates replication and additional investigations of other SNPs of both endocannabinoid genes.

As binge eating is a core feature of BN, it is intuitive that genes related to food intake are explored as candidates for influencing liability to BN. Although research has been sparse and little can be concluded without well-powered replication studies, preliminary results suggest that genetic polymorphisms of the estrogen and endocannabinoid systems may be implicated in BN. Nonetheless, it is almost certain that these genes do not tell the entire story and that other systems are involved, acting both independently and in tandem. For example, the neural networks affected by both estrogens and 5-HT significantly overlap and have been hypothesized to act synergistically with regard to their contribution to BN (Hildebrandt et al. 2010). Additional research is needed to explore the role of genes related to food intake in liability to BN, with particular emphasis on the interaction between genetic systems.

Other Genes

Several additional genes associated with body weight and eating regulation have been hypothesized to play a potential role in the etiology of BN. One study screened 81 participants with BN for mutations in the *MC4R* gene and found that one extremely obese patient had a haplotype insufficiency mutation (Hebebrand et al. 2004). Genetic variants of *BDNF* have also been implicated in BN. Specifically, Ribasés et al. (2004) found that the −270C/T polymorphism and the Val66Met variant, both located in the promoter region of the *BDNF* gene, were significantly associated with BN. However, another investigation failed to replicate the significant association between theVal66Met polymorphism and BN (Friedel et al. 2005). The role of the common *FTO* gene SNP rs9939609 in BN has also been explored (Müller et al. 2012), and results revealed a significant association between the obesity-risk A allele and BN. Although these investigations provide interesting preliminary data, findings are not conclusive, and contradictory findings are abundant.

Summary and Future Directions

Although twin studies suggest consistently that BN is influenced by genetic factors, molecular genetic studies have not yet been adequate in scope or design to identify susceptibility loci. Conducting an adequately powered GWAS of BN is a reasonable next step that could guide future genetic explorations. Further, pending the collection of large sample sizes, future research should consider examining genetic liability by symptom cluster within the BN diagnosis. Individuals with BN who engage in self-induced vomiting may differ genetically from those who engage in excessive exercise or another type of purging behavior. Addressing these gaps in the literature base would fill in the next pieces of the puzzle necessary to further elucidate the genetic underpinnings of BN.

BINGE EATING DISORDER

BED is receiving increasing scientific attention. However, because the disorder has been more recently operationalized than AN and BN, less research on the genetics of BED has emerged. Although nascent, extant family, twin, and molecular research largely suggests familial and genetic factors influence risk.

Family Studies

A small number of family studies have been conducted for BED. In one of the first family studies, Fowler & Bulik (1997) compared 20 obese women with BED and 20 obese nonbinge-eating control women on a number of variables including family psychiatric history. The percentage of participants with BED who reported having at least one first-degree relative who also had BED was significantly greater than was the percentage for control participants. A large direct-interview family study (Hudson et al. 2006) interviewed overweight or obese individuals with BED and without BED, along with all available first-degree relatives. BED aggregated strongly in families, independent of obesity. Similarly, Lilenfeld et al. (2008) conducted a family history study assessing the prevalence of comorbid psychopathology (including BED) in nontreatment-seeking women with BED and control women without BED, and their first-degree relatives. Significantly increased rates of BED were reported in first-degree family members of individuals with BED. With the exception of a family study (Lee et al. 1999) that failed to show a significant familial relationship for BED, the majority of research suggests that BED is familial. This has been further corroborated by twin studies.

Twin Studies

Two population-based twin studies have estimated the heritability of the DSM-IV diagnosis of BED in a combined-sex model (Javaras et al. 2008, Mitchell et al. 2010). In the first investigation, Javaras et al. (2008) estimated the heritability of BED in men and women from two samples (one comprising 150 overweight or obese individuals with lifetime DSM-IV BED, 150 overweight or obese individuals without lifetime DSM-IV BED, and 888 of their first-degree relatives from the United States, and one including 7,831 twins from Norway). In the US sample, BED aggregated in families, with 45% liability due to additive genetic effects and 41% due to unique environmental factors. Findings from the Norwegian sample were similar, with 39% liability due to additive genetic effects and the rest of the variance attributable to unique environmental factors. A second investigation by Mitchell et al. (2010) included same-sex female twins from the United States ($N = 1{,}224$) and reported a heritability estimate of 45%—identical to the first report.

Molecular Genetic Studies

Candidate gene association studies of binge eating have examined neurotransmitter systems or genetic variants implicated in appetite and obesity, including the 5-HT and DA systems.

Serotonergic genes. Only one known small study has investigated the role of the *5-HTTLPR* polymorphism in BED. Monteleone et al. (2006c) conducted a case control association study with obese or nonobese women with BED and normal-weight control women without BED. The homozygous long-allele and the heterozygous long-allele genotypes of the *5-HTTLPR* gene were found to be significantly more frequent in individuals with BED. Although results suggest that *5-HTTLPR* may contribute to the genetic susceptibility to BED, the authors note that results should be considered preliminary, as this study was limited by a relatively small sample size.

Dopaminergic genes. Several investigations have examined genetic polymorphisms of the DA system in BED, with a particular focus on the *DRD2* gene. A 2008 study (Davis et al. 2008) included individuals with BED, normal-weight individuals, and obese control individuals who were genotyped for several DRD2 SNPs including Taq1A, −141 Ins/Del, and C957T.

However, no significant differences were found between the three groups with regard to genotype frequencies for any of the SNPs. In a second study by Davis et al. (2009), genetic comparisons were made between three functional polymorphisms of the *DRD2* gene (Taq1A, C957T, −141 Ins/Del) including individuals with BED and obese controls. Significantly more individuals with BED had the G allele of Taq1A (associated with increased DA function) compared to obese controls. No significant differences were found between the two groups for the other two polymorphisms.

A larger investigation by the same group (Davis et al. 2012) compared 230 obese individuals with and without BED on five genotype markers of the *DRD2* receptor: Taq1A, −141C Ins/Del, C957T, rs12364283, and rs6277. Individuals with BED were significantly more likely to be homozygous for the A2 allele of the Taq1A polymorphism and to be homozygous for the T genotype of the C957T marker, both reflecting enhanced DA transmission. The authors conclude that their findings suggest that obese adults with BED differ biologically from obese adults without BED and that BED may be characterized by hypersensitivity to reward.

Overall, studies exploring the association between polymorphisms of the *DRD2* gene and BED have been inconsistent. However, the first two studies previously discussed had small sample sizes and were likely underpowered. The most recent investigation (Davis et al. 2012), which revealed significant findings, has had the largest sample size to date. Although this study provides interesting data that suggest a possible role of the *DRD2* polymorphisms Taq1A and C958T in BED, additional large-sample replication studies are needed.

Other genes. Additional genetic factors have been explored for their potential role in BED. However, investigations have been sparse and replication is lacking. The 10 *MC4R* variant that has been previously investigated for its relation to BED, secondary to its known role in severe obesity. Branson et al. (2003) sequenced the complete *MC4R* coding region in 460 obese individuals and 25 normal-weight controls without a self-reported history of dieting. Twenty-four severely obese individuals and one normal-weight individual had a genetic mutation in *MC4R*, and all of these individuals met criteria for DSM-IV BED. On the other hand, 14.2% and 0% of obese and normal-weight individuals without an *MC4R* mutation met DSM-IV criteria for BED, respectively. The authors propose that *MC4R* may be a candidate gene for BED; however, Hebebrand et al. (2004) failed to find an association between binge eating behavior (all BED criteria required except duration) and variants of the *MC4R* gene. A study by Potoczna et al. (2004) revealed findings similar to those of Branson et al. In this investigation of 300 obese individuals undergoing laparoscopic gastric binding, 19 carriers of the *MC4R* variant were identified, and all had a diagnosis of BED, compared with 18.1% of noncarriers.

A significant association between the Leu73Met polymorphism of the ghrelin gene and BED has also been found (Monteleone et al. 2007). This investigation examined the association between two variants of the ghrelin gene, Arg51GIn and the Leu73Met, in BED obese and nonobese women and in normal-weight controls. The Leu72Met variant of the ghrelin gene occurred significantly more often in individuals with BED and was associated with a moderate but significant risk of developing BED in a small sample. Another investigation (Davis et al. 2009) found that the G allele of the A118G polymorphism of the *ORMP1* gene occurred with greater frequency in obese individuals with BED than in obese individuals without BED. The relation between BED and several other candidate genes, including the Val66Met polymorphism of *BDNF* gene (Monteleone et al. 2006d) and the 3111T/C polymorphism of the *CLOCK* gene (Monteleone et al. 2006a), have also been explored and revealed unremarkable and nonsignificant findings.

Summary and Future Directions

Although family and twin studies suggest the role of genetic factors in BED, candidate gene studies have not clearly confirmed the involvement of any one gene or genetic pathway. One particular point of consideration is that the majority of these investigations have been conducted in overweight or obese individuals. Individuals with BED are frequently overweight or obese; however, this is not always the case (de Zwaan 2001, Yanovski 2003). The potentially confounding role of obesity status should be considered in future investigations.

THE HERITABILITY OF EATING DISORDER SYMPTOMS AND TRAITS

Twin and molecular genetic studies have also shed light on the heritability of component symptoms (e.g., binge eating, self-induced vomiting) and dimensional measures of core features of eating disorders (e.g., restrained eating or drive for thinness). The value of this approach is that many eating disorder symptoms are transdiagnostic and exist on a continuum; thus, understanding genetic contributions to them may inform classification.

DSM-IV Criteria

An item-factor approach (Neale et al. 2006) has been used to examine the genetic and environmental contributions to isolated diagnostic criteria comprising AN, BN, and BED (Mazzeo et al. 2009, 2010; Mitchell et al. 2010). Similar to the univariate model, in an item-factor model, the variance of the latent trait (or diagnosis) is partitioned into additive genetic, shared environmental, and unique environmental influences. In addition to obtaining information about the genetic and environmental contributions to the latent trait (i.e., eating disorder diagnosis), heritability estimates and confidence intervals (CIs) for these estimates can be obtained for each individual item (i.e., diagnostic criterion). These estimates provide information about the extent to which genetic and environmental factors influence each individual criterion and how strongly each item is related to the latent diagnostic trait.

An item-factor approach to AN was conducted in a sample of female Norwegian twins (Mazzeo et al. 2009). For a number of items (i.e., whether participants had ever lost a lot of weight, how participants felt about themselves at their lowest weight, lowest BMI), heritability estimates ranged from 29% to 34%. Heritability estimates of items related to weight concerns were lower, with estimates between 18% and 23%. Additive genetic effects contributed 16% of the variance in amenorrhea, which was most strongly influenced by unique environment (including measurement error). In addition, amenorrhea did not load highly on the latent AN factor. These findings are consistent with the proposal to remove amenorrhea from the DSM-5 diagnostic criteria for AN and indicate this criterion is likely of minimal value to the diagnosis (Bulik et al. 2007a). When the same approach was applied to BN by Mazzeo et al. (2010), the highest heritability estimates were reported for criteria assessing compensatory behaviors, namely excessive exercise (35%) and vomiting (53%). All inappropriate compensatory behaviors loaded fairly high on the latent construct, with factor loadings ranging from 0.51 to 0.82. Factor loadings for the binge-eating items (ever had eating binges, eating out of control during eating binges, and frequency of binges per month) ranged from 0.65 to 0.75, and heritability estimates ranged between 34% and 41%. Other psychological symptoms, such as undue influence of weight on self-evaluation, yielded lower heritability estimates. Clearly, the diagnostic criteria for BN comprise symptoms that are neither equally heritable nor equally central to the construct of BN. The same approach applied to BED (Mitchell et al. 2010) yielded heritability estimates across individual diagnostic

criteria items ranging from 29% (absence of compensatory behaviors) to 43% (binge eating). Factor analysis indicated that each DSM-IV criterion was strongly related to BED, capturing a significant proportion of variance in the latent construct. Taken together, results from item-factor models highlight the importance of continuing to examine eating-disordered behavior at the symptom level rather than focusing only on aggregate diagnoses. Symptoms found to be particularly heritable include extreme weight loss, fear of weight gain, and feeling fat for AN; vomiting for BN; and binge eating for both BN and BED.

Eating Disorder Symptoms and Traits

Relevant constructs that have been explored in twin studies include restrained eating, intentional weight loss, drive for thinness, binge eating, and self-induced vomiting.

Restrained eating. Restrained eating, a form of attempted weight regulation marked by cognitive control over food intake, has been associated with the development of disordered eating in prospective studies (Fairburn et al. 1998, Stice & Whitenton 2002). Twin studies of two widely used measures of restrained eating, the restraint scale (RS; Herman & Polivy 1980) and the restraint subscales of the Three Factor Eating Questionnaire (TFEQ; Stunkard & Messick 1985), have resulted in conflicting findings. When adjusting for BMI, the heritability of restraint as measured by the RS was estimated to be 43% (Schur et al. 2009), whereas another study measuring cognitive restraint by the TFEQ yielded a heritability estimate of 0% (95% CI: 0, 0.30; Neale et al. 2003).

Several association studies have investigated genetic factors involved in restrained eating and implicated the 5-HT and olfactory systems. Specifically, Sanhueza et al. (2011) reported a significant association between the short-allele homozygous genotype for the *5-HTTLPR* polymorphism of the *SLC6A4* gene and restrained eating. In a study by Choquette et al. (2012), a sequence variant (rs2878329 G>A) of the olfactory receptor gene *OR7-4D* also showed a significant association with reduced cognitive dietary restraint.

Overall, twin studies examining the heritability of restrained eating have revealed inconsistent findings, likely secondary to a lack of construct reliability and validity across studies (Heatherton et al. 1988). Well-established measures of cognitive restraint exist; however, these instruments capture slightly different characteristics of the behavior (Schur et al. 2009). Further, a substantial percentage of individuals with eating disorders do not report high scores on measures of dietary restraint (Peñas-Lledó et al. 2009). Although molecular genetics studies of restrained eating have implicated 5-HT and olfactory genes, replication studies are lacking.

Intentional weight loss. Intentional weight loss reflects the attempt to restrict food intake and avoid fatty and calorie-dense foods. One investigation estimated the heritability of intentional weight loss to be 66% in women and 38% in men (Keski-Rahkonen et al. 2005b). A bivariate twin study (Wade et al. 2009), examining the degree of shared genetic and environmental factors between lifetime intentional weight loss and overeating in women, reported a slightly lower heritability estimate of 30% for intentional weight loss. Together these investigations suggest that intentional weight loss is at least somewhat heritable. Molecular genetic approaches have not been applied to intentional weight loss.

Drive for thinness. Drive for thinness, as measured by the Eating Disorder Inventory (EDI; Garner et al. 1984), assesses excessive attention to dieting and preoccupation with weight and is considered to be a core dimensional feature of many eating disorders. Rutherford et al. (1993)

investigated drive for thinness in 147 monozygotic and 99 dizygotic female twins. Additive genetic factors accounted for 44% of the variance in phenotype liability. In a study of Finnish twins (Keski-Rahkonen et al. 2005a), additive genetic factors accounted for 50.1% of the variance in drive for thinness for females, but only 1.2% of the variance in males, suggesting considerable sex differences in this trait.

Several molecular genetics investigations of drive for thinness have been conducted and implicate the 5-HT and DA systems. In a 2002 genomewide linkage analysis, Devlin et al. (2002) incorporated EDI drive for thinness as a covariate in an affected sibling pair linkage analysis. Drive for thinness was selected as a covariate because preliminary analyses indicated that there was a subset of affected sibling pairs who were extreme, relative to most individuals in the population, and highly concordant for this trait. Incorporating this variable both alone and in combination with a second trait (obsessionality) yielded two regions suggestive of linkage on chromosomes 1 (drive for thinness and obsessionality) and 13 (drive for thinness).

Association studies of drive for thinness have also been conducted. Frieling and colleagues (2006) focused on the 5-HT transporter promoter *5-HTTLPR* in female inpatients with eating disorders. Carriers of the deletion of *5-HTTLPR* reported significantly higher scores on the EDI drive-for-thinness subscale. In a mixed sample of women with AN and BN, Mikolajczyk et al. (2010) found that individuals with the AA genotype (associated with lower COMT activity) of the Val66Met polymorphism of the *COMT* gene scored higher than controls in drive for thinness.

DRD2 has also been implicated in drive for thinness. Nisoli et al. (2007) found that the Taq1A polymorphism was associated with higher scores on the EDI drive for thinness in eating disorder patients without a history of substance abuse. Most recently, a GWAS of eating disorder behaviors, including drive for thinness, was conducted (Boraska et al. 2012). In total, 2,698 individuals were meta-analyzed for drive for thinness; however, no SNPs met significance. Although association studies have revealed significant findings, sample sizes are small and replication studies are lacking. Drive for thinness is a core feature of many eating disorders, yet the state of the science is such that we currently do not understand the genes responsible for this central trait or the manner in which they are responsible.

Binge eating and self-induced vomiting. An early study conducted by Sullivan et al. (1998) applied bivariate twin modeling to examine the nature of the association between binge eating ("during which you ate a lot of food in a short period of time") and self-induced vomiting ("as a means of controlling shape or weight") in females. The heritability estimates for binge eating and vomiting were 46% and 72%, respectively, and the genetic correlation between them was 0.74. Wade et al. (2008) applied an analogous bivariate analysis to a sample of Australian twins. They defined binge eating as occurring at least twice a week for three months, with no binge-free intervals of more than two weeks. Heritability estimates for binge eating and vomiting (17% and 8%, respectively) were substantially lower than those reported by Sullivan et al. (1998). One possible explanation for this discrepancy is the use of a stringent frequency criterion in the Wade et al. investigation, which may have resulted in a substantially lower prevalence estimate for binge eating (3.8% versus 23.6%). The prevalence estimate reported by Wade et al. for self-induced vomiting was also slightly lower (3.8%) than that reported by Sullivan et al. (4.8%). CIs across studies for both binge eating and vomiting did not overlap, suggesting a statistically significant difference between the estimates.

A similar bivariate approach examined the nature of the relationship between binge eating and obesity (Bulik et al. 2003b) and reported a heritability estimate of 49% for binge eating and 86% for obesity. In addition, a modest genetic correlation (0.34) was found, suggesting that some of the same genetic factors may influence both conditions.

Finally, Root et al. (2010) investigated the heritability of binge eating and night eating using a bivariate twin design. For women, the heritability estimates for binge eating and night eating were 70% and 35%, respectively, and the genetic correlation between the two traits was 0.66. For men, the estimates were 74% and 44%, respectively, and the correlation could not be calculated.

rGE: gene-by-environment correlation

One linkage analysis specifically incorporated vomiting into the design by selecting a subset of families with a BN proband in which at least two affected relatives reported self-induced vomiting (Bulik et al. 2003a). Significant linkage was reported on chromosome 10 for this phenotype. Authors conclude that chromosome 10 may harbor important susceptibility loci for BN. These results further underscore the value of self-induced vomiting as an important trait for BN. In part, this may be due to the ease of measurement. Self-induced vomiting is a clearly defined behavioral indicator that may have less error of measurement than binge eating and other dimensional measures of disordered eating. One Dutch candidate gene study reported that the minor C allele of *TPH2* (rs1473473) was associated with self-induced vomiting in patients with eating disorders (Slof-Op't Landt et al. 2011).

In summary, a focus on the component behaviors of binge eating and self-induced vomiting is a valuable approach to understanding the genetics of eating disorders. First, especially self-induced vomiting is readily measurable, and with the exception of the results of Wade et al. (2008), heritability estimates have been fairly high. Second, binge eating is a transdiagnostic feature of eating disorders, being a core symptom in AN binge eating/purging type, BN, and BED, and therefore carries important information about a considerable majority of individuals who suffer from eating disorders. Thus, future investigations should consider the value of exploring these readily measurable and cross-cutting variables rather than simply relying on diagnostic categories.

Summary and Conclusions

Genetic studies at the symptom and trait levels are important for furthering our understanding of the etiology of disordered eating from a biological perspective. These investigations may provide critical information about novel pathways that lead to core eating disorder symptoms and behaviors. Twin studies have revealed that eating disorder symptoms are differentially heritable. Although relatively high heritability estimates have been reported for some eating disorder symptoms (e.g., binge eating and self-induced vomiting), estimates have varied widely across studies. The number of association studies comparing populations of eating-disordered patients and controls on the allele or haplotype frequencies of selected candidate genes is substantial; however, this work is characterized by methodological inconsistencies and few reliably replicated findings. Optimizing existing samples with genomewide data by exploring symptoms and traits may yield more refined genetic information than analyses of diagnostic criteria only.

FUTURE DIRECTIONS IN EATING DISORDERS AND GENETICS RESEARCH

Genes and Environment: Interactions and Correlations

In all of the reported twin studies, additive genetic factors clearly did not act alone in influencing liability to eating disorders. The working hypothesis is that genetic and environmental factors work in concert to influence risk for eating disorders. Gene-by-environment correlations (rGE) and G × E are thought to be essential to understanding how and when genetic factors operate in eating disorders.

An rGE occurs when there is a correlation between one's genotype and exposure to an environment (Kendler & Prescott 2006). In other words, environmental exposure is influenced by

genetic factors. rGE arises in three ways (Scarr & McCartney 1983). Passive rGE occurs when the effects of the parental genotype are correlated with the family environment to which offspring are exposed. Evocative rGE occurs when individuals evoke reactions from others consistent with their genetic predisposition. Finally, active rGE refers to the active selection of environments based on genetic propensities.

rGE is relevant to eating disorder risk in that the genetic risk for eating disorders may be expressed through exposure to high-risk environments, and the exposure to these environments may be influenced by genetic factors. For example, individuals who have a genetic propensity for an eating disorder may be more likely to expose themselves to high-risk environments (i.e., active rGE), such as engaging in sports or activities that place an extreme importance on weight and shape (e.g., gymnastics, wrestling, ballet). Further, individuals who inherit a genetic propensity to eating disorder risk may also be exposed to disordered-eating attitudes and behaviors in their family environment, from parents who themselves may suffer from an eating disorder (i.e., passive rGE). Despite the relevance and importance of rGE to the etiology of eating disorders, studies have not addressed this question empirically. This is likely due to the difficulty in statistically distinguishing between the genetic and environmental factors involved in the correlation and between the three different rGE mechanisms as well as the need for prospective data.

G × E interactions occur when genetic propensities are expressed differently in differing environments (Kendler & Prescott 2006). In other words, G × E interactions occur when genetic factors influence response to an environment or when the environment enhances or buffers genetic risk. G × E interactions are particularly relevant to the study of eating disorders, given Western society's cultural ideal of extreme slenderness (Bulik 2005, Striegel-Moore & Bulik 2007). Although exposure to this thin ideal is virtually ubiquitous, not all young girls develop an eating disorder. Exposure to this pressure may increase risk for an eating disorder only in those girls with a genetic predisposition toward an eating disorder. In other words, girls with a genetic predisposition toward an eating disorder may be more likely to internalize the cultural thin ideal and be rewarded by engaging in dieting behaviors. In contrast, girls with less of a genetic predisposition may engage in dieting behaviors in response to the cultural thin ideal but find this experience aversive and thus return to normal eating (Bulik 2005). In essence, exposure to the cultural thin ideal and its internalization may serve as an environmental trigger for individuals with a greater genetic propensity toward eating disorders.

In studies examining G × E, the interactions between the variables of interest are examined statistically to ascertain whether genetic propensity is expressed differently in various degrees of the environmental risk factor. One twin study examined whether the heritability of eating disorder symptoms changed at differing levels of exposure to an environmental factor, namely divorce. The heritability of body dissatisfaction was significantly higher in individuals from divorced versus intact families (Suisman et al. 2011). Further, the heritability of eating disorder symptoms increases substantially in girls with higher levels of estradiol and after puberty (Culbert et al. 2009; Klump et al. 2007, 2010a,b). Although estradiol levels and puberty are not environmental factors in the traditional sense, these findings highlight the potential for modifiers of the genetic risk for eating disorders.

Molecular genetic study designs have also explored the role of G × E interactions in eating disorder risk, with a majority of studies focusing on BN. In this framework, specific candidate genes and environmental factors are chosen based on their hypothesized role in eating disorder risk. Several studies have explored the interaction between *5-HTTLPR* and childhood maltreatment on psychopathological traits common to women with BN. In general, results suggest a significant interaction between the *5-HTTLPR* short allele and childhood maltreatment such that women with BN who are carriers of the short allele and experienced childhood maltreatment exhibit increased

psychopathological traits (i.e., sensation seeking, insecure attachment, dissocial behavior; Steiger et al. 2007, 2008, 2009) Further, an interaction between the *DRD1* Taq1A polymorphism and childhood sexual abuse was also reported for women with BN. Carriers of the Taq1A risk allele who experienced childhood sexual abuse exhibited higher scores on sensation seeking compared to those without the risk allele (Groleau et al. 2012). Finally, a significant G × E interaction was observed between season of birth and the hypofunctional 7-repeat allele of *DRD4* for maximum lifetime BMI in women with BN (Levitan et al. 2010).

One study has explored G × E interactions for AN, addressing whether there is an interaction between *5-HTTLPR* and a number of environmental factors (Karwautz et al. 2011). A significant interaction was observed between the short allele and parenting style such that those who reported experiencing problematic parenting styles (e.g., parental criticism, parental control, parental high expectations) and who were carriers of the short allele were at increased vulnerability for AN. Further, as the number of problematic parenting styles increased, the risk for AN in the short-allele homozygous group increased twofold.

Finally, as the genetic etiology of eating disorders is likely complex and involves the interaction of many genes, it is also important to consider G × G interactions. Three reports have explored this possibility for AN. A synergistic effect was observed between the *5-HTTLPR* and monoamine oxidase (*MAOA*) transporter genes such that individuals homozygous for the short allele of *5-HTTLPR* who also had a long allele of the *MAOA* gene were eight times more likely to have AN than individuals without a *5-HTTLPR* short allele (Urwin & Nunn 2005). Additionally, having the *MAOA* long allele doubled the risk for developing restricting type AN in individuals who are also homozygous for the long allele of the *SL6A2* polymorphism of the NE transporter region (Urwin et al. 2003a). An investigation of a G × G interaction between *5-HTTLPR* and the *SL6A2* polymorphism found no significant interaction for AN (Urwin et al. 2003b). Finally, a significant interaction between the exon 3 VNTR polymorphism of *DRD4* and the Val66Met polymorphism of the *BDNF* gene was observed for maximal lifetime BMI in women with BN (Kaplan et al. 2008).

Together, these findings highlight the importance of integrating genetic and environmental factors in research rather than examining each in isolation. It is likely that environmental factors alter gene expression, and these same genetic factors may increase vulnerability to experiencing these environmental factors. Further, although these G × G interaction studies are intriguing, ultimately much more complex and comprehensive system-based analyses will be required to fully elucidate the manner in which a number of genetic and environmental factors interact to influence risk. It is perhaps naïve to think that two selected genes out of the 23,000 or so known genes in the human genome would selectively and uniquely interact to influence risk for a complex trait like an eating disorder. These early investigations play a role in developing our thinking about how genetic factors could act in concert to influence risk, but they will ultimately be proven to be overly simplistic.

Epigenetics

Epigenetics focuses on heritable changes in gene expression, which are not caused by changes in DNA sequence but rather by environmental exposures (Petronis 2010). Although the epigenome has the ability to react and adapt to a rapidly changing environment, the actual genetic sequence does not. Epigenetic modifications may, however, be passed down to succeeding generations.

Epigenetics may inform the inconsistent associations found between eating disorder phenotypes and gene sequencing by identifying independent, environmentally induced mechanisms involved in the regulation of gene expression. For example, the exposure to different nutrients, drugs, or other exogenous compounds can affect the epigenome. Epigenetic processes may, for

example, lead to the increasing number of phenotypic differences between monozygotic twins across the life span. The study of epigenetics may contribute substantially to our understanding of genetic processes underlying complex traits (Petronis 2010).

The most widely studied epigenetic mechanisms involved in gene expression regulation are DNA methylation and histone modifications. DNA methylation consists of the addition of a methyl group at cytosine of the DNA template, resulting in an alteration in the gene expression patterns of cells. Histone modifications are covalent modifications of histone residues that can alter chromatin states. Gene regulation may have a repressing or activating effect (reviewed in Campbell et al. 2011).

Only a very small number of epigenetic studies in eating disorders exist. A team of German researchers focused on an array of genes including alpha synuclein (*AS*) gene, atrial natriuretic peptide (*ANP*), propiomelanocortin (*POMC*), and the *DAT*, and the *DRD2* and *DRD4* genes. The first study (Frieling et al. 2007) found that the *AS* gene was hypermethylated in AN but not in BN (despite presenting a similar trend). However, a second study by the same team reported the opposite pattern: The *ANP* gene was hypermethylated in BN but not in AN (Frieling et al. 2010). Indeed, *ANP* hypermethylation was characteristic of all individuals who purged, regardless of their eating disorder diagnosis. In their third study focusing on DNA methylation levels of the *POMC* gene, the authors found differences in the functionally relevant long *POMC* mRNA in individuals with active AN compared with individuals recovered from AN or controls (Ehrlich et al. 2010). A fourth study evaluating the methylation of the *DAT*, *DRD2*, and *DRD4* found higher methylation and gene expression of the *DAT* in patients with AN and BN than in controls. Additionally, AN showed hypermethylation of *DRD2*, but gene expression was down-regulated in AN and BN (Frieling et al. 2008).

Although all epigenetic studies in eating disorders have evaluated DNA methylation, many of the transcripts across the genome that do not encode proteins have not yet been empirically explored. Areas for future study include epigenetic changes that may increase risk of developing an eating disorder, such as perinatal or early development risk factors including maternal dietary patterns, under/overeating behaviors, stress, pubertal changes, or BMI changes (underweight and obesity).

Cross-Disorder Analyses

Psychiatric comorbidity raises fundamental concerns regarding diagnostic classification and whether psychiatric disorders are etiologically distinct or represent cross-diagnostic endophenotypes with common etiology (Williams et al. 2011). Currently, the major psychiatric disorders are delineated by descriptive criteria (signs and symptoms). It is widely suspected that clinically derived groupings may not "carve nature at the joints" with respect to underlying genetic architecture. As our understanding of genetic and neurobiological factors in psychiatric disorders advances, the boundaries between many disorders have become blurred (Huang et al. 2010, Williams et al. 2011).

GWAS have been remarkably successful in medicine and have shed new light on etiological considerations of psychiatric illnesses (Sullivan et al. 2012). An added value of GWAS might lie in their ability to identify susceptibility loci with pleiotropic effects that influence several psychiatric illnesses, thereby providing critical information for understanding diagnostic boundaries. Cross-disorder investigations, and particularly cross-disorder GWAS, are useful in identifying genotype-phenotype associations that are common to overlapping disorders with cross-cutting features, and such studies can assist with determining whether psychiatric disorders are etiologically distinct or share etiopathogenic roots. Cross-disorder investigations in psychiatry have revealed common

genetic influences across several psychiatric phenotypes including schizophrenia, bipolar disorder, and major depressive disorder (Huang et al. 2010, Williams et al. 2011).

Eating disorders are ideal candidates for inclusion in cross-disorder analyses because they are either comorbid or share core features with many psychiatric disorders, particularly with mood disorders. One major study found that more than 70% of AN cases and approximately 60% of BN cases have at least one additional comorbid Axis 1 disorder (Herzog et al. 1992). Lifetime Axis I comorbidities of up to 97% in individuals with eating disorders have also been reported (Blinder et al. 2006). The lifetime prevalence of mood disorders varies from 31% to 88.9% in individuals with AN and from 21% to 90% in individuals with BN (Godart et al. 2007). Moreover, there appears to be some shared genetic influence on depression and AN (Wade et al. 2000) and between depression and BN (Walters et al. 1992).

ADRs: adverse drug reactions

SSRIs: selective serotonin reuptake inhibitors

Other psychiatric disorders for which cross-disorder analyses would be sensible include autism spectrum disorders (Zucker et al. 2007), anxiety disorders (Swinbourne et al. 2012), obsessive-compulsive disorder (Altman & Shankman 2009), substance use disorders (Baker et al. 2010), and attention deficit-hyperactivity disorder (Biederman et al. 2007).

In the future, pending the collection of large sample sizes for genetic analysis, including eating disorders in cross-disorder analyses will be critical for the field. This approach would overcome the limitations of prior methodology by identifying shared genetic variants that transcend diagnostic boundaries and contribute to comorbidity. Single-phenotype association studies have already identified several genetic variants that are significantly associated with a number of psychiatric disorders (Hong et al. 2011, Hosák 2007). Cross-disorder analyses including multiple phenotypes would assist in identifying susceptibility loci that have pleiotropic effects and might reveal shared etiology and underlying biological mechanisms that could be targeted for developing improved treatments.

Pharmacogenetics

A review of the evidence base for the treatment of eating disorders reveals that the literature is particularly weak for the pharmacologic treatment of AN. Although the evidence base is stronger for BN and BED, a considerable number of individuals either do not respond to pharmacologic interventions or experience adverse drug reactions (ADRs; Aigner et al. 2011). Genetic variability is relevant for both pharmacokinetic and pharmacodynamic mechanisms, which are involved in the vulnerability to ADRs or the lack of therapeutic effect of drugs used for the treatment of psychiatric disorders (Malhotra et al. 2012).

Pharmacogenomics, or the study of how an individual's genetic makeup affects his or her response to medication, is a burgeoning field of research, particularly within psychiatry (Zandi & Judy 2010). Because psychotropic medications are often used as part of a multipronged approach to eating disorder treatment, a better understanding of pharmacogenomics may have important implications for drug treatment planning. To date, the efficacy of several drugs has been investigated in eating disorder treatment, including antipsychotics, antidepressants [selective serotonin reuptake inhibitors (SSRIs)], lithium, and opiate agonists. However, these medications have not demonstrated a clear and consistent therapeutic effect for AN (Ramoz et al. 2007). Although SSRIs may be more efficacious in treating BN and BED (Zhu & Walsh 2002), a substantial proportion of individuals with BN and BED either do not respond adequately or experience ADRs (Monteleone & Maj 2008).

The limited therapeutic effect and ADRs of psychotropic medication in eating disorder treatment may be due to individual differences in drug response, which may be the result of environmental and/or genetic variability (i.e., liver enzyme metabolism, brain neurotransmission, etc.). For example, SSRIs are partly metabolized by hepatic cytochrome P450 (CYP) enzymes. CYP

enzymes are encoded by genes, and some of them are polymorphic. Therefore, variation of DNA within these coding genes can affect the metabolic rate of certain drugs and the production of some metabolites. CYP2D6 and many other CYP enzymes (e.g., CYP2C9, CYPC19) show genetic polymorphisms and therefore present variability with regard to the enzyme hydroxylation capacity. One study observed an association between *CYP2D6* gene copy number distribution in individuals with eating disorders, who were observed to have an atypical allele distribution characterized by an increased frequency in individuals with two or more active genes and a decreased frequency in individuals with one or zero active genes (Peñas-Lledó et al. 2012). This pattern suggests increased CYP2D6 activity, which is relevant given the widespread use of CYP2D6 substrates and could be of significance not only for drug response but also for eating disorder vulnerability and outcome (suicide intent or antidepressant drug discontinuation), as recently reported (Peñas-Lledó et al. 2011, 2013).

Although research investigating the pharmacogenomics of eating disorders is in its earliest stages, understanding how the interaction of genetic and environmental factors influences response to pharmacological treatment is an important next frontier (Monteleone & Maj 2008). In the distant future, with sufficient progress in genetics, a stratified and ultimately personalized medicine approach could be applied; pharmacogenomically informed treatment guidelines could be developed for eating disorders in order to decrease ADRs and improve drug response by titrating dosages and treatment regimens, using pharmacogenetic information as a guide.

CLINICAL IMPLICATIONS

Understanding the interplay between the genetic and environmental factors that increase risk for an eating disorder has important implications for prevention, detection, early intervention, and treatment. The genes that influence a disorder do not necessarily have to be identified first in order for genetic research to have utility in the clinic. In fact, results of genetic research can have far-reaching impact on practice prior to this stage.

Prevention

Eating disorder prevention is complicated, but genetic information can assist. Targeting prevention efforts to individuals at high genetic risk is a promising approach and can include psychoeducation and intervention for mothers with eating disorders as well as interventions aimed at the offspring of individuals with eating disorders. Such interventions could help break the cycle of risk associated with eating disorders by providing parents with useful buffering strategies (Slof-Op't Landt et al. 2005). Although such efforts may be effective in identifying familial cases, there are also sporadic cases of eating disorders that would not be reached through such prevention strategies. The identification of genetic variants that confer risk for eating disorders could assist with developing a risk equation that could better indicate who is most vulnerable.

As our study of the genetics and biology of eating disorders progresses, we hope to be able to separate biomarkers of starvation from biomarkers of disease. The ability to identify premorbid biomarkers or genetic markers of risk could also allow us to focus early intervention efforts on those who are most vulnerable. Theoretically, this could preempt many disabling and deleterious aspects related to the evolution of the disease into more severe clinical stages.

Treatment

As part of recovery, it is common for patients and families to express a desire to know what "caused" their illness. Patients and parents often benefit from incorporating psychoeducation about the role

of genes and environment into the therapeutic process. A recent study (Easter 2012) found that most women with eating disorders ($N = 50$; half recovered and half in treatment at the time of interview) anticipated that genetic reframing would be stigma reducing and decrease guilt and self-blame associated with the eating disorder. Educating patients about the complex interplay of genetic and environmental factors in the etiology of eating disorders can replace simplistic conceptualizations of eating disorders as either wholly socially caused or entirely biologically based disorders. As clinicians, it is our responsibility to provide patients with accurate and understandable information about genetic and environmental risk factors. Discussing this with patients and families can help them integrate this new information into their own personal illness narrative (or that of their family member).

Patients may also benefit from developing family trees to map how these disorders aggregate in their family. By directly addressing the complex interplay of genes and environment, patients may better understand the onset and maintenance of their illness and become more aware of why they are particularly sensitive to certain environments. Appreciating their genetically influenced sensitivity to environments can serve as the backdrop for developing skills that allow patients to exert personal control over environmental risk factors and manage their biology effectively.

Integrating this knowledge into the therapeutic process may also help improve outcome by focusing efforts on minimizing environmental risk. Given that we are not yet able to alter the genome, we can work with patients and families to promote buffering environments. Clinical programs should consider how best to work with the patient and family to strengthen protective environmental influences and to minimize the risks associated with exposure to toxic environments. Such interventions may be the best approach to reducing risk for these pernicious and devastating disorders.

Understanding genetic risk can also assist parents and other family members with comprehending why recovery can be so challenging, which may improve empathy and patience. Additionally, educating parents can help eliminate parental blame. For far too long, parents were thought to cause eating disorders. An understanding of the complexity of gene-environment interactions allows parents to rise above this misconception and to focus more on optimizing buffering environments and on the important task of supporting their children in recovery.

Finally, this knowledge can be especially valuable to parents who have a history of eating disorders. Parents can understand that the familial pattern is akin to passing down high blood pressure or diabetes, and they can focus on long-term management of risk for themselves and their children. Ultimately, if our molecular genetic investigations yield responsible genes, pharmacogenomics research may open the door to biological targets and eventually tailored, genetically informed pharmacologic interventions.

CONCLUSIONS

With advances in science, our understanding of the genetic mechanisms underlying eating disorders is evolving. Family and twin studies reveal that genetic factors play an important role in eating disorders, although they clearly do not act alone. Molecular genetic investigations have provided few definitive conclusions, but have implicated several systems, particularly 5-HT and DA. Most recently, GWAS have opened the door to explore the genome in an unbiased fashion, implicating genes not typically considered among the "usual suspects."

Currently, research on the genetics of eating disorders is hampered by small sample sizes and inconsistent definitions of diagnoses, symptoms, and traits. Collecting large population-based samples, collaborating across disorder groups, and using burgeoning molecular genetic techniques that have shown promise in other areas of medicine are paramount. With the upcoming publication of DSM-5, the limitations of the current diagnostic system are resoundingly clear. Pending

the collection of large, well-powered samples, genetics research has the potential to reform our diagnostic classification system both within diagnoses (by determining which genetic factors are most heritable and load the highest on the latent construct) and across diagnoses (through cross-disorder investigations and identification of endophenotypes). Ultimately, a thorough understanding of the genetics of eating disorders may lead to personalized medicine, characterized by pharmacogenomics coupled with treatment targeting environmentally mediated symptoms.

DISCLOSURE STATEMENT

All authors reported no biomedical financial interests or potential conflicts of interest.

LITERATURE CITED

Aigner M, Treasure J, Kaye W, Kasper S. 2011. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. *World J. Biol. Psychiatry* 12:400–43

Altman SE, Shankman SA. 2009. What is the association between obsessive-compulsive disorder and eating disorders? *Clin. Psychol. Rev.* 29:638–46

Am. Psychiatr. Assoc. 2000. *Diagnostic and Statistical Manual of Mental Disorders.* Washington DC: Am. Psychiatr. Assoc. 4th ed., text rev.

Ando T, Ishikawa T, Hotta M, Naruo T, Okabe K, et al. 2012. No association of brain-derived neurotrophic factor Val66Met polymorphism with anorexia nervosa in Japanese. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 159B:48–52

Ando T, Komaki G, Naruo T, Okabe K, Takii M, et al. 2006. Possible role of preproghrelin gene polymorphisms in susceptibility to bulimia nervosa. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 141B:929–34

Ando T, Komaki G, Nishimura H, Naruo T, Okabe K, et al. 2010. A ghrelin gene variant may predict crossover rate from restricting-type anorexia nervosa to other phenotypes of eating disorders: a retrospective survival analysis. *Psychiatr. Genet.* 20:153–59

Bachner-Melman R, Lerer E, Zohar AH, Kremer I, Elizur Y, et al. 2007. Anorexia nervosa, perfectionism, and dopamine D4 receptor (DRD4). *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 144B:748–56

Baker JH, Mitchell KS, Neale MC, Kendler KS. 2010. Eating disorder symptomatology and substance use disorders: prevalence and shared risk in a population based twin sample. *Int. J. Eat. Disord.* 43:648–58

Bergen AW, van den Bree MB, Yeager M, Welch R, Ganjei JK, et al. 2003. Candidate genes for anorexia nervosa in the 1p33–36 linkage region: serotonin 1D and delta opioid receptor loci exhibit significant association to anorexia nervosa. *Mol. Psychiatry* 8:397–406

Bergen AW, Yeager M, Welch RA, Haque K, Ganjei JK, et al. 2005. Association of multiple DRD2 polymorphisms with anorexia nervosa. *Neuropsychopharmacology* 30:1703–10

Biederman J, Ball SW, Monuteaux MC, Surman CB, Johnson JL, Zietlin S. 2007. Are girls with ADHD at risk for eating disorders? Results from a controlled, five-year prospective study. *J. Dev. Behav. Pediatr.* 28:302–7

Blinder BJ, Cumell EJ, Sanathara VA. 2006. Psychiatric comorbidities of female inpatients with eating disorders. *Psychosom. Med.* 68:454–62

Boraska V, Davis OS, Cherkas LF, Helder SG, Harris J, et al. 2012. Genome-wide association analysis of eating disorder-related symptoms, behaviors, and personality traits. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 159B:803–11

Brandys MK, Kas MJ, van Elburg AA, Ophoff R, Slof-Op't Landt MC, et al. 2011. The Val66Met polymorphism of the BDNF gene in anorexia nervosa: new data and a meta-analysis. *World J. Biol. Psychiatry* doi: 10.3109/15622975.2011.605470

Brandys MK, Slof-Op't Landt MC, van Elburg AA, Ophoff R, Verduijn W, et al. 2012. Anorexia nervosa and the Val158Met polymorphism of the COMT gene: meta-analysis and new data. *Psychiatr. Genet.* 22:130–36

Brandys MK, van Elburg AA, Loos RJ, Bauer F, Hendriks J, et al. 2010. Are recently identified genetic variants regulating BMI in the general population associated with anorexia nervosa? *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 153B:695–99

Branson R, Potoczna N, Kral JG, Lentes KU, Hoehe MR, Horber FF. 2003. Binge eating as a major phenotype of melanocortin 4 receptor gene mutations. *N. Engl. J. Med.* 348:1096–103

Brown KM, Bujac SR, Mann ET, Campbell DA, Stubbins MJ, Blundell JE. 2007. Further evidence of association of OPRD1 & HTR1D polymorphisms with susceptibility to anorexia nervosa. *Biol. Psychiatry* 61:367–73

Brown LM, Clegg DJ. 2010. Central effects of estradiol in the regulation of food intake, body weight, and adiposity. *J. Steroid Biochem. Mol. Biol.* 122:65–73

Bulik CM. 2005. Exploring the gene-environment nexus in eating disorders. *J. Psychiatry Neurosci.* 30:335–38

Bulik CM, Devlin B, Bacanu SA, Thornton L, Klump KL, et al. 2003a. Significant linkage on chromosome 10p in families with bulimia nervosa. *Am. J. Hum. Genet.* 72:200–7

Bulik CM, Hebebrand J, Keski-Rahkonen A, Klump KL, Reichborn-Kjennerud T, et al. 2007a. Genetic epidemiology, endophenotypes, and eating disorder classification. *Int. J. Eat. Disord.* 40:S52–60

Bulik CM, Slof-Op't Landt MC, van Furth EF, Sullivan PF. 2007b. The genetics of anorexia nervosa. *Annu. Rev. Nutr.* 27:263–75

Bulik CM, Sullivan PF, Kendler KS. 2003b. Genetic and environmental contributions to obesity and binge-eating. *Int. J. Eat. Disord.* 33:293–98

Bulik CM, Sullivan PF, Wade TD, Kendler KS. 2000. Twin studies of eating disorders: a review. *Int. J. Eat. Disord.* 27:1–20

Calati R, De Ronchi D, Bellini M, Serretti A. 2011. The 5-HTTLPR polymorphism and eating disorders: a meta-analysis. *Int. J. Eat. Disord.* 44:191–99

Campbell DA, Sundaramurthy D, Gordon D, Markham AF, Pieri LF. 1999. Association between a marker in the UCP-2/UCP-3 gene cluster and genetic susceptibility to anorexia nervosa. *Mol. Psychiatry* 4:68–70

Campbell IC, Mill J, Uher R, Schmidt U. 2011. Eating disorders, gene-environment interactions and epigenetics. *Neurosci. Biobehav. Rev.* 35:784–93

Castellini G, Ricca V, Lelli L, Bagnoli S, Lucenteforte E, et al. 2012. Association between serotonin transporter gene polymorphism and eating disorders outcome: a 6-year follow-up study. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 159B:491–500

Cellini E, Nacmias B, Brecelj-Anderluh M, Badia-Casanovas A, Bellodi L, et al. 2006. Case-control and combined family trios analysis of three polymorphisms in the ghrelin gene in European patients with anorexia and bulimia nervosa. *Psychiatr. Genet.* 16:51–52

Choquette AC, Bouchard L, Drapeau V, Lemieux S, Tremblay A, et al. 2012. Association between olfactory receptor genes, eating behavior traits and adiposity: results from the Quebec Family Study. *Physiol. Behav.* 105:772–76

Culbert KM, Burt SA, McGue M, Iacono WG, Klump KL. 2009. Puberty and the genetic diathesis of disordered eating attitudes and behaviors. *J. Abnorm. Psychol.* 118:788–96

Dardennes RM, Zizzari P, Tolle V, Foulon C, Kipman A, et al. 2007. Family trios analysis of common polymorphisms in the obestatin/ghrelin, BDNF and AGRP genes in patients with anorexia nervosa: association with subtype, body-mass index, severity and age of onset. *Psychoneuroendocrinology* 32:106–13

Davis C, Levitan RD, Kaplan AS, Carter J, Reid C, et al. 2008. Reward sensitivity and the D2 dopamine receptor gene: a case-control study of binge eating disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 32:620–28

Davis CA, Levitan RD, Reid C, Carter JC, Kaplan AS, et al. 2009. Dopamine for "wanting" and opioids for "liking": a comparison of obese adults with and without binge eating. *Obesity (Silver Spring)* 17:1220–25

Davis C, Levitan RD, Yilmaz Z, Kaplan AS, Carter JC, Kennedy JL. 2012. Binge eating disorder and the dopamine D2 receptor: genotypes and sub-phenotypes. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 38:328–35

Devlin B, Bacanu SA, Klump KL, Bulik CM, Fichter MM, et al. 2002. Linkage analysis of anorexia nervosa incorporating behavioral covariates. *Hum. Mol. Genet.* 11:689–96

de Zwaan M. 2001. Binge eating disorder and obesity. *Int. J. Obes. Relat. Metab. Disord.* 25:S51–55

Dmitrzak-Weglarz M, Skibinska M, Slopien A, Szczepankiewicz A, Rybakowski F, et al. 2007. BDNF Met66 allele is associated with anorexia nervosa in the Polish population. *Psychiatr. Genet.* 17:245–46

Easter MM. 2012. "Not all my fault": genes, stigma, and personal responsibility for women with eating disorders. *Soc. Sci. Med.* 75:1408–16

Eastwood H, Brown K, Markovic D, Pieri LF. 2002. Variation in the ESR1 and ESR2 genes and genetic susceptibility to anorexia nervosa. *Mol. Psychiatry* 7:86–89

Ehrlich S, Weiss D, Burghardt R, Infante-Duarte C, Brockhaus S, et al. 2010. Promoter specific DNA methylation and gene expression of POMC in acutely underweight and recovered patients with anorexia nervosa. *J. Psychiatr. Res.* 44:827–33

Fairburn CG, Doll HA, Welch SL, Hay PJ, Davies BA, O'Connor ME. 1998. Risk factors for binge eating disorder: a community-based, case-control study. *Arch. Gen. Psychiatry* 55:425–32

Fowler S, Bulik CM. 1997. Family environment and psychiatric history in women with binge eating disorder and obese controls. *Behav. Change* 14:106–12

Friedel S, Horro FF, Wermter AK, Geller F, Dempfle A, et al. 2005. Mutation screen of the brain derived neurotrophic factor gene (*BDNF*): identification of several genetic variants and association studies in patients with obesity, eating disorders, and attention-deficit/hyperactivity disorder. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 132B:96–99

Frieling H, Bleich S, Otten J, Romer KD, Kornhuber J, et al. 2008. Epigenetic downregulation of atrial natriuretic peptide but not vasopressin mRNA expression in females with eating disorders is related to impulsivity. *Neuropsychopharmacology* 33:2605–9

Frieling H, Gozner A, Romer KD, Lenz B, Bonsch D, et al. 2007. Global DNA hypomethylation and DNA hypermethylation of the alpha synuclein promoter in females with anorexia nervosa. *Mol. Psychiatry* 12:229–30

Frieling H, Romer KD, Scholz S, Mittelbach F, Wilhelm J, et al. 2010. Epigenetic dysregulation of dopaminergic genes in eating disorders. *Int. J. Eat. Disord.* 43:577–83

Frieling H, Romer KD, Wilhelm J, Hillemacher T, Kornhuber J, et al. 2006. Association of catecholamine-O-methyltransferase and 5-HTTLPR genotype with eating disorder-related behavior and attitudes in females with eating disorders. *Psychiatr. Genet.* 16:205–8

Frisch A, Laufer N, Danziger Y, Michaelovsky E, Leor S, et al. 2001. Association of anorexia nervosa with the high activity allele of the COMT gene: a family-based study in Israeli patients. *Mol. Psychiatry* 6:243–45

Garner DM, Olmsted MP, Polivy J. 1984. *Eating Disorders Inventory Manual*. New York: Psychol. Assess. Resourc.

Gerard N, Pieters G, Goffin K, Bormans G, Van Laere K. 2011. Brain type 1 cannabinoid receptor availability in patients with anorexia and bulimia nervosa. *Biol. Psychiatry* 70:777–84

Godart NT, Perdereau F, Rein Z, Berthoz S, Wallier J, et al. 2007. Comorbidity studies of eating disorders and mood disorders. Critical review of the literature. *J. Affect. Disord.* 97:37–49

Gorwood P, Kipman A, Foulon C. 2003. The human genetics of anorexia nervosa. *Eur. J. Pharmacol.* 480:163–70

Grice DE, Halmi KA, Fichter MM, Strober M, Woodside DB, et al. 2002. Evidence for a susceptibility gene for anorexia nervosa on chromosome 1. *Am. J. Hum. Genet.* 70:787–92

Groleau P, Steiger H, Joober R, Bruce KR, Israel M, et al. 2012. Dopamine-system genes, childhood abuse, and clinical manifestations in women with bulimia-spectrum disorders. *J. Psychiatr. Res.* 46:1139–45

Han L, Nielsen DA, Rosenthal NE, Jefferson K, Kaye W, et al. 1999. No coding variant of the tryptophan hydroxylase gene detected in seasonal affective disorder, obsessive-compulsive disorder, anorexia nervosa, and alcoholism. *Biol. Psychiatry* 45:615–19

Heatherton TF, Herman CP, Polivy J, King GA, McGree ST. 1988. The (mis)measurement of restraint: an analysis of conceptual and psychometric issues. *J. Abnorm. Psychol.* 97:19–28

Hebebrand J, Geller F, Dempfle A, Heinzel-Gutenbrunner M, Raab M, et al. 2004. Binge-eating episodes are not characteristic of carriers of melanocortin-4 receptor gene mutations. *Mol. Psychiatry* 9:796–800

Herman CP, Polivy J. 1980. Restrained eating. In *Obesity*, ed. AJ Stunkard, pp. 208–25. Philadelphia, PA: Saunders

Herzog DB, Keller MB, Sacks NR, Yeh CJ, Lavori PW. 1992. Psychiatric comorbidity in treatment-seeking anorexics and bulimics. *J. Am. Acad. Child Adolesc. Psychiatry* 31:810–18

Hildebrandt T, Alfano L, Tricamo M, Pfaff DW. 2010. Conceptualizing the role of estrogens and serotonin in the development and maintenance of bulimia nervosa. *Clin. Psychol. Rev.* 30:655–68
Himmerich H, Schonknecht P, Heitmann S, Sheldrick AJ. 2010. Laboratory parameters and appetite regulators in patients with anorexia nervosa. *J. Psychiatr. Pract.* 16:82–92
Hinney A, Bornscheuer A, Depenbusch M, Mierke B, Tölle A. 1998. No evidence for involvement of the leptin gene in anorexia nervosa, bulimia nervosa, underweight or early onset extreme obesity: identification of two novel mutations in the coding sequence and a novel polymorphism in the leptin gene linked upstream region. *Mol. Psychiatry* 3:539–43
Hinney A, Schmidt A, Nottebom K, Heibult O, Becker I, et al. 1999a. Several mutations in the melanocortin-4 receptor gene including a nonsense and a frameshift mutation associated with dominantly inherited obesity in humans. *J. Clin. Endocrinol. Metab.* 84:1483–86
Hinney A, Schneider JL, Ziegler A, Lehmkuhl G, Poustka F, et al. 1999b. No evidence for involvement of polymorphisms of the dopamine D4 receptor gene in anorexia nervosa, underweight, and obesity. *Am. J. Med. Genet.* 88:594–97
Hoek HW. 2006. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. *Curr. Opin. Psychiatry* 19:389–94
Hong CJ, Liou YJ, Tasi SJ. 2011. Effects of BDNF polymorphisms on brain function and behavior in health and disease. *Brain Res. Bull.* 86:287–97
Hosák L. 2007. Role of the COMT gene Val158Met polymorphism in mental disorders: a review. *Eur. Psychiatry* 22:276–81
Hotta M, Ohwada R, Akamizu T, Shibasaki T, Takano K, Kangawa K. 2009. Ghrelin increases hunger and food intake in patients with restricting-type anorexia nervosa: a pilot study. *Endocr. J.* 56:1119–28
Hu X, Karwautz A, Wagner G, Holliday J, Li T, et al. 2007. No association between a promoter polymorphism in the noradrenaline transporter gene and anorexia nervosa. *Psychiatr. Genet.* 17:247–48
Huang J, Perlis RH, Lee PH, Rush AJ, Fava M, et al. 2010. Cross-disorder genomewide analysis of schizophrenia, bipolar disorder, and depression. *Am. J. Psychiatry* 167:1254–63
Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. 2007. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol. Psychiatry* 61:348–58
Hudson JI, Lalonde JK, Berry JM, Pindyck LJ, Bulik CM, et al. 2006. Binge-eating disorder as a distinct familial phenotype in obese individuals. *Arch. Gen. Psychiatry* 63:313–19
Ishiguro H, Onaivi ES, Horiuchi Y, Imai K, Komaki G, et al. 2011. Functional polymorphism in the *GPR55* gene is associated with anorexia nervosa. *Synapse* 65:103–8
Javaras KN, Laird NM, Reichborn-Kjennerud T, Bulik CM, Pope HG Jr, Hudson JI. 2008. Familiality and heritability of binge eating disorder: results of a case-control family study and a twin study. *Int. J. Eat. Disord.* 41:174–79
Jonassaint CR, Szatkiewicz JP, Bulik CM, Thornton LM, Bloss C, et al. 2011. Absence of association between specific common variants of the obesity-related FTO gene and psychological and behavioral eating disorder phenotypes. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 156B:454–61
Kanbur N, Mesci L, Derman O, Turul T, Cuhadaroğlu F, et al. 2008. Tumor necrosis factor alpha-308 gene polymorphism in patients with anorexia nervosa. *Turk. J. Pediatr.* 50:219–22
Kaplan AS, Levitan RD, Yilmaz Z, Davis C, Tharmalingam S, Kennedy JL. 2008. A DRD4/BDNF gene-gene interaction associated with maximum BMI in women with bulimia nervosa. *Int. J. Eat. Disord.* 41:22–28
Karwautz AF, Wagner G, Waldherr K, Nader IW, Fernandez-Aranda F, et al. 2011. Gene-environment interaction in anorexia nervosa: relevance of non-shared environment and the serotonin transporter gene. *Mol. Psychiatry* 16:590–92
Kaye WH, Strober M, Jimerson D. 2004. The neurobiology of eating disorders. In *The Neurobiology of Mental Illness*, ed. D Charney, E Nestler, pp. 1112–28. New York: Oxford Univ. Press
Kendler KS, Prescott CA. 2006. *Genes, Environment, and Psychopathology: Understanding the Causes of Psychiatric and Substance Use Disorders*. New York: Guilford
Keski-Rahkonen A, Bulik CM, Neale BM, Rose RJ, Rissanen A, Kaprio J. 2005a. Body dissatisfaction and drive for thinness in young adult twins. *Int. J. Eat. Disord.* 37:188–99
Keski-Rahkonen A, Neale BM, Bulik CM, Pietilainen KH, Rose RJ, et al. 2005b. Intentional weight loss in young adults: sex-specific genetic and environmental effects. *Obes. Res.* 13:745–53

Kiezebrink K, Mann ET, Bujac SR, Stubbins MJ, Campbell DA, Blundell JE. 2010. Evidence of complex involvement of serotonergic genes with restrictive and binge purge subtypes of anorexia nervosa. *World J. Biol. Psychiatry* 11:824–33

Kim YR, Woo JM, Heo SY, Kim JH, Lim SJ, Yu BH. 2009. An association study of the A218C polymorphism of the tryptophan hydroxylase 1 gene with eating disorders in a Korean population: a pilot study. *Psychiatry Investig.* 6:44–49

Kindler J, Bailer U, de Zwaan M, Fuchs K, Leisch F, et al. 2011. No association of the neuropeptide Y (Leu7Pro) and ghrelin gene (Arg51Gln, Leu72Met, Gln90Leu) single nucleotide polymorphisms with eating disorders. *Nord. J. Psychiatry* 65:203–7

Kipman A, Bruins-Slot L, Boni C, Hanoun N, Ades J, et al. 2002. 5-HT_{2A} gene promoter polymorphism as a modifying rather than a vulnerability factor in anorexia nervosa. *Eur. Psychiatry* 17:227–29

Klump KL, Burt SA, Spanos A, McGue M, Iacono WG, Wade TD. 2010a. Age differences in genetic and environmental influences on weight and shape concerns. *Int. J. Eat. Disord.* 43:679–88

Klump KL, Culbert KM. 2007. Molecular genetic studies of eating disorders: current status and future directions. *Curr. Dir. Psychol. Sci.* 16:37–41

Klump KL, Keel PK, Sisk CL, Burt SA. 2010b. Preliminary evidence that estradiol moderates genetic influences on disordered eating attitudes and behaviors during puberty. *Psychol. Med.* 40:1745–53

Klump KL, Miller KB, Keel PK, McGue M, Iacono WG. 2001. Genetic and environmental influences on anorexia nervosa syndromes in a population-based twin sample. *Psychol. Med.* 31:737–40

Klump KL, Perkins PS, Burt SA, McGue M, Iacono WG. 2007. Puberty moderates genetic influences on disordered eating. *Psychol. Med.* 37:627–34

Koronyo-Hamaoui M, Danziger Y, Frisch A, Stein D, Leor S, et al. 2002. Association between anorexia nervosa and the hsKCa3 gene: a family-based and case control study. *Mol. Psychiatry* 7:82–85

Koronyo-Hamaoui M, Frisch A, Stein D, Denziger Y, Leor S, et al. 2007. Dual contribution of NR2B subunit of NMDA receptor and Ca^{2+}-activated K^+ channel to genetic predisposition to anorexia nervosa. *J. Psychiatr. Res.* 41:160–67

Koronyo-Hamaoui M, Gak E, Stein D, Frisch A, Danziger Y, et al. 2004. CAG repeat polymorphism within the KCNN3 gene is a significant contributor to susceptibility to anorexia nervosa: a case-control study of female patients and several ethnic groups in the Israeli Jewish population. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 131B:76–80

Kortegaard LS, Hoerder K, Joergensen J, Gillberg C, Kyvik KO. 2001. A preliminary population-based twin study of self-reported eating disorder. *Psychol. Med.* 31:361–65

Lee Y, Abbott D, Seim H, Crosby R, Monson N, et al. 1999. Eating disorders and psychiatric disorders in the first-degree relatives of obese probands with binge eating disorder and obese non-binge eating disorder controls. *Int. J. Eat. Disord.* 26:322–32

Lee Y, Lin PY. 2010. Association between serotonin transporter gene polymorphism and eating disorders: a meta-analytic study. *Int. J. Eat. Disord.* 43:498–504

Levitan RD, Kaplan AS, Davis C, Lam RW, Kennedy JL. 2010. A season-of-birth/DRD4 interaction predicts maximal body mass index in women with bulimia nervosa. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 35:1729–33

Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnikov K, et al. 1998. A controlled family study of restricting anorexia and bulimia nervosa: comorbidity in probands and disorders in first-degree relatives. *Arch. Gen. Psychiatry* 55:603–10

Lilenfeld LR, Ringham R, Kalarchian MA, Marcus MD. 2008. A family history study of binge-eating disorder. *Compr. Psychiatry* 49:247–54

Malhotra AK, Zhang JP, Lencz T. 2012. Pharmacogenetics in psychiatry: translating research into clinical practice. *Mol. Psychiatry* 17:760–69

Martásková D, Slachtová L, Kemlink D, Záhoráková D, Papezová H. 2009. Polymorphisms in serotonin-related genes in anorexia nervosa. The first study in Czech population and metaanalyses with previously performed studies. *Folia Biol. (Praha)* 55:192–97

Mazzeo SE, Mitchell KS, Bulik CM, Aggen SH, Kendler KS, Neale MC. 2010. A twin study of specific bulimia nervosa symptoms. *Psychol. Med.* 40:1203–13

Mazzeo SE, Mitchell KS, Bulik CM, Reichborn-Kjennerud T, Kendler KS, Neale MC. 2009. Assessing the heritability of anorexia nervosa symptoms using a marginal maximal likelihood approach. *Psychol. Med.* 39:463–73

Merle JV, Haas V, Burghardt R, Dohler N, Schneider N, et al. 2011. Agouti-related protein in patients with acute and weight-restored anorexia nervosa. *Psychol. Med.* 41:2183–92

Michaelovsky E, Frisch A, Leor S, Stein D, Danziger Y, et al. 2005. Haplotype analysis of the *COMT-ARVCF* gene region in Israeli anorexia nervosa family trios. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 139B:45–50

Mikolajczyk E, Grzywacz A, Samochowiec J. 2010. The association of catechol-*O*-methyltransferase genotype with the phenotype of women with eating disorders. *Brain Res.* 1307:142–48

Mikolajczyk E, Smiarowska M, Grzywacz A, Samochowiec J. 2006. Association of eating disorders with catechol-*O*-methyltransferase gene functional polymorphism. *Neuropsychobiology* 54:82–86

Mitchell KS, Neale MC, Bulik CM, Aggen SH, Kendler KS, Mazzeo SE. 2010. Binge eating disorder: a symptom-level investigation of genetic and environmental influences on liability. *Psychol. Med.* 40:1899–906

Miyasaka K, Hosoya H, Sekime A, Ohta M, Amono H, et al. 2006. Association of ghrelin receptor gene polymorphism with bulimia nervosa in a Japanese population. *J. Neural Transm.* 113:1279–85

Monteleone P, Bifulco M, Di Filippo C, Gazzerro P, Canestrelli B, et al. 2009. Association of *CNR1* and *FAAH* endocannabinoid gene polymorphisms with anorexia nervosa and bulimia nervosa: evidence for synergistic effects. *Genes Brain Behav.* 8:728–32

Monteleone P, Maj M. 2008. Genetic susceptibility to eating disorders: associated polymorphisms and pharmacogenetic suggestions. *Pharmacogenomics* 9:1487–520

Monteleone P, Santonastaso P, Mauri M, Bellodi L, Erzegovesi S, et al. 2006a. Investigation of the serotonin transporter regulatory region polymorphism in bulimia nervosa: relationships to harm avoidance, nutritional parameters, and psychiatric comorbidity. *Psychosom. Med.* 68:99–103

Monteleone P, Tortorella A, Castaldo E, Di Filippo C, Maj M. 2006b. No association of the Arg51Gln and Leu72Met polymorphisms of the ghrelin gene with anorexia nervosa or bulimia nervosa. *Neurosci. Lett.* 398:325–27

Monteleone P, Tortorella A, Castaldo E, Di Filippo C, Maj M. 2007. The Leu72Met polymorphism of the ghrelin gene is significantly associated with binge eating disorder. *Psychiatr. Genet.* 17:13–16

Monteleone P, Tortorella A, Castaldo E, Maj M. 2006c. Association of a functional serotonin transporter gene polymorphism with binge eating disorder. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 141B:7–9

Monteleone P, Zanardini R, Tortorella A, Gennarelli M, Castaldo E, et al. 2006d. The 196G/A (val66met) polymorphism of the BDNF gene is significantly associated with binge eating behavior in women with bulimia nervosa or binge eating disorder. *Neurosci. Lett.* 406:133–37

Müller TD, Greene BH, Bellodi L, Cavallini MC, Cellini E, et al. 2012. Fat mass and obesity-associated gene (*FTO*) in eating disorders: evidence for association of the rs9939609 obesity risk allele with bulimia nervosa and anorexia nervosa. *Obes. Facts* 5:408–19

Müller TD, Reichwald K, Brönner G, Kirschner J, Nguyen TT, et al. 2008. Lack of association of genetic variants in genes of the endocannabinoid system with anorexia nervosa. *Child Adolesc. Psychiatry Ment. Health* 2:33

Müller TD, Tschop MH, Jarick I, Ehrlich S, Scherag S, et al. 2011. Genetic variation of the ghrelin activator gene ghrelin O-acyltransferase (*GOAT*) is associated with anorexia nervosa. *J. Psychiatr. Res.* 45:706–11

Nakabayashi K, Komaki G, Tajima A, Ando T, Ishikawa M, et al. 2009. Identification of novel candidate loci for anorexia nervosa at 1q41 and 11q22 in Japanese by a genome-wide association analysis with microsatellite markers. *J. Hum. Genet.* 54:531–37

Nakai Y, Hamagaki S, Takagi R, Taniguchi A, Kurimoto F. 1999. Plasma concentrations of tumor necrosis factor-alpha (TNF-alpha) and soluble TNF receptors in patients with anorexia nervosa. *J. Clin. Endocrinol. Metab.* 84:1226–28

Nakazato M, Hashimoto K, Shimizu E, Kumakiri C, Koizumi H, et al. 2003. Decreased levels of serum brain-derived neurotrophic factor in female patients with eating disorders. *Biol. Psychiatry* 54:485–90

Neale BM, Mazzeo SE, Bulik CM. 2003. A twin study of dietary restraint, disinhibition and hunger: an examination of the eating inventory (three factor eating questionnaire). *Twin Res.* 6:471–78

Neale MC, Aggen SH, Maes HH, Kubarych TS, Schmitt JE. 2006. Methodological issues in the assessment of substance use phenotypes. *Addict. Behav.* 31:1010–34

Nilsson M, Naessen S, Dahlman I, Lindén Hirschberg A, Gustafsson JA, Dahlman-Wright K. 2004. Association of estrogen receptor beta gene polymorphisms with bulimic disease in women. *Mol. Psychiatry* 9:28–34

Nishiguchi N, Matsushita S, Suzuki K, Masanobu M, Shirakawa O, Higuchi S. 2001. Association between 5HT2A receptor gene promoter region polymorphism and eating disorders in Japanese patients. *Biol. Psychiatry* 50:123–28

Nisoli E, Brunani A, Borgomainerio E, Tonello C, Dioni L, et al. 2007. D2 dopamine receptor (DRD2) gene Taq1A polymorphism and the eating-related psychological traits in eating disorders (anorexia nervosa and bulimia) and obesity. *Eat. Weight Disord.* 12:91–96

Peñas-Lledó EM, Dorado P, Agüera Z, Gratacós M, Estivill X, et al. 2011. High risk of lifetime history of suicide attempts among CYP2D6 ultrarapid metabolizers with eating disorders. *Mol. Psychiatry* 16:691–92

Peñas-Lledó EM, Dorado P, Agüera Z, Gratacós M, Estivill X, et al. 2012. CYP2D6 polymorphism in patients with eating disorders. *Pharmacogenomics J.* 12:173–75

Peñas-Lledó E, Fernández-Aranda F, Jiménez-Murcia S, Granero R, Penelo E, et al. 2009. Subtyping eating disordered patients along drive for thinness and depression. *Behav. Res. Ther.* 47:513–19

Peñas-Lledó EM, Trejo HD, Dorado P, Ortega A, Jung H, et al. 2013. CYP2D6 ultrarapid metabolism and early dropout from fluoxetine or amitriptyline monotherapy treatment in major depressive patients. *Mol. Psychiatry.* 18:8–9

Petronis A. 2010. Epigenetics as a unifying principle in the aetiology of complex traits and diseases. *Nature* 465:721–27

Polsinelli GN, Levitan RN, De Luca V. 2012. 5-HTTLPR polymorphism in bulimia nervosa: a multiple-model meta-analysis. *Psychiatr. Genet.* 22:219–25

Potoczna N, Branson R, Kral JG, Piec G, Steffen R, et al. 2004. Gene variants and binge eating as predictors of comorbidity and outcome of treatment in severe obesity. *J. Gastrointest. Surg.* 8:971–81

Ramoz N, Versini A, Gorwood P. 2007. Eating disorders: an overview of treatment responses and the potential impact of vulnerability genes and endophenotypes. *Expert Opin. Pharmacother.* 8:2029–44

Rask-Andersen M, Olszewski PK, Levin AS, Schiotch HB. 2010. Molecular mechanisms underlying anorexia nervosa: focus on human gene association studies and systems controlling food intake. *Brain Res. Rev.* 62:147–64

Ribasés M, Gratacos M, Armengol L, de Cid R, Badia A, et al. 2003. Met66 in the brain-derived neurotrophic factor (BDNF) precursor is associated with anorexia nervosa restrictive type. *Mol. Psychiatry* 8:745–51

Ribasés M, Gratacos M, Fernandez-Aranda F, Bellodi L, Boni C, et al. 2004. Association of BDNF with anorexia, bulimia and age of onset of weight loss in six European populations. *Hum. Mol. Genet.* 13:1205–12

Ribasés M, Gratacos M, Fernandez-Aranda F, Bellodi L, Boni C, et al. 2005. Association of BDNF with restricting anorexia nervosa and minimum body mass index: a family-based association study of eight European populations. *Eur. J. Hum. Genet.* 13:428–34

Ricca V, Nacmias B, Cellini E, Di Bernardo M, Rotella CM, Sorbi S. 2002. 5-HT2A receptor gene polymorphism and eating disorders. *Neurosci. Lett.* 323:105–8

Root TL, Thornton LM, Lindroos AK, Stunkard AJ, Lichtenstein P, et al. 2010. Shared and unique genetic and environmental influences on binge eating and night eating: a Swedish twin study. *Eat. Behav.* 11:92–98

Rosenkranz K, Hinney A, Ziegler A, Hermann H, Fichter M. 1998. Systematic mutation screening of the estrogen receptor beta gene in probands of different weight extremes: identification of several genetic variants. *J. Clin. Endocrinol. Metab.* 83:4524–27

Rutherford J, McGuffin P, Katz R, Murray R. 1993. Genetic influences on eating attitudes in a normal female twin population. *Psychol. Med.* 23:425–36

Sanhueza JA, Herrera CL, Salazar LA, Silva JR. 2011. CRF-BP and SLC6A4 gene polymorphisms among restrained eaters. *Rev. Med. Chile* 139:1261–68 (in Spanish)

Scarr S, McCartney K. 1983. How people make their own environments: a theory of genotype greater than environment effects. *Child Dev.* 54:424–35

Scherag S, Hebebrand J, Hinney A. 2010. Eating disorders: the current status of molecular genetic research. *Eur. Child Adolesc. Psychiatry* 19:211–26

Schur E, Noonan C, Polivy J, Goldberg J, Buchwald D. 2009. Genetic and environmental influences on restrained eating behavior. *Int. J. Eat. Disord.* 42:765–72

Siegfried Z, Kanyas K, Latzer Y, Karni O, Bloch M, et al. 2004. Association study of cannabinoid receptor gene (*CNR1*) alleles and anorexia nervosa: differences between restricting and binging/purging subtypes. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 125B:126–30

Slof-Op't Landt MC, Meulenbelt I, Bartels M, Suchiman E, Middeldorp CM, et al. 2011. Association study in eating disorders: TPH2 associates with anorexia nervosa and self-induced vomiting. *Genes Brain Behav.* 10:236–43

Slof-Op't Landt MC, van Furth EF, Meulenbelt I, Slagboom PE, Bartels M, et al. 2005. Eating disorders: from twin studies to candidate genes and beyond. *Twin Res. Hum. Genet.* 16:467–82

Smink FR, van Hoeken D, Hoek HW. 2012. Epidemiology of eating disorders: incidence, prevalence and mortality rates. *Curr. Psychiatry Rep.* 14:406–14

Stamatakis EA, Hetherington MM. 2003. Neuroimaging in eating disorders. *Nutr. Neurosci.* 6:325–34

Steiger H, Bruce KR, Groleau P. 2011. Neural circuits, neurotransmitters, and behavior: serotonin and temperament in bulimic syndromes. *Curr. Top. Behav. Neurosci.* 6:125–38

Steiger H, Richardson J, Joober R, Gauvin L, Israel M, et al. 2007. The 5HTTLPR polymorphism, prior maltreatment and dramatic-erratic personality manifestations in women with bulimic syndromes. *J. Psychiatry Neurosci.* 32:354–62

Steiger H, Richardson J, Joober R, Israel M, Bruce KR, et al. 2008. Dissocial behavior, the 5HTTLPR polymorphism, and maltreatment in women with bulimic syndromes. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 147B:128–30

Steiger H, Richardson J, Schmitz N, Joober R, Israel M, et al. 2009. Association of trait-defined, eating-disorder sub-phenotypes with (biallelic and triallelic) 5HTTLPR variations. *J. Psychiatr. Res.* 43:1086–94

Stice E, Whitenton K. 2002. Risk factors for body dissatisfaction in adolescent girls: a longitudinal investigation. *Dev. Psychol.* 38:669–78

Striegel-Moore RH, Bulik CM. 2007. Risk factors for eating disorders. *Am. Psychol.* 62:181–98

Strober M, Freeman R, Lampert C, Diamond J, Kaye W. 2000. Controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndromes. *Am. J. Psychiatry* 157:393–401

Stunkard AJ, Messick S. 1985. Three-factor eating questionnaire to measure dietary restraint, disinhibition, and hunger. *J. Psychosom. Res.* 29:71–83

Suisman JL, Burt SA, McGue M, Iacono WG, Klump KL. 2011. Parental divorce and disordered eating: an investigation of a gene-environment interaction. *Int. J. Eat. Disord.* 4:169–77

Sullivan PF, Bulik CM, Kendler KS. 1998. The genetic epidemiology of binging and vomiting. *Br. J. Psychiatry* 173:75–79

Sullivan PF, Daly MJ, O'Donovan M. 2012. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat. Rev. Genet.* 13:537–51

Swinbourne J, Hunt C, Abbot M, Russell J, St Clare T, Touyz S. 2012. The comorbidity between eating disorders and anxiety disorders: prevalence in an eating disorder sample and an anxiety disorder sample. *Aust. N. Z. J. Psychiatry* 46:118–31

Tauscher J, Pirker W, Willeit M, de Zwaan M, Bailer U, et al. 2001. [^{123}I] beta-CIT and single photon emission computed tomography reveal reduced brain serotonin transporter availability in bulimia nervosa. *Biol. Psychiatry* 49:326–32

Urwin RE, Bennetts B, Wilcken B, Lampropoulos B, Beumont P, et al. 2002. Anorexia nervosa (restrictive subtype) is associated with a polymorphism in the novel norepinephrine transporter gene promoter polymorphic region. *Mol. Psychiatry* 7:652–57

Urwin RE, Bennetts B, Wilcken B, Lampropoulos B, Beumont PJ, et al. 2003a. Gene-gene interaction between the monoamine oxidase A gene and solute carrier family 6 (neurotransmitter transporter, noradrenalin) member 2 gene in anorexia nervosa (restrictive subtype). *Eur. J. Hum. Genet.* 11:945–50

Urwin RE, Bennetts BH, Wilcken B, Beumont PJ, Russell JD, Nunn KP. 2003b. Investigation of epistasis between the serotonin transporter and norepinephrine transporter genes in anorexia nervosa. *Neuropsychopharmacology* 28:1351–55

Urwin RE, Nunn KP. 2005. Epistatic interaction between the monoamine oxidase A and serotonin transporter genes in anorexia nervosa. *Eur. J. Hum. Genet.* 13:370–75

Vemuri M, Steiner H. 2007. Historical and current conceptualizations of eating disorders: a developmental perspective. In *Eating Disorders in Children and Adolescents*, ed. T Jaffa, B McDermott, pp. 3–11. Cambridge, UK: Cambridge Univ. Press

Versini A, Ramoz N, Le Strat Y, Scherag S, Ehrlich S, et al. 2010. Estrogen receptor 1 gene (ESR1) is associated with restrictive anorexia nervosa. *Neuropsychopharmacology* 35:1818–25

Vink T, Hinney A, van Elburg AA. 2001. Association between an agouti-related protein gene polymorphism and anorexia nervosa. *Mol. Psychiatry* 6:325–28

Wade TD, Bulik CM, Neale M, Kendler KS. 2000. Anorexia nervosa and major depression: shared genetic and environmental risk factors. *Am. J. Psychiatry* 157:469–71

Wade TD, Treloar S, Martin NG. 2008. Shared and unique risk factors between lifetime purging and objective binge eating: a twin study. *Psychol. Med.* 38:1455–64

Wade TD, Treloar SA, Heath AC, Martin NG. 2009. An examination of the overlap between genetic and environmental risk factors for intentional weight loss and overeating. *Int. J. Eat. Disord.* 42:492–97

Walters EE, Neale MC, Eaves LJ, Heath AC, Kessler RC, Kendler KS. 1992. Bulimia nervosa and major depression: a study of common genetic and environmental factors. *Psychol. Med.* 22:617–22

Wang K, Zhang H, Bloss CS, Duvvuri V, Kaye W, et al. 2011. A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa. *Mol. Psychiatry* 16:949–59

Williams HJ, Craddock N, Russo G, Hamshere ML, Moskvina V, et al. 2011. Most genome-wide significant susceptibility loci for schizophrenia and bipolar disorder reported to date cross-traditional diagnostic boundaries. *Hum. Mol. Genet.* 20:387–91

Yanovski SZ. 2003. Binge eating disorder and obesity in 2003: Could treating an eating disorder have a positive effect on the obesity epidemic? *Int. J. Eat. Disord.* 34:S117–20

Zandi PP, Judy JT. 2010. The promise and reality of pharmacogenetics in psychiatry. *Psychiatr. Clin. North Am.* 33:181–224

Zhu AJ, Walsh BT. 2002. Pharmacologic treatment of eating disorders. *Can. J. Psychiatry* 47:227–34

Zucker NL, Losh M, Bulik CM, LaBar KS, Piven J, Pelphrey KA. 2007. Anorexia nervosa and autism spectrum disorders: guided investigation of social cognitive endophenotypes. *Psychol. Bull.* 133:976–1006

Annual Review of
Clinical Psychology
Volume 9, 2013

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Clinical Psychology* articles may be found at http://clinpsy.annualreviews.org